بسم الله الرحمن الرحيم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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التوثيق الإلكتروني والميكروفيلم

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات

يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار

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INTRODUCTION

Type 1 diabetes mellitus (T1DM) is characterized by the infiltration of immune cells into the pancreas, followed by the destruction of insulin-producing β-cells. Which often beginning during infancy and continuing over the many months or years that follow. At the time of clinical diagnosis of T1DM, about >80% of the Beta-cells have been destroyed. The islets are infiltrated with chronic inflammatory mononuclear cells (insulitis), including CD8+ cytotoxic T cells. Once islet cell autoimmunity has begun, progression to islet cell destruction is quite variable, with some patients rapidly progress to clinical diabetes, while others remain in a non-progressive state ***(Szybinski, 2016)***.

The term 'gut microbiota' represents a complex microbial community within the body, one capable of affecting health by contributing to nutrition, prevention of colonisation of the host by pathogens, and through influencing the development and maintenance of the immune system ***(Turnbaugh et al., 2007)***.

The role of the intestinal microbiota as an integral determinant of human health has become increasingly evident in the past decade ***(Borody and Campbell, 2012; Lozupone et al., 2012)***. The connection between an altered gut microbiota and metabolic disorders such as obesity, diabetes, and cardiovascular disease is well established. Defects in preserving

the integrity of the mucosal barriers can result in systemic endotoxaemia that contributes to chronic low-grade inflammation, which further promotes the development of metabolic syndrome ***(Wang et al., 2014)***. Gut microbiota have been proposed as a main actor in the pathogenesis of T1DM ***(Mclean et al., 2015; Knip and Siljander, 2016)***.

The gut microbiota interacts with the adjacent mucosal environment directly, impacting on the intestinal permeability, and influencing local and systemic inflammatory activity ***(Knip and Siljander, 2016)***. The intestinal microbiota thrives mainly on diet derived nutrients, while the host benefits from its metabolites, which in turn modulate host mucosal immune response throughout different mechanisms ***(Shapiro et al., 2014; Knip and Siljander, 2016)***.

Mucosal homeostasis depends on physical and molecular interactions between three components: the resident microbiota, the epithelial layer and the local immune system. The cytokine Interleukin (IL)-22 helps to orchestrate this three-way interaction. IL-22 is produced by immune cells present beneath the epithelium and is induced by bacteria present in the intestine ***(Schreiber et al., 2015)***. IL-22 exerts essential roles in eliciting antimicrobial immunity and maintaining mucosal barrier integrity within the intestine. IL-22 shows diverse metabolic benefits, as it improves insulin sensitivity, preserves gut mucosal barrier and endocrine functions, decreases

endotoxaemia and chronic inflammation, and regulates lipid metabolism in liver and adipose tissues ***(Wang et al., 2014)***.

Interleukin (IL)-21 is a type 1 cytokine that has been implicated in the pathogenesis of type 1 diabetes ***(Sutherland et al., 2009)***. IL-21 is mainly produced by activated T lymphocytes, particularly the inflammatory Th_{17} subset, and is believed to be a key factor in the transition between innate and acquired immunity. IL-21 has been associated with different autoimmune and inflammatory diseases ***(Pelletier and Girard, 2007)***.

Probiotics are live micro-organisms that, when administered in adequate amounts, confer health benefits on the host ***(Homayouni et al., 2008; Ejtahed et al., 2012)***. Probiotics have been used to ameliorate gastrointestinal symptoms since ancient times. Over the past 40 years, probiotics have been shown to exert major effects on the immune system, both *in vivo* and *in vitro*. This interaction is clearly linked to gut microbes, their polysaccharide antigens, and key metabolites produced by these bacteria ***(Liu et al., 2018)***.

Probiotics improve epithelial barrier function as *Lactobacilli* were found to reinforce the barrier function of epithelial cells by increasing the levels of adhesion proteins, including beta-catenin and E-cadherin ***(Hummel et al., 2012)***.

Probiotics confer immunological protection to the host through the regulation, stimulation, and modulation of immune

responses. A probiotic strains have a significant influence on the gut barrier by stimulating B cells for the production of IgA. Probiotics have been reported to influence cytokine production by antigen presenting cells (APCs), which initiates adaptive responses. Cytokines also enhance the defense system against invasion by bacterial, fungal, viral, and any pathogenic components ***(Azad et al., 2018)***.

Researchers have shifted their attention to better understand the immunomodulatory effects of probiotics, which have the potential to prevent or alleviate certain pathologies for which proper medical treatment is as yet unavailable. Isolating new probiotic strains and investigating their immunomodulatory effects on cytokine profiles in humans remain a topical issue ***(Azad et al., 2018)***.

It is important to design a prevention-based probiotic approach to therapy in which microbiota beneficial to disease attenuation could be introduced/expanded ***(Atkinson and Chervonsky, 2012)***. Probiotics have been found to have a wide application in diseases such as autoimmune, inflammatory, and allergic conditions. The efficacy of probiotics in diabetes has been proven by their ability to lower fasting glucose and insulin levels in a preclinical setting as well as in human trials. However, there is heterogeneity in these studies, including the species used, probiotic dosage, and the magnitude of efficacy ***(Shah and Swami, 2017)***.

Aim of the Work

The aim of this study was to assess effect of probiotics supplementation on glycemic control and blood glucose levels as well as the levels of IL-21 and IL-22 in pediatric patients with T1DM.

Chapter 1

TYPE 1 DIABETES MELLITUS (T1DM)

Definition:

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defect in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidney, nerves, heart, and blood vessels ***(ISPAD, 2018).***

The classical symptoms of diabetes are polyuria, polydepsia, and polyphagia ***(Delamater et al., 2018).*** The major forms of diabetes are divided into those caused by deficiency of insulin secretion due to pancreatic Beta-cell damage (T1DM), and those that are consequence of insulin resistance occurring at the level of skeletal muscles, liver, and adipose tissue with various degrees of Beta-cell impairment (type 2 DM) ***(Zheng et al., 2018).***

Classification:

WHO classified DM into clinical types (normoglycemia, impaired glucose tolerance (IGT)/ impaired fasting glucose (IFG), diabetes) and etiological types ***(Laakso, 2016).*** The Etiological classification of diabetes according to ISPAD (2018) is shown in Table 1.

Table (1): Etiological classification of diabetes mellitus

I. Type I-DM : (B-cell destruction, usually leading to absolute insulin deficiency) Immune mediated. Idiopathic.	**II. Type II-DM:** (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance).
III. other specific types	
A. Genetic defects of β-cell function: 1. MODY3 (Chromosome 12, HNF1α) 2. MODY1 (Chromosome 20 HNF4α) 3.MODY2 (Chromosome7glucokinase) 4. Other very rare forms of MODY (e.g. MODY4: Chromosome 13, insulin Promoter factor-1, MODY6: Chromosome9, carboxyl ester lipase) 5. Transient neonatal diabetes 6. Permanent neonatal diabetes 7. Mitochondrial DNA 8. Others	**B. Genetic defect in insulin action** 1.Type A insulin resistance 2.Leprechaunism 3.Rabson-Mendenhall syndrome 4.Others
C. Diseases of exocrine pancreas 1.Pancreatitis 2.Truama/ pancreatectomy 3.Neoplasia 4.Cystic fibrosis 5.Haemochromatosis 6.Fibrocalculous pancreatopathy 7.Others	**D. Endocrinopathies** 1.Acromegaly 2.Cushing's syndrome 3.Glucagonoma 4.Pheochromocytoma 5.Hyperthyroidism 6.Somatostatinoma 7.Aldosteronoma 8.Others
E. Drugs or chemical- induced 1.Vacor 2.Pentamidine 3.Nictotinic acid 4.Glucocorticoids 5.Thyroid hormone 6.Diazoxide 7.B-adrenegic agonist 8.Thiazides 9.Dilantin 10.γ-interferon 11.Others	**F. Infections** 1.Congenital rubella 2.cytomegalo virus 3.Others
G. Uncommon forms of immune-mediated Diabetes 1."Stiff-man" syndrome 2.Anti-insulin receptor antibodies 4.Others	**H. Other genetic syndromes sometimes** Associated with diabetes 1.Down syndrome 2.Klinfelter syndrome 3.Turner syndrome 4.Wolfram syndrome 5.Friedreich's ataxia 6.Huntington's chorea 7.Laurence-Moon-Biedle syndrome 8.Myotonic dystrophy 9.Porphyria 10.Prader-Willi syndrome 11.Others
IV. Gestational diabetes.	

(ISPAD, 2018)

MODY: Maturity onset diabetes of the young, **HNF-4α:** Hepatocyte Nuclear Factor**.**

The vast majorities of cases with diabetes fall into two etiopathogenetic categories; type 1 and type 2 diabetes mellitus ***(ISPAD, 2018).*** The comparison between both types is presented in Table 2.

Table (2): Clinical characteristics of type 1 diabetes, type 2 diabetes and Monogenic diabetes in children and adolescents

Characteristics	Type 1	Type 2	Monogenic
Genetics	Polygenic	Polygenic	Monogenic
Clinical presentation	6 months to young Adulthood	Usually pubertal (or later)	Often post pubertal except GlucoKinase and neonatal diabetes
Association			
Autoimmunity	Yes	No	No
Ketosis	Common	Uncommon	Common in neonatal diabetes, Rare in other form
Obesity	Population Frequency	Increased Frequency	Population Frequency
Acanthosis nigricans	No	Yes	No
Frequency (% of all diabetes in young people)	Usually 90%+	Most countries <10%	?1-3%
Parent with diabetes 2	2-4%	80%	90%

(Mayer-Davis et al., 2018)

Global burden:

Diabetes in all its forms imposes unacceptably high human, social and economic costs on countries at all income levels ***(IDF Diabetes Atlas, 2014)*** (Figure 1):

387 million people have diabetes; by 2035 this will rise to 592 million. The number of people with type 2 diabetes is

increasing in every country. 80% of people with diabetes live in low- and middle-income countries. The greatest number of people with diabetes is between 40 and 59 years of age. 175 million people with diabetes are undiagnosed. Diabetes caused 4.9 million deaths in 2014; every seven seconds a person dies from diabetes. Diabetes caused at least USD 612 billion dollars in health expenditure in 2014 – 11% of total spending on adults. More than 79, 000 children developed type 1 diabetes in 2013. More than 21 million live births were affected by diabetes during pregnancy in 2013.

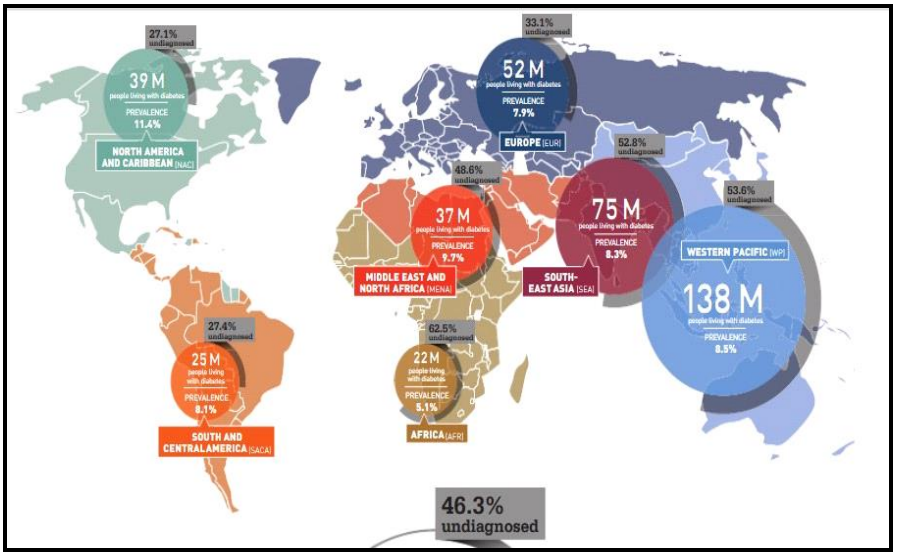

Figure (1): Global diabetes prevalence ***(IDF Diabetes Atlas, 2014).***

Type 1 diabetes Mellitus

In most of western countries, type 1 diabetes accounts for over 90% of childhood and adolescent diabetes, although less than half of individuals with type 1 diabetes are diagnosed before the age of 15 years. Type 2 diabetes is becoming more common and accounts for a significant proportion of youth onset of diabetes in certain risk populations ***(Diaz-Valencia et al., 2015).***

Type 1 diabetes is classified to the following subtypes (Table 3):

Type 1a (The autoimmune form):

This form of diabetes, which accounts for only 5-10% of those with diabetes, previously known insulin dependent diabetes, type 1 diabetes, or juvenile-onset diabetes, results from a cellular-mediated autoimmune destruction of pancreatic Beta-cells representing about 90% of type 1 cases in Europe. The presence of other autoimmune disorders is highly raised ***(ADA, 2015a).***

Type 1b (the idiopathic form):

The cause of insulin deficiency is not related to autoimmunity and it remains undefined. These cases are categorized as type 1b or idiopathic T1DM and are relatively more common in African and Asian population. This category is heterogeneous, may be caused by different mechanisms in

different population, and remain poorly understood at this time ***(Fayfman et al., 2017).*** Individuals with this form of diabetes suffer from episodic ketoacidosis and exhibit varying degrees of insulin deficiency between episodes. This form of diabetes is strongly inherited, lacks immunological evidence for beta-cell autoimmunity, and is not HLA associated ***(ADA, 2015a).***

Type 1c:

It is the fulminant type 1 diabetes mellitus (FT1DM), it was first reported by ***Wang et al. (2017)*** and it is a unique subtype of diabetes. It is characterized by a short clinical history, before the first acute metabolic decompensation with impairment of beta and alpha cells of pancreatic islet and no autoimmune etiology ***(Arai et al., 2012).***

Table (3): The clinical and biological characteristics of different subtypes of type 1 diabetes

	Type 1a	**Type 1b**	**Type 1c**
Signs of anti-insulin autoimmunity	+	-	-
Duration of symptoms before diagnosis	8 months	7 months	<1 week
Ketosis, Ketoacidosis At diagnosis	Frequent	Frequent	Constant
Blood glucose level At diagnosis	↑↑↑	↑↑	↑↑↑
HbA1c at diagnosis	↑↑	↑↑	Normal or slightly elevated

(Wang et al., 2017)

Prevalence and incidence of T1DM:

WHO estimates that more than 180 million people worldwide have diabetes mellitus and this number is likely to be more than double by 2030; about 10% have T1DM ***(Jensen et al., 2011).*** There are approximately 500, 000 children aged under 15 with type 1 diabetes in the world ***(Patterson et al., 2014)***. The International Diabetes Federation estimates that 79, 000 children developed type 1 diabetes in 2013 ***(IDF Diabetes Atlas, 2015)***.

Of the 500, 000 children with type 1 diabetes in the world, the most live in Europe (129, 000) and North America (108, 700). Countries with the highest estimated numbers of new cases annually (highest incidence) were the United States (13, 000), India (10, 900) and Brazil (5000) ***(Patterson et al., 2014).*** The factors contributing to the prevalence and incidence of T1DM are:

Sex:

Girls and boys are almost equally affected but there is a modest female preponderance in some low-risk populations (e.g., the Japanese); there is no apparent correlation with socioeconomic status ***(Zheng et al., 2018).***