INTERLEUKIN - ١٧ IN CHILDHOOD DIABETES

Thesis

Submitted for partial fulfillment of
Master degree in Pediatrics

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الانترليوكين -١٧ في مرض البول السكري
عند الأطفال

رسالة

توطئة للحصول على درجة الماجستير
في طب الأطفال

مقدمة من

الطبيبة / مروة محمود البلحي

بكالوريوس الطب والجراحة
كلية الطب – جامعة عين شمس ٢٠٠٥

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بسم الله الرحمن الرحيم

وَأَنْزَلَ اللهُ
عَلَيْكَ الْكِتَابَ
وَالْحِكْمَةَ
وَعَلَّمَكَ مَا لَمْ
تَكُنْ تَعْلَمُ
وَكَانَ فَضْلُ
اللهِ عَلَيْكَ
عَظِيمًا

صدق الله العظيم
سورة النساء آية
(١١٣)

Acknowledgement

*My greatest gratitude is to **ALLAH** whose guidance and support were the main motive behind accomplishing this work.*

I would like to express my profound gratitude and sincere appreciation to Prof. Dr. Mohammed Abo El Asrar Mohammed El-Bayomy Afify, *Professor of Pediatrics, Faculty of Medicine, Ain Shams University, for his great help and support and gentle guidance and insistence. Without his help, this work would never been accomplished.*

I would also like to express my appreciation to Dr. Abeer Ahmed Abd Elmaksoud, Assistant Professor of Pediatrics, Faculty of Medicine, Ain Shams University, for her continous help, guidance and encouragement.

Last but not least, thanks are also due to Dr. Wessam El-Sayed Saad, Assistant Professor of Clinical and Chemical Pathology, Faculty of Medicine, Ain Shams University for her great effort and help in this study.

Marwa Mahmoud El-Balahy

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LIST OF ABBREVIATIONS

Abbrev.	Full term
Ag	Antigen
APCs	Antigen-presenting cell
CGMS	Continuous Glucose Monitoring System
CSII	Continuous subcutaneous insulin infusion
CTLs	Cytotoxic lymphocytes
DC	Dendritic cells
DKA	Diabetic ketoacidosis
DPT-١	The Diabetes Prevention Trial ١
DTH	Delayed type hypersensitivity
EAE	Experimental encephalomyelitis
ESRD	End-stage renal disease
FOXP٣	Forkhead box ٣
GAD	Glutamic acid decarboxylase
hES	Human embryonic stem
HLA	Human leukocyte antigen
IA-٢	Protein tyrosine phosphatase
IAA	Auto-antibodies to the insulin
ICAM-١	Intracellular adhesion molecule ١
ICAs	Islet cell antibodies
IFN-γ	Interferon γ
IL-١٧	Interleukin-١٧
IL-٢٣	Interleukin-٢٣
IL-٤	Interleukin-٤
IL-٦	Interleukin-٦
iPS	Induced pluripotent stem

LIST OF ABBREVIATIONS (Cont...)

Abbrev.	Full term
LDL	Low-density lipoprotein
MHC	Major histocompatibility complex
MINC	Mouse insulinoma cells
MODY	Maturity onset diabetes of young
MZ	Monozygotic
NK cells	Natural killer cell
NOD	None obese diabetic mouse
nTh١٧	Natural Th١٧
PBMC	Peripheral blood mononuclear cell
PHA	Phytohemagglutinin
RORC٢	Retinoic acid-related orphan receptor C isoform ٢
STAT	Signal transducer and activator of transcription
T-bet	T-Box expressed in T-cell
TCR	T-cell receptor
Teff	Teffector cells
TGF- β	Transforming growth factor- β
Th	T-helper
TNF	Tumor necrosing factor
Tregs	Regulatory t-cell
Type ٢ DM	Type ٢ diabetes mellitus
Type IDM	Type ١ diabetes mellitus
ZnT٨	Zinc transporter ٨

INTRODUCTION

Type ١ diabetes mellitus (T١DM) is one of the most common chronic diseases in children. Most of the cases of T١DM presenting at this age have an autoimmune basis, the destruction of pancreatic beta cells caused by cytotoxic lymphocytes followed by deficit of insulin and symptoms of hyperglycemia and it's long-term complications including cardiovascular disease, blindness and kidney failure, can be devastating *(Bluestone et al., ٢٠٠٨).*

T١DM diabetes is considered as an autoimmune disease which is developed due to T-cell-mediated destruction of β cells in the islets of Langerhans of the pancreas. In children with active β-cell destruction auto antibodies against β-cell structures appear in the circulation. In T١DM the cause for β-cell destruction is not known. T١DM is the most common form of diabetes in children worldwide, and approximately ٨٠٪ of the children with diabetes have T١DM. In addition, there are several rare forms of diabetes diagnosed in the early childhood or in late youth *(Harjutsalo et al., ٢٠٠٨).*

T cells were shown to produce cytokines. Interleukin-١٧ was among these cytokines, and the T cells that preferentially produce interleukin-١٧, were named Th١٧ cells *(Harrington et al., ٢٠٠٥).*

Th١٧ cells are identified as a novel subset of CD٤+ T helper cells that produce IL-١٧A and IL-١٧F *(Park et al., ٢٠٠٥).*

A novel therapy based on immunopathogenesis is desperately needed in this incurable disease. The breakdown of beta cell-specific self-tolerance by T lymphocytes involves a number of dysregulated events intrinsic and extrinsic to T cell *(Bluestone et al., ٢٠٠٨).*

IL-١٧-producing T cells have been associated with the pathogenesis of T١DM. IL-١٧ enhances the generation of inducible nitric oxide synthase, and elevates the release of NO from the pancreatic β cells *(Vukkadapu et al., ٢٠٠٥).*

IL-١٧-induced NO is toxic to β cells, thus driving the β cells to the apoptotic and necrotic pathway. The administration of IL-١٧-neutralizing antibody reduced the release of NO from the pancreatic cells and diminish the damage induced by activated T cells *(Miljkovic et al., ٢٠٠٥).*

Better understanding of the mechanisms generating and regulating T-cell responses is required for the development of effective therapies for T١DM *(Miljkovic et al., ٢٠٠٥).*

AIM OF THE WORK

To asses interleukin ١٧ level in children and adolescents with newly diagnosed type ١ diabetes mellitus, in those with type ١ diabetes mellitus for five year or more and in matched age and sex healthy control subjects.

DIABETES MELLITUS

Definition:

Diabetes mellitus is a common chronic metabolic syndrome characterized by hyperglycemia as a cardinal biochemical feature. Type-I DM is the most common form of DM. in children and adolescents (٩٠٪ of cases) and account for only ٥-١٠٪ of all cases of D.M *(Wyatt, ٢٠٠٨).*

It's an autoimmune disorder characterized by T-cell mediated destruction and progressive loss of pancreatic β-cells leading to eventual insulin deficiency and hyperglycemia. This disorder has strong genetic component, inherited mainly through HLA complex, but the factors that trigger onset of clinical disease remain largely unknown *(Denis-Deneman, ٢٠٠٦).*

The pathogenesis of T١D has been considered to result from a breakdown of immunologic tolerance towards β-cell antigens. Immunologic tolerance is maintained by two major phenomenon; central and peripheral tolerance. Peripheral tolerance is dictated by the fine balance between effector T cells and so called regulatoryT cells (Treg*) (Zhou et al., ٢٠٠٩).*