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Review Article

Contemporary Perspectives in Diabetes Mellitus

Gajjela Sirichandana[1]* and Nikhil Kumar Vanjari[2]

[1]*Pharm-D, Department of Clinical Pharmacy, Vaageswari College of Pharmacy, Karimnagar, Telangana, India*

[2]*Pharm-D, Clinical Assistant professor, Diabetes Educator, Department of Clinical Pharmacy, Vaageswari College of Pharmacy, Karimnagar, Telangana, India*

***Corresponding Author**: Gajjela Sirichandana, Pharm-D, Department of Clinical Pharmacy, Vaageswari College of Pharmacy, Karimnagar, Telangana, India.

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Abstract

Diabetes mellitus is a deep-rooted disorder characterized by hyperglycemia. It currently a worldwide public health issue and may be a burden to society due to its disabling and customary complications. Diabetes is multifactorial and also induces the onset of other diseases. Current review specialize in gut microbiota induced diabetes. Aside from digestion, the gut microbiota is vital in up keeping the optimal state of host health, mostly fewer *Firmicutes*, including *Clostridia, Betaproteobacteria* and the Gram-negative *Bacteroidetes* and *Proteobacteria* plays a major role in pathogenesis of diabetes, but it's also implicated within the pathogenesis of various metabolic diseases, like obesity, chronic renal disorder, diabetes and atherosclerosis and intestinal diseases, like inflammatory bowel diseases and colorectal cancer. This review also focuses on new delivery systems like pump therapy, aerosols and new monitoring systems like continuous blood glucose monitoring, HbA1c measurement.

Keywords: *Gut Microbial Flora; Diabetes; Insulin Pump Therapy; Continuous Blood Sugar Monitoring*

Introduction

Definition

Diabetes mellitus may be a sort of disorder whereby patients are unable to manage glycaemia. It is currently a worldwide public health issue and may be a burden to society due to its disabling and customary complications. Diabetes is multifactorial and also induces the onset of other diseases [1].

Epidemiology

The incidence of diabetes is rising, globally it is estimated that 415 million people had diabetes in 2015 (10% of the world adult population). A pronounced rise in the prevalence of type 2 diabetes occurs in migrant populations to industrialized countries, as in Asian and Afro-Caribbean immigrants to the UK or the USA the incidence of Diabetes in China, India and Venezuela is only Type 1 diabetes is most common in Caucasians, and more people are diagnosed in the winter months. Globally, in 2015 health-care expenditure attributed to diabetes was estimated to be at least 673 billion US dollars or 12% of total health-care and diabetes caused 5 million deaths in those aged 20 - 79 years [2].

Gut microbiota

The microorganisms present in the gastrointestinal tract are known as the gut microbiota majorly divided in to *Proteobacteria, Firmicutes, Actinobacteria* and *Bacteroidetes*. These microbiotas are plays a major role in the host metabolism and physiology regulation [3]. Apart from digestion, the gut microbiota is important in up keeping the optimal state of host health, but it is also implicated in the pathogenesis of numerous metabolic diseases, like obesity [5,6], chronic kidney disease [11,12], diabetes [7-10] and atherosclerosis [13-15], and intestinal diseases [4], such as inflammatory bowel diseases [16] and colorectal cancer [17-19]. Nowadays, there is a violent changes in the human diet as a result of the common consumption of highly processed foods, with an increased intake of carbohydrates, decreased intake of dietary fiber results in development of diabetes [20]. This is an example of a typical "Western diet" where individuals consume approximately only half the recommended intake of 30 g of fiber daily [21]. As fibers cannot be digested by the human digestive fluid, they are fermented by the gut microbiota, thereby generating short-chain fatty acids (SCFAs) as metabolites [22]. SCFAs produce immunoglobulin A and immunosuppressive cytokines results in systemic anti-inflammatory effects [22]. Loss of early-life exposure due to the increased use of antibiotics and a decrease in fiber intake results in dysbiosis [23,24], which is implicated in the increased incidences observed in inflammatory diseases, including diabetes [25]. SCFAs play vital roles in type 2 diabetes. There have been several studies reporting that the number of bacteria involved in SCFA production was significantly lower in people with type 2 diabetes. SCFAs binds to G-protein coupled receptors and exerts their actions. SCFAs promote the secretion of the incretin hormone, it is a glucagon-like peptide-1 which is made by enteroendocrine L cells. Glucagon-like peptide-1 impedes secretion of glucagon, hampers gluconeogenesis within the liver, improves insulin sensitivity and augments central satiety, thereafter leading to bodyweight loss. Furthermore, the low-grade inflammatory response caused by bacteria migration from the intestines into the mesenteric fat and therefore the blood hindered directly by SCFAs.

Gut microbial flora induced Type 2 diabetes:

The major risk factor for diabetes is obesity, some studies show that there is a correlation between obesity and gut microbiota. A lowered abundance of butyrate-producing microbes and an increased abundance of *Lactobacillus* sp [9, 10,26], Larsen., *et al.* [26] noted that in human male type 2 diabetes patients, as compared with-diabetic healthy subjects, there were significantly fewer *Firmicutes*, including *Clostridia, Betaproteobacteria* was more abundant in type 2 diabetes patients. These observations hint that the Gram-negative *Bacteroidetes* and *Proteobacteria* might induce the pathogenesis of type 2 diabetes through an endotoxin-induced inflammatory response as the endotoxin, lipopolysaccharide, exists in high concentrations as a main outer cell membrane component [26]. Gut metagenome-based computational models could predict the type 2 diabetes-associated phenotypes in glucose-intolerant patients [10]. The abundance of Gram-positive bacteria that produce butyrate were decreased in patients suffer with metabolic syndrome, treatment with vancomycin this results in lowered levels of butyrate-producing gut microbes and this was correlated with impaired insulin sensitivity results in pathogenesis of type 2 diabetes [27].

Mechanisms of gut microbiota in the pathogenesis of type 1 diabetes

1. The gut microbes increases mucus degradation, results in reduced integrity and increased permeability of intestinal mucosa that leads to bacterial penetration [32]. The penetration of bacteria into intestinal mucosa, then gut microbiota activates the immune system results in production of antibodies [32], there is a cross-reaction between the antibodies and surface antigens of pancreatic beta cells, as well as T cell cross-reactivity leads to destruction of beta cells and the formation of type 1 diabetes [32].

2. Zonulin is a protein that plays a major role in mucosal integrity and gut permeability [31]. Zonulin also modulates the intercellular junctions and macromolecular passage through them [31]. Some bacterial groups such as *Bacteroides* spp. and *Veillonella* spp can alter mucosal integrity results in impaired gut permeability. In Type, 1diabetic individuals can be more attributed to the

binding of *Veillonella* to colonic crypt cells rather than a change in zonulin levels. *Veillonella* produces lactate is pushed to the luminal surface and weakens tight junctions [31].

3. Butyrate is a major by-product of the metabolism of gut microbes and it plays a major role in colonic T-reg induction, down-regulation of proinflammatory macrophages and enhancement of gut barriers integrity through increasing mucin production [33,34].

4. Gut microbiota produces short-chain fatty acids (SCFA) by ingesting and fermenting the fibers [35-37]. SCFAs enter the blood circulation and modulate T-reg differentiation; thus autoimmunity is prevented [28,38-40]. Genera *Bacteroides* and *Prevotella* were increased in most of the Type1diabetes individuals, can alter the gut microbial flora by succinate and acetate, these are the by-products' of anaerobic metabolism results in weakening of epithelial tight junctions, decrease gut mucosal integrity, block T-reg differentiation and activates inflammatory pathways [30,31]. These bacteria can also produce Glutamic acid decarboxylase (GAD) which can stimulate GAD autoimmunity by molecular mimicry [29].

Other new perspectives

Less do we known about the long-term effect of weight loss on the development of T2DM and CVD outcomes in the form of death, myocardial infarction, and stroke. Currently ongoing are clinical trials that use health-promoting lifestyle interventions, new drugs and even surgery, which are all aimed at weight loss, reduction in disease manifestations, and improved outcomes [41]. It is showed the alterations of the abundance and diversity of the intestinal microbiota and the perturbation of metabolites in ZDF rats (fa/fa) [42]. It is found three potential biomarkers of intestinal microbiota that may lead to perturbation in plasma metabolites [42]. This may promotes new pathogenesis of obesity-related T2DM, but we also need to study further about the causal relationship between intestinal microbe and T2DM, so as to find the target of T2DM treatment or preventive measures [42] *E. hirae* WEHI01 has the potential to ameliorate type 2 diabetes in rats and provide a promising rationale for further research into the prevention and treatment of T2DM [43].

New delivery systems

Continuous subcutaneous insulin infusion (pump therapy): The development of technology within the Nineteen Seventies and Nineteen Eighties, pump medical aid has been reintroduced for the effective treatment of polygenic disorder. A rapid-acting hypoglycaemic agent analogue are infused, typically in little amounts into the abdomen or buttocks and additional boluses are calculated supported each meal and snack. The key advantage of pump medical aid is improved hypoglycaemic agent material medica. Variable the basal rate will facilitate regulate nightlong glucose levels. Pump medical aid is appropriate for people suffered with frequent hypoglycemic episodes and it's conjointly helpful in individual's unknowingness of hypoglycaemia, previous evidences shows that reduced hypoglycemic states in pump medical aid users [44,45], the pump medical aid has some limitations as a result of the infused hypoglycemic agent is rapid-acting, mechanical interruption of the pump will speedily cause ketonemia, it should be in physiological state, to avoid this issues frequent blood sugar observation is critical. The key disadvantage of pump medical aid use in population is high value and there's no accessibility of state funds. However, some non-public insurance firms currently accessible to subsidize the price of the pump medical aid. This could be helpful in once the patient may be a kid or adolescent.

Aerosols

Hypoglycemic agent conjointly accessible in aerosols forms however solely phase III {clinical trial phase III| clinical trial clinical test} clinical trial studies were completed. These aerosols contains long hypoglycemic agent use once daily. However, aerosol delivery needs six fold the most quantity of hypoglycemic agent for a similar effective dose as Associate in Nursing injection, ends up in increase the price

burden on the people and this can be the key barrier to widespread use. The key disadvantage of aerosols is use massive amounts of hypoglycemic agent ends up in aspect effects and long run safety isn't better-known. Today all hypoglycemic agent delivery systems deliver hypoglycemic agent to the circulation instead of the enter portal circulation. However major disadvantage of general delivery system was it contributes the hypoglycemic agent resistance associated with fatness and adolescence and should be a serious barrier to physiological hypoglycemic agent replacement. However, a way of accessing the enter portal circulation isn't presently visible.

New monitoring systems

Continuous blood sugar monitoring

Its accustomed live intermittent capillary blood sugar levels and conjointly provides a limited glimpse of blood sugar levels that can fluctuate wide over twenty four hours.

Continuous glucose observation is a sophisticated technological system [46,47]. It's helpful in assessment of fluctuations in postprandial glucose and nocturnal hypoglycemia, particularly continuous glucose observation helpful in programming nightlong basal hypoglycemic agent rates for pump medical aid. In Australia Continuous observation systems are accessible to live interstitial blood sugar via Associate in nursing inward cannula within the abdomen or buttocks. however major disadvantage is pricey ($5000 or more) and, Devices beneath investigation have alarms to alert patients to aldohexose levels outside and conjointly provides immediate read-outs, at present, are most applicable to be used by polygenic disorder canters that lend devices to patients for restabilization.

Non-invasive blood sugar monitoring

Frequent automatic aldohexose readings are often obtained non-invasively through the method of reverse ionic medication, throughout which a coffee current pulls aldohexose molecules through the skin for assortment in an exceedingly gel disc. A tool that's worn sort of a watch is approved for patients aged over seven years within the U.S., however its value (about US$1000 for the device and quite US$100 per disposable 12-hour sensor) limits a lot of widespread use.

HbA1c measurement

Measuring of glycosylated Hb (HbA1c) remains the criterion standard 5: Glycosylated Hb (HbA1c) levels and polygenic disorder complications:

1. In traditional aldohexose tolerance, HbA1c level is typically < five-hitter.
2. In polygenic disorder, Associate in Nursing HbA1c level > V-E Day indicates poor glycaemic management and a desire to assess medical aid and adherence.
3. A decrease in HbA1c level of one mathematical notation has been shown to steer to: a 10% reduction in microvascular complications in kind two polygenic disorder (UKPDS trial13) and a 20% - 30% reduction in microvascular complications in kind one polygenic disorder (DCCT trial3), with associated less important reductions in macro vascular complications.
4. In treating polygenic disorder, the advantages of decreasing HbA1c level should be weighed against the chance of aspect effects and also the ability of the patient to comply; therefore, the "target" HbA1c level should be personalized.
5. HbA1c levels < 6 June 1944 are terribly troublesome to attain in polygenic disorder while not serious aspect effects, like grave hypoglycaemia. To gauge the end result of polygenic disorder management.

Conclusion

Our study shows that significant association between the alterations in intestinal microbial flora composition and diabetes, reduce the intake of carbohydrates and highly processed food, use of prebiotics, probiotics, and fecal microbial transplantation to modulate gut microbiome can reduce HbA1c level so it is often considered as a complementary strategy for T1D management, so as to detect early evidence of dysbiosis and prevention of T1D progression, serial stool exams in genetically susceptible children are often done by employing a specific kit that semi-quantitatively compares microbiota composition of healthy control and suspected individual. In designing the kit, Firmicutes: Bacteroidetes ratio should be considered, and this review also gives the knowledge regarding the advances in insulin delivery systems (such as Pump therapy and aerosols) to manage overnight blood sugar levels and also explains the new monitoring systems in diabetic individuals like continuous blood glucose monitoring and HBA1c measurement to stop recurrent hypoglycaemic states in diabetic individuals.

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