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Review Article

**ROLE OF GUT MICROFLORA IN THE DEVELOPMENT OF
OBESITY AND TYPE II DIABETES**Roshni Acha Biju*¹, Anu Anna Varghese², Renuka R³, Elesy Abraham⁴^{1,2} Fourth Year Pharm D Student, Nazareth College of Pharmacy, Othara P. O, Thiruvalla, Kerala, India.³ Assistant Professor, Department of Pharmacy Practice, Nazareth College of Pharmacy, Othara P.O, Thiruvalla, Kerala, India.⁴ Principal, Nazareth College of Pharmacy, Othara P. O, Thiruvalla, Kerala, India.**Abstract:**

Obesity and its associated complications like Type II diabetes are reaching epidemic stages. Increased food intake and lack of exercise are two main contributing factors. Recent work has been highlighting an increasingly more important role of gut microbiota in metabolic disorders. The human gut harbours more than 100 trillion microbial cells, which have an essential role in human metabolic regulation via their symbiotic interactions with the host. The gut microbiota plays a major role in the development of food absorption and low grade inflammation, two key processes in obesity and diabetes. The present review discusses new findings that may explain how gut microbiota can be involved in the development of obesity and insulin resistance. It will further look at the possible ways to harness the beneficial aspects of the gut microbiota to combat these metabolic disorders and reduce their impact.

Key words: Gut microbiota, obesity, type II diabetes, metabolic regulation, low grade inflammation.**Correspondence to Author:****Ms. Roshni Acha Biju,**

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INTRODUCTION:

The prevalence of obesity and its associated disorders, such as type II diabetes mellitus (T2DM), has increased substantially worldwide over the last decades. Sedentary lifestyle and increased food consumption has been considered the main underlying causes for this obesity epidemic. Genetic and other environmental factors including changes in the gut microbiota play an role in the development of obesity and other metabolic disorders. It is well established facts that gut microbiota can increase energy production from diet, contribute to low-grade inflammation and regulate fatty acid tissue composition. Obesity is a cause of metabolic diseases such as Type II diabetes mellitus, fatty liver, cardiovascular diseases and cancer. T2DM is one of the most common severe metabolic diseases caused by obesity-linked insulin resistance. In among different triggering events, low-grade inflammation enhance production of inflammatory molecules such as interleukins and tumor necrosis factor alpha (TNF- α) now considered the pathological hallmarks of obesity and diabetes.

However, the exact contribution of gut microbiota to the development of obesity and diabetes is not very clear due to many reasons including the complexity and diversity of gut microbes, ethnic variation in studied populations and large variations between individuals studied. Nonetheless, modulation of gut microbiota holds a tremendous therapeutic potential to treat the growing obesity epidemic especially when combined with diet and exercise. This review will examine the role of the gut microbiota in energy harvest and fat storage, explore differences in the microbiota in obese and lean individuals, and evaluate potential mechanisms for modulating the gut microbiota to influence metabolic parameters in humans.

COMPOSITION OF THE HUMAN GUT MICROBIOTA

Gut microbiota of the human is mainly composed of bacteria, archaea, viruses, and some unicellular eukaryotes. Microbiota of the human digestive tract comprises of complex and heterogeneous community of over 1,000 species, which reach the concentrations ranging from 10^7 to 10^{12} cells/g intestinal content, from the small intestine to colon based on metagenomic analysis.

Many of the gut microbes stay with their hosts in symbiotic relationships and act together in many physiological processes including immune network activities of the host. However, distribution of the microbial community composition throughout the gastrointestinal tract is not homogenous due to peristalsis and secretions of gastric, bile and pancreatic juice. Diversity of the human gut

microbiome is comparatively simple in infants, but becomes more heterogeneous and complex in adults. Lifestyle, diet and environmental factors can also affect the composition and diversity of gut microbial community. Taxonomic analysis of 16S rRNA gene sequences has shown that community composition of the gut microbiota is host-specific and relatively stable over time.

The main bacterial phyla are: Firmicutes (Gram-positive), Bacteroidetes (Gram-negative), and Actinobacteria (Gram-positive). Firmicutes is found in the highest proportion (60%), with more than 200 genera, the most important of which are: *Mycoplasma*, *Bacillus*, and *Clostridium*; Bacteroidetes and Actinobacteria each comprise about 10% of the gut microbiota, with the rest belonging to over 10 minority families. In total, there are more than 1000 different species in the gut. It has also been suggested that the microbiota of most individuals can be categorized into three predominant enterotypes dominated by three different genera: *Bacteroides*, *Prevotella*, and *Ruminococcus*, which are independent of age, gender, ethnicity, or body mass index.

Several possible mechanisms were proposed to explain the impact of structural and functional differences in gut microbiota in lean and obese individuals that may contribute to host adiposity and whether an obese phenotype is transmissible by transplantation of gut microbiota. However, most of these studies were conducted in experimental animals which exhibited different anatomical, physiological, and bacterial colonisation patterns from humans.

ROLE OF GUT MICROBIOTA IN METABOLIC DISEASES

Recent decades have seen an increase in the prevalence of metabolic diseases in developed countries. Environmental factors, such as the increase in energy intake and the decrease in physical activity, have been considered causes of this spectacular increase in the prevalence of metabolic diseases. However, even when the energy intake does not increase and physical activity does not decrease; the prevalence continues growing exponentially, so other environmental factors must be taken into account, including changes in gut microbiota. One of the challenges is to elucidate the molecular origin of metabolic diseases, though the great diversity and social differences among humans make this difficult. During the last half century, with the advances in molecular biology, researchers have been investigating the genetics of metabolic diseases. In spite of the great efforts and the identification of some mutations in the genome, no global view has yet been established. The discovery of candidate genes in studies of pan genomic associations

(GWAS – genome-wide association studies) has helped to identify new genes associated with sensitivity/resistance to diabetes and extreme metabolic phenotypes. However, the global diversity of metabolic diseases cannot be explained, especially given the studies in monozygotic twins, discordant for TDM2 and obesity.

A second step toward the comprehension of the origin of metabolic diseases involves epigenetic and environmental factors. A drastic change in feeding habits in which dietary fibre has been replaced by a high fat diet contributes to the origin of metabolic diseases. However, this simple concept cannot explain why some people are sensitive and others are resistant to the development of these metabolic diseases. In mice, a metabolic adaptation is frequently observed. Genetically identical mice in the same box and with a fat-rich diet for 6–9 months can develop both obesity and diabetes or only one of the diseases. There is a need to find a new paradigm that takes into account the genetic diversity, the environmental factor impact, the rapid development of metabolic diseases, and the individual behaviour to develop diabetes and obesity. The conclusion reached concerns the concept of personalized medicine in which the individual characteristics should be identified in order to adapt a suitable therapeutic strategy for small patient groups.

INFLUENCE OF MICROBIOTA COMPOSITION IN THE DEVELOPMENT OF OBESITY

Studies during the last decade have associated the gut microbiota with the development of metabolic disorders, especially diabetes and obesity. Although incompletely understood, the gut microbiota is implicated in the programming and control of many physiological functions, including gut epithelial development, blood circulation, innate and adaptative mechanisms. A new theory shows microbiota as a contributor to the regulation of energy homeostasis. Thus, with the environmental vulnerabilities, gut microbiota could provoke the development of impairment in energy homeostasis, causing metabolic diseases. The first discovery was related to the fact that mice with a mutation in the leptin gene (metabolically obese mice) have different microbiota as compared with other mice without the mutation. In this obese animal model, the proportion of the dominant gut phyla, Bacteroidetes and Firmicutes, is modified with a significant reduction in Bacteroidetes and a corresponding increase in Firmicutes were the first to report an altered gut microbiota similar to that found in obese mice (a larger proportion of Firmicutes and relatively fewer Bacteroidetes) in 12 obese subjects compared with 2 lean controls.

Later, confirmed a reduction in Bacteroidetes accompanied by a rise in *Lactobacillus* species belonging to the Firmicutes phylum.

The shift in the relative abundance observed in these phyla is associated with the increased capacity to harvest energy from food and with increased low-grade inflammation. The increase in Firmicutes and the decrease in the proportion of Bacteroidetes observed in obese mice could be related with the presence of genes encoding enzymes that break down polysaccharides that cannot be digested by the host, increasing the production of monosaccharide and short-chain fatty acids (SCFA) and the conversion of these SCFA to triglycerides in the liver. These SCFAs are able to bind and activate two G-protein-coupled receptors (GPR41 and GPR43) of the gut epithelial cells. The activation of these receptors induces peptide YY secretion, which suppresses gut motility and retards intestinal transit. By this mechanism of SCFA-linked G-protein-coupled receptor activation, the gut microbiota may contribute markedly to increased nutrient uptake and deposition, contributing to the development of metabolic disorders. Moreover, gut microbiota have also been shown to decrease the production of the fasting-induced adipose factor [FIAF; a secreted lipoprotein lipase (LPL)] by the intestinal cells, which inhibits LPL activity, increasing the storage of liver-derived triglycerides.

MICROBIOTA AND ITS RELATIONSHIP WITH TYPE II DIABETES MELLITUS

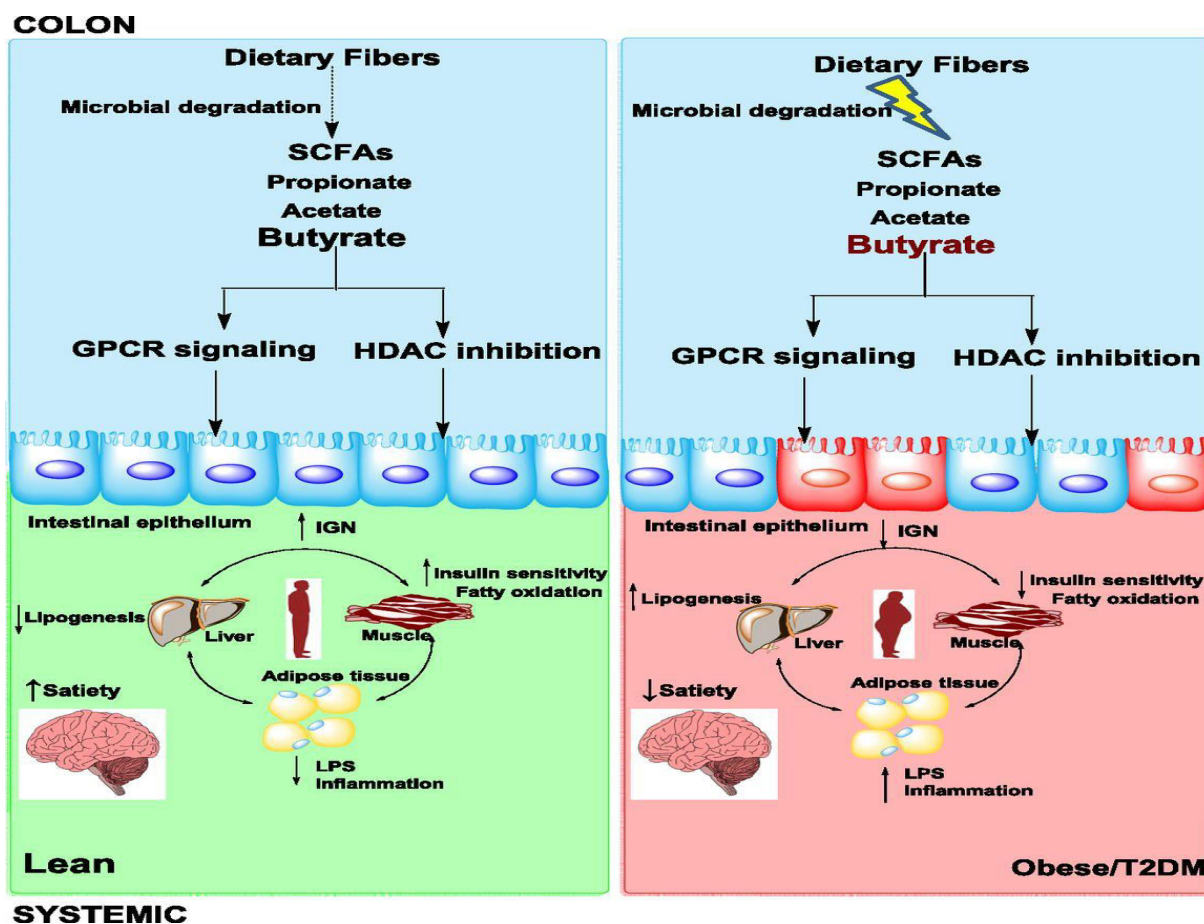
Type 2 diabetes mellitus is the consequence of an increase in the production of glucose in the liver and a deficit in the secretion and action of insulin. Other physiological functions are altered, such as the central and autonomous nervous systems, leading to an impaired secretion of hormones like glucagon and incretins. However, a common feature of obesity and TDM2 is the presence of a low-grade inflammatory component described in tissues involved in metabolism regulation, such as the liver, adipose tissue, and muscles. This metabolic inflammation is characterized by a moderate excess in cytokine production, including interleukin (IL)-6, IL-1 or tumour necrosis factor alpha (TNF- α), that injures cellular insulin signals and contributes to insulin resistance and diabetes. Weight increase would be an initiating factor of low-grade inflammation. When adipocyte hypertrophy is produced as a response to excess energy intake, an increase in TNF- α production in the adipose tissue is also produced and this stimulates the production of chemotactic factors resulting in adipose tissue being infiltrated by proinflammatory macrophages that produce an increase in the production of IL-6 and IL-1. Recently, two studies have shown that the intestinal

micro biome might be an important contributor to the development of TDM2. Both studies also showed that TDM2 subjects were characterized by a reduction in the number of Clostridiales bacteria (*Roseburia* species and *Faecalibacteriumprausnitzii*), which produce the SCFA butyrate. Also, another study found microbiota changes in patients with diabetes or insulin resistance as compared with subjects without alterations in carbohydrate metabolism. In addition, changes in the amount of *Bifidobacterium*, *Lactobacillus*, and *Clostridium* as well as a reduced Firmicutes to Bacteroidetes ratio in gut microbiota have also been recently reported in type II diabetic children. This study also showed that bacteria involved in the maintenance of gut integrity were significantly lower in diabetic patients than in healthy controls. Similar changes in the composition of intestinal microbiota have also been reported in TDM2 patients.

Moreover, probiotic and prebiotic treatments control gut microbiota and metabolic diseases. Various mechanisms have been proposed to explain the influence of the microbiota on insulin resistance and TDM2, such as metabolic endotoxemia, modifications in the secretion of the incretins and butyrate production. The lipopolysaccharides (LPS) are endotoxins commonly found in the outer membrane of Gram negative bacteria that cause metabolic endotoxemia, which is characterized by the release of proinflammatory molecules. A rise in LPS levels has been observed in subjects who increased their fat intake. Similar results were found in mice and in mutant mice (like the leptin-deficient mice) even feeding with a normal diet, which suggests that a change in the proportion of Gram-negative bacteria in the gut or a change in the gut permeability were produced by the LPS rise in serum and this increase is directly related with the degree of insulin resistance reported that modulation of the intestinal microbiota by using prebiotics in obese mice acts favourably on the intestinal barrier, lowering the high-fat diet-induced LPS endotoxemia and systemic and liver inflammation. LPS are absorbed by enterocytes and they are conveyed into plasma coupled to chylomicrons. In this way, dietary fats can be

associated with increased absorption of LPS which in turn can be related with changes in the gut microbiota distinguished by a decrease in the *Eubacteriumrectale-C.*, *Cocoides* group, Gram-negative *Bacteroides* and in *Bifidobacterium*). This causal role of LPS was demonstrated by infusing LPS in mice with a normal diet inducing hepatic insulin resistance, glucose intolerance, and an increase in the weight of adipose tissue. It has been recently shown that the LPS-induced signaling cascade via Toll-like receptor 4 (TLR4) impairs pancreatic β -cell function via suppressed glucose-induced insulin secretion and decreased mRNA expression of pancreas-duodenum homeobox-1 (PDX-1). LPS binds to the CD14/TLR4 receptor present on macrophages and produces an increase in the production of proinflammatory molecules. When LPS injections were administered to mice with a genetic absence of the CD14/TLR4 receptor they did not develop these metabolic characteristics and there was no start of TDM2 or obesity, showing the important role of LPS in the mechanism of CD14/TLR4. Moreover, knock out CD14/TLR4 mice were even more sensitive to insulin than wild type controls. LPS can also promote the expression of NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells) and activation of the MAPK (mitogen-activated protein kinase) pathway in adipocytes with several target genes.

An increase of *Bifidobacterium* spp modulate inflammation in obese mice by an increase in the production of incretins like the glucagon-like peptide (GLP), also reducing intestinal permeability. There is evidence that the rise in *Bifidobacterium* spp. produced by some prebiotics is accompanied by an increase in GLP1 and YY peptide secretions by the intestine. These two molecules have favourable effects, decreasing insulin resistance and the functionality of beta cells. In addition, modulation of the gut flora with prebiotics increases GLP2 production in the colon and this increase in GLP2 production is associated with higher expression of zonula occludens-1 (ZO-1), which improves the mucosal barrier function leading to a decrease in plasma LPS.



(Fig 1) —Role of gut microbiota– produced SCFAs in human glucose metabolism in obese subjects. Fermentation of dietary fibres by intestinal bacteria generates SCFAs, including butyrate, that have both metabolic and epigenetic effects. Obese insulin-resistant subjects are characterized by altered SCFA production compared with lean subjects. Researchers hypothesize that in these subjects, this adversely affects satiety, hepatic glucose, and lipid production as well as inflammatory tone.

THERAPEUTIC POTENTIAL OF MANIPULATING THE GUT MICROBIOAL ECOLOGY

The study of the metabolic, signaling and immune interactions between gut microbes and the host, and how these interactions modulate host brain, muscle, liver and gut functions, has raised the concept of therapeutic microbial manipulation to combat or prevent diseases. In particular, the selection of specific gut bacterial strains and the enhancement of the gut microbial ecology represent a promising therapeutic approach to control energy intake and reduce the prevalence of obesity and the metabolic syndrome. Fecal transplantation is an efficient way to reshape the gut microbial ecosystem after antibiotic treatment to help fight intestinal infection with *Clostridium difficile* and can be used as therapy for inflammatory bowel diseases. A study also showed that nine men with the metabolic syndrome who underwent faecal transplantation with stools from healthy lean individuals had lower fasting levels of triglycerides and developed greater hepatic and peripheral insulin sensitivity after

transplantation than nine men who received a transplant of their own stool. Therefore, fecal transplantation may be useful in the struggle against obesity, although the procedure is still at an experimental stage and the mechanisms involved require further understanding.

The use of probiotics and prebiotics to improve the interactions between gut microbes and host metabolism in obesity and other metabolic diseases has been extensively investigated. Probiotics are live microorganisms that, when used as food supplements, beneficially affect the host by improving intestinal microbial balance and changing the composition of the colonic microbiota. Specific bacterial species such as *Bifidobacterium* spp. have been shown to improve glucose homeostasis, reduce weight gain and fat mass, and restore glucose-mediated insulin secretion in mice fed a high-fat diet.

Prebiotics are food ingredients that beneficially affect the host by selectively stimulating the growth

and/or activity of one or a restricted number of bacteria present in the colon. Prebiotics are composed of oligosaccharides or short-chain polysaccharides.

They are found in common dietary products, such as vegetables and whole-grain cereals, and can be added in yoghurt. The best-characterized prebiotics are fructosyl-oligosaccharides (FOS), including inulin (long-chain fructosyl-oligosaccharide), galactosyl-oligosaccharides (GOS), and other oligosaccharides present in milk, which are transformed by the gut microbiota into SCFAs and simultaneously promote proliferation of selected commensal bacteria in the colon. For example, inulin has been found to stimulate the growth of bifidobacteria and may reduce caloric intake and fat mass in animals and may reduce caloric intake and fat mass in animals. Prebiotic stimulation of the growth of bifidobacteria is correlated with increased glucose tolerance, improved glucose induced insulin secretion, and normalization of inflammation in rodents. GOS also modulate the uptake of transporters, which in turn results in activation of glycolytic pathways. Consumption of prebiotics has also been associated with a reduction in hepatic, renal, and plasma lipid levels in rodents. In particular, GOS supplementation in healthy mice decreased hepatic triglyceride levels by lowering the activity of lipogenic enzymes, fatty acid synthase and microsomal triglyceride transfer proteins, which are involved in VLDL synthesis. Therefore, ingestion of prebiotics might lower lipogenic activity and increase lipolytic activity. The effects of prebiotics and probiotics on anti-inflammatory pathways, weight gain, and glucose metabolism in rodents have been largely attributed to SCFA production. SCFAs interact with GPCRs (for example, GPR41 and GPR43) in the immune cells of the human colon and promote expression of specific chemokines in the colonic epithelium. SCFAs repress NF- κ B and affect the production of proinflammatory markers, such as IL-2 and IL-10, in leukocytes. SCFAs enhance satiety by increasing the synthesis of PYY and proglucagon in epithelial cells and by inhibiting the expression of neuroendocrine factors such as leptin. Other studies have indicated that the effects of prebiotics on intestinal health and inflammation are also mediated by the secretion of glucagon-like proteins (GLP-1 and GLP-2) in entero endocrine L cells. Cani and colleagues showed that *ob/ob* mice fed a high-carbohydrate diet supplemented with oligofructose have increased intestinal representation of bifidobacteria and lactobacilli, improved connections between tight junctions, lower gut permeability, lower systemic endotoxemia, and lower systemic and hepatic inflammation than *ob/ob* mice fed with a high-carbohydrate diet alone. These physiological

changes were correlated with GLP-2 levels and disappeared when the mice were treated with a GLP-2 antagonist.

Another study also pointed out that a synbiotic treatment combining polydextrose and *Bifidobacterium lactis* B420 lowered the abundance of Porphyromonadaceae in mice fed a high-fat diet. This dietary supplement is thought to inhibit T helper 17 (Th17) cell infiltration in the small intestine, preventing metabolic inflammation and the development of type II diabetes.

In humans, probiotic intervention studies have revealed a positive effect of these approaches on glucose metabolism. For example, during a 6-week randomized placebo-controlled study of 60 overweight healthy Indian individuals, the probiotic mix decreased systemic glucose and insulin levels. However, evidence of the anti-obesity effects of prebiotics remain to be demonstrated. Many human studies highlight moderate or no changes in weight loss after prebiotic interventions. Randomized controlled studies have identified surrogate markers of prebiotic treatment (such as plasma PYY, GLP-1, ghrelin) to be negatively correlated with weight gain, inflammation, and impaired glucose metabolism, which support the mechanisms observed in rodents. However, there is no evidence to suggest that prebiotic supplementation in infant formula improves growth or clinical outcomes or causes adverse effects in term infants. Studies in children, adults, and the elderly vary in quality and outcomes. However, prebiotics have been shown to modulate the fecal microbiota and immune function in elderly individuals and to reduce the levels of markers of the metabolic syndrome in overweight adults. The effect of prebiotics and probiotics in obesity and related pathologies in humans requires further exploration. In particular, carefully designed studies using appropriate doses of probiotics or prebiotics and controlled diets will be valuable to underpin the individual responses to different types of interventions and their dependence on genetic, environmental, and gut microbial factors.

CONCLUSION:

The evidence for a strong contribution of the gut microbiota to the onset of obesity and metabolic diseases is growing. The use of germ-free rodent models has enabled us to establish the molecular basis of the interactions between gut microbes and the physiology of the host. The modifications in the gut microbial ecology by dietary factors, antibiotics, probiotics or prebiotics that were observed in rodents and humans have further highlighted the key modulatory roles of the gut microbiota and its contribution to host obesity and metabolic diseases. In particular, some metabolic disorders of the host are thought to be associated

with an inflammation-related composition of the gut microbiota. However, how external factors (such as diet, stress, age, drug intake, and circadian cycles) affect the gut microbial composition and the effectiveness of microbial functions in rodents and humans is still unclear. In the future, it seems essential to promote top-down analytical approaches on an epidemiological scale, integrating data from dietary questionnaires, data about relevant environmental factors (such as stress or factors that influence circadian rhythms) and history of drug or antibiotic use to understand more deeply the functions of gut bacteria in the physiopathology of human obesity. In combination with animal studies, these integrated epidemiological analyses will enable us to unravel the missing connections within the metabolic axis linking gut microbes and the host and to optimize therapeutic strategies to reshape the gut microbial ecology. Using this knowledge, we also hope to improve the stratification of populations at risk of developing metabolic diseases and offer novel perspectives for personalized healthcare, within which clinicians might be able to tailor therapy on the basis of individual habits and predispositions.

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