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Entero-Metabolic Imbalance Theory: Redefining Gut Microbiota Alterations in Diabetic Disorders : A Review

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ABSTRACT

Diabetes is a multifactorial pathological condition characterized by sustained high blood glucose level. It may be due to defective insulin dynamics, beta cell dysfunction or gut derived metabolic modulators. Specifically, Type 2 diabetes mellitus is marked by a combination of progressive dysfunction of pancreatic â-cells and diminished insulin responsiveness which tends to develop chronic hyperglycemia. Though new research points out that gut microbial colony and diabetes are closely related. The concept of entero-metabolic imbalance theory proposes that fluctuations in the commensal microbes contribute in the development of diabetes. In this systematic review, we emphasized on the potential action of different bacterial taxa undermined or afflicted diabetes. The concept of entero-metabolic imbalance theory proposes that variations in the intestinal microbiome play a crucial role in the development and course of diabetes. The intestine of healthy person is colonized by beneficial bacterial phyla such as Firmicutes and Bacteroidetes, with important genera including Roseburia, Bifidobacterium. By means of the production of short chain fatty acids, immunological regulation and epithelial integrity, these microorganisms preserve the function of gut barrier and improve insulin tolerance. This review examines microbial shifts in diabetes, investigate the biological connection between the development of diabetes and gut dysfunction and also evaluates therapeutic proposal.

Figure : 00 References : 28 Table : 00

KEY WORDS : Bifidobacterium, Gut Microbiota, Metabolic Dysfunction, Roseburia, Type 2 Diabetes.

Introduction

The complicated, diversified metabolic disease known as type 2 diabetes (T2D) is typified by persistent hyperglycemia driven by low levels of insulin and progressive β-cell malfunction.

The pancreatic centric model has been used to characterize the pathogenesis of this disease which is caused by a combination of two main factors: impaired insulin secretion by pancreatic β-cells and the inability of insulin-sensitive tissues to respond to insulin[18]. Recent data show that metabolic regulation extends beyond endocrine tissues and involves dynamic link between the gut ecosystem and the host.

Trillions of bacteria like Bifidobacterium, Roseburia, Actinobacteria[20] and many other are present in human gut. By providing short chain fatty acids they promote intestinal health and aids in nutrient metabolism, immune modulation[10 ,15]. They exert systemic effects on glucose and lipid homeostasis. This host–microbe symbiosis maintains epithelial barrier integrity and limits inflammatory activation.

Recent researches show that people with T2D frequently exhibit microbialdysbiosis characterized by reduction of butyrate-producing bacteria, and enrichment of endotoxin-producing Gram-negative bacteria. These kinds of variations are linked with impaired tight junction function, increased intestinal permeability, and translocation of lipopolysaccharide (LPS) into systemic circulationa phenomenon known as metabolic endotoxemia[3]. LPS-mediated activation of innate immune pathways promote chronic low-grade inflammation, a recognized driver of insulin resistance. These findings state that gut-derived inflammatory signaling may serve as a mechanistic bridge linking microbial dysbiosis to metabolic impairment and in progression of diabetes.

Composition of Normal Gut Microbiota

The human intestinal microbiota is a biome of bacteria, archaea, viruses, and fungi. Bacteria is the most dominant component among them. The majority

of gut bacteria belong to several major phyla, primarily Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria[21].

A large array of human metabolic disorders like obesity and diabetes are linked to disturbance in intestinal microbiota[11]. The class Firmicutes and bacteroidetes make up the vast majority of healthy gut microbes[8]. The overall microbial diversity of the gastric flora is established by Helicobacter,themost prevalent genera in the stomach. In particular, when *Helicobacter pylori (H. Pylori)* is present in the stomach as a commensal bacterium, there is a rich diversity comprised of other favoured genera, such as *Streptococcus* (most dominant), *Prevotella, Veillonella* are most closely associated to disease states[13]. A well-functioning gut microbiota could be suggested by the phylum proteobacteria's notably low abundance and the high abundance of the hallmark genera like *Bacteroidetes, Prevotella* and *Ruminococcus*[9]. The most common type of Bacteria found in the lumen of human intestine, also reflect in the stool are *Bacteroides, Bifidobacterium, Streptococcus, Enterobacteriacae, Enterococcus, Clostridium, Lactobacillus* and *Ruminococcus.* On the other hand, *Enterococcus* and *Akkermansia* are the predominant mucosa and mucus associated genera reflect in the epithelial crypts of the small intestine and mucosal layer[24].

Role of enterotypes for maintenance of a healthy gut

Enterotypes are intestinal microbes characterized by specific taxa and metabolicfunction.Three types of enterotypes are there, Enterotype 1 which is marked by *Bacteroides,* enterotypes 2 dominates as *Prevotella* while Enterotype 3 is characterized by greater abundance of *Ruminococcus*[9]. Enterotype 1 has propensity to break sugar protein as they code for the enzymes like proteases, hexoaminidases and galactosidases. This shows that these organisms extract energy from dietary carbohydrates and proteins. Enterotype 2 have a tendency to break the mucin glycoproteins that covers the gut mucosal layer. Enterotype 3 aids in membrane transport of sugars.

The intestinal microorganisms extract most part of their nutrients from the carbohydrates we take in the diet. Short chain fatty acids (SCFA) such as butyrate, propionate and acetate are rich sources of energy for the host[14,20], produced by the colonic bacteria such as *Bacteroides, Roseburia, Bifidobacterium, Fecalibacterium* and *Enterobacteria via* the fermentation of dietary carbs. These Short-chain fatty acids (SCFAs), play a major role in maintaining intestinal barrier integrity by acting as an energy source for colon microbes. Additionally, SCFAs exert anti-inflammatory effects and contribute to improved insulin sensitivity, thereby supporting metabolic homeostasis. Other gut microbes, such as *Lactobacillus* and *Faecali bacterium,* also help in microbial balance and anti-inflammatory processes. In healthy individuals, these microorganisms exist in a balanced proportion. Conjugated linoleic acid is known to have antidiabetic and immune boosting property, synthesized by *Bacteroides* and other gut microbes[1,5,6].

Gut Microbiota Alterations in Diabetes

Recent findings indicates that people with Diabetes show significant variations in the microbial diversity of their gut in comparison to healthy individuals. Reduced microbial variety and greater abundance of specific bacterial genera are hallmark of these changes.

The drop in beneficial SCFA-producing bacteria, including *Roseburia* and *Bifidobacterium* are one of the most consistent findings in the progression of diabetes. These bacteria are essential for controlling the host metabolism and intestinal barrier integrity. Their decline may impair intestinal health and metabolic regulation. One of the most significant microbiota related parameters linked to beginning and progression of T2D appears to be a reduction in butyrate producing species such as *Faecali bacterium prausnitzii* and *Roseburia intestinalis*[11].

The relative abundance of *Bifidobacterium, Clostridium, Firmicutes* phylum in diabetics was significantly decreased, while the proportion of *Bacteroidetes* and *β-Proteus* was significantly increased. These are the key features of development of diabetes.

The microbial community in the intestine of diabetic patient has shown a rise in the number of pathogenic bacteria such as *Entero bacteriaceae*, various *Clostridiales, Escherichia coli, Bacteroides caccae,* as well as *Prevotella copri* and *Bacteroides vulgates.* A decline in the number of LPS producing gram negative bacteria named *Bacteroidetes* is responsible for lowering the risk of metabolic endotoxemia and inflammation in the gut lining. The higher level of LPS produced by Bacteroidetes is responsible for the production of inflammatory cytokines, such as Interleukin-1 (IL-1), IL-6, and Tumour Necrosis Factor-α (TNF-α)[26], gradually drive the development of insulin resistance and T2D. *Proteobacteria* are highly pro-inflammatory[17].It is well-known that this subclinical pro-inflammatory status due to LPS-dependent production of inflammatory cytokines, such as Interleukin-1 (IL-1), IL-6, and Tumour Necrosis Factor-α (TNF-α), drives the development of insulin resistance and T2D.

However, some species display anti-inflammatory qualities. For instance, the genus *Lactobacillus* also has a positive correlation with T2D, it induces the production of the anti-inflammatory cytokine IL-10, which enhances insulin sensitivity in muscles, while inhibit the synthesis of proinflammatory cytokines like IL-1β, IL-8, Interferon-γ (IFN-γ)[18].

These changes in the intestinal microbial community lead to irregular production of beneficial metabolites and increased generation of inflammatory molecules such as lipopolysaccharides (LPS). Which ultimately leads to metabolic endotoxemia and systemic inflammation, which are key factors in the development of glucose intolerance and Insulin irresponsiveness.

Altered gut microbiota derived endotoxemia

According to this concept, gut dysbiosis leads to impaired intestinal barrier integrity and irregular microbial metabolite generation. An impaired intestinal barrier allows bacterial endotoxins, particularly lipopolysaccharides, to squeeze into the bloodstream. This condition, known as metabolic endotoxemia, triggers chronic inflammation. Persistent inflammatory signaling interferes with insulin receptor pathways and disrupts glucose metabolism. Fluctuations in the level of gut microbes is also related to metabolic disorders such as obesity, diabetes [18,27].

By controlling immunological responses, energy balance and food metabolism, intestinal microbial community plays a critical role in protecting metabolic health. Metabolic imbalance such as obesity, insulin resistance and type 2 diabetes is directly linked to alteration in gut microbial community[7].

Role of Microbial Metabolites

Short chain fatty acids act as a signaling molecule on GI cells and other tissue cells which can bind to four receptors to stimulate intracellular signaling cascade. They are free fatty acid Receptor 3 (FFAR3), free fatty acid receptor 2 (FFAR2), G protein-coupled receptor 109a (GPR109a) and G protein-coupled receptor 42 (GPR42). Furthermore, SCFAs activate specific targets through blood circulation, systemic circulation and other pathways, such as AMP-activated protein kinases in the liver (and maybe the heart), promote lipid oxidation and enhance glucose homeostasis in mice.

Bile Acid Metabolites

To order to enable metabolic signalling cascades like FXR and TGR5, are essential for glucose metabolism and homeostasis, the Gut microbiota converts primary bile acids into secondary bile acids.

Secondary bile acids generated by gut microbes can act as signaling molecules that fine-tune intestinal hormone secretion, especially glucagon-like peptide-1 (GLP-1), thereby regulating insulin sensitivity and Glucose control. However, the alterations in the microbial population of gut microbes connected with metabolic disorders, may impair bile acid composition and signaling, leading to altered FXR and TGR5 activation. Such disturbances in bile acid metabolism can disrupt glucose regulation, promote systemic inflammation, and contribute to the progression of insulin irresponsiveness and type 2 diabetes. The gut microbiota–bile acid axis represents a crucial metabolic interface linking intestinal microbial ecology with host glucose homeostasis and metabolic health.

A change in the bile acid metabolism due to microbial dysbiosis may contribute to impaired glucose regulation and metabolic disorders.

Branched-Chain Amino Acids (BCAAs)

Some gut bacteria contribute in the synthesis of branched-chain amino acids such as leucine, isoleucine, and valine. Elevated circulating levels of BCAAs have been strongly connected to insulin irresponsiveness and increased risk of type 2 diabetes[17].

Mechanically, higher level of BCAAs triggers the activation of rapamycin (mTOR) signaling cascade, may disrupt insulin signaling pathways and leads to impaired insulin receptor substrate activity and reduce glucose uptake in peripheral tissues. In addition, increased BCAA levels may contribute to mitochondrial dysfunction and lipid accumulation in skeletal muscle, further aggravating metabolic stress and insulin resistance. Gut microbial dysbiosis, characterized by enrichment of BCAA-producing bacterial taxa, has therefore been proposed as an important factor contributing to metabolic imbalance in diabetic conditions. Thus, the change in microbial composition may develop as a potential therapeutic strategy to regulate BCAA metabolism and improve metabolic outcomes in individuals with type 2 diabetes mellitus.

Disruption of gut barrier and development of Insulin Resistance

Variations in intestinal microbial composition, commonly called to as intestinal dysbiosis, have been recognized as important contributor to insulin resistance and barrier disruption. By producing beneficial metabolites such as short-chain fatty acids (SCFAs)[2] gut microbiota maintains intestinal barrier integrity and maintain host metabolic pathways. However, disruption of microbial balance leads to decreased number of beneficial bacteria including *Bifidobacterium, Roseburia* and *Faecalibacterium*, along with an increase

in opportunistic Gram-negative bacteria. This imbalance compromises intestinal barrier function and increases gut permeability, allowing bacterial endotoxins such as lipopolysaccharides (LPS) to translocate into systemic circulation. The presence of circulating LPS triggers chronic low-grade inflammation through activation of immune signaling cascades, disrupts insulin receptor signaling in metabolic tissues such as liver, adipose tissue, and skeletal muscle. Additionally, reduced production of SCFAs weakens anti-inflammatory responses and disrupts metabolic signaling mechanisms involved in glucose homeostasis. Collectively, these processes contribute to impaired insulin sensitivity and promote the progression of type 2 diabetes.

Therapeutic Perspectives: Targeting Gut Microbiota in Diabetes

Recent data suggest that Diabetes can be treated by the modulation of intestinal microbiota and this represents a promising therapeutic strategy to prevent the development of Diabetes. Restoration of microbial balance can improve intestinal barrier integrity, regulate inflammatory responses, and enhance metabolic signaling pathways involved in glucose homeostasis[2,24]. Fermentable fibers rich diet are known to enhance the growth of gut friendly bacteria such as *Bifidobacterium, Lactobacillus* and *Roseburia*, which are known to increase the production of short-chain fatty acids (SCFAs)[28,8,12]. These secondary metabolites of gut microbes, contribute to improved insulin sensitivity, maintains blood glucose, reduced systemic inflammation[4].

Probiotic Dietary support has been found as a potential approach to restore microbial equilibrium and strengthen intestinal barrier function. Several findings have demonstrated that probiotic strains belonging to *Lactobacillus* and *Bifidobacterium* can improve metabolic parameters by reducing endotoxin levels and modulating immune responses[7,26,15]. In addition, prebiotics, which serve as substrates for beneficial gut microbes, can selectively stimulate microbial populations that produce protective metabolites. Several therapeutic microbiome-targeted dietary strategies are currently being explored for their capability to restore gut microbial diversity and improve metabolic functions in individuals with diabetes. Collectively, interventions aimed at modulating gut microbiota may represent an effective adjunct policy for the management of metabolic disorders.

Future perspective

As growing evidence suggests the significant role of intestinal microbiota in the development and progression of diabetes. Upcoming studies should focus on exploring specific microbial species involved in insulin resistance and metabolic dysfunction. Techniques like sequencing, metabolomics, metagenomics may help in studying biomarkers before the onset of diabetes[7].

We can explore personalized microbiome-based therapies that integrate host metabolic profiles with microbial composition to develop targeted strategy for declining insulin resistance. A deeper understanding of host–microbiota interactions may help in developing novel microbiota-focused techniques for improving metabolic health and preventing the development of diabetes.

Advanced medical techniques such as metagenomics, metabolomics, and next-generation sequencing may help in innovating new novel biomarkers for early detection and therapeutic targeting of diabetes.

Furthermore, personalized microbiome-based therapeutic strategies integrating host metabolic profiles with microbial composition may enable targeted interventions to reduce insulin resistance and metabolic complications.

Conclusion

In this study we have observed that disturbances in the intestinal microbial ecosystem may drastically alter the generation of key microbial metabolites, compromise gut barrier integrity, and promote systemic inflammatory responses. Insulin resistance and metabolic dysfunction linked to Diabetes get worse by these inflammatory changes. The Entero-Metabolic Imbalance Theory explains how microbial imbalance, impaired intestinal barrier integrity, and fluctuations in the microbial metabolites collectively influence metabolic pathways.

A fall in beneficial bacteria may initiate many inflammatory processes lead to disruption of insulin signalling pathways. Understanding these interactions between intestinal microbiome and host metabolism may open new ideas for microbiota-targeted therapeutic strategies aimed at restoring microbial balance, improving insulin sensitivity, and preventing the progression of diabetic disorders.

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