"Study the interplay of Sfrp5 and WISP1 in obesity and type 2 diabetes mellitus patients"

A thesis submitted by

Nada Salah El Din Habib Ahmed

Demonstrator of Biochemistry, Faculty of Pharmacy,
Ain Shams University
B. Ph. Sci., Ain Shams University (2013)

for the partial fulfillment of Master Degree in Pharmaceutical Sciences (Biochemistry)

Supervised by

Prof. Dr. Hala Osman El- Mesallamy

Professor of Biochemistry
Head of the Biochemistry Department
Faculty of Pharmacy, Ain Shams University

Prof. Dr. Mohamed Hesham El Hefnawy

Professor of Endocrinology
Dean of the National Institute of Diabetes and Endocrinology

Biochemistry Department
Faculty of Pharmacy
Ain Shams University
2018

بســـــــم الله الرحـــــــمن الرحـــــــــيم

"قَالُواْ سُبْحَانَكَ لاَ عِلْمَ لَنَا إِلاَّ مَا عَلَّمْتَنَا إِنَّكَ أَنتَ الْعَلِيــمُ الْحَكِيمُ"

صدق الله العظيم

سورة البقرة آية (٣٢)

ACKNOWLEDGEMENTS

Acknowledgements

First of all I thank ***God*** for his blessing, answered prayers and for lighting my way to eventually reach my aims, as without His help, this work would have never seen the light.

I owe my deepest sincere gratitude and respect for accomplishing this work to my supervisor **Prof. Dr. Hala Osman El-Mesallamy, Professor and Head of Biochemistry Department, Faculty of Pharmacy, Ain Shams University,** for her keen, continuous, enthusiastic support patient guidance, faithful encouragement, invaluable suggestion and enlightening advice throughout the whole work. I hope that one day I can return back part of her great favor.

I would like to thank **Prof. Dr. Mohamed Hesham El Hefnawy, Dean of the National Institute of Diabetes and Endocrinology** for his keen guidance, following up the patients and facilitating samples collection.

I would also like to thank **Prof. Veronica Murahovschi, Department of Clinical Nutrition, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany; Department of Endocrinology, Diabetes and Nutrition, Campus Benjamin Franklin, Charite – Universitatsmedizin, Berlin, Germany** for her assistance and support in answering questions through her expertise in WISP1research field to help accomplish this work.

I would like to thank all our study volunteers, participated physicians, the nursing staff and laboratory technicians for their assistance in performing the mentioned study.

Finally, No words can repay my heartily thanks, gratitude and appreciation to **my family and colleagues**, for their continuous patience, understanding, and support during the whole thesis tiring period.

Contents

LIST OF ABBREVIATIONS

ATP	Adenosine triphosphate
BMI	Body mass index
CCN	Cysteine rich 61 (CYR 61) Connective tissue growth factor (CTGF) Nephroblastoma overexpressed (NOV)
CTGF	Connective tissue growth factor
CYR 61	Cysteine rich 61
DM	Diabetes mellitus
FFAs	Free Fatty acids
FPG	Fasting plasma glucose
HbA_{1C}	Glycated haemoglobin
HDL-C	High density lipoprotein cholesterol
hs-CRP	High sensitivity C-reactive protein
HOMA	Homeostatic Model Assessment
IR	Insulin resistance
JNK	c-Jun N-terminal kinase
LDL-C	Low density lipoprotein cholesterol
Met	Metformin
NIDE	National institute of diabetes and endocrinology
NOV	Nephroblastoma overexpressed
OHA	Oral hypoglycemic agents
PI	Proinsulin
Sfrp	Secreted frizzled-related protein
Su	Sulphonylureas
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TC	Total cholesterol
TCF7L2	Transcription factor 7-like 2
TG	Triglycerides
WC	Waist circumference
WISP	Wnt inducible signaling pathway protein
WHO	World Health Organization

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION AND AIM OF THE WORK

1. Introduction and Aim of the Work

The global pandemic of obesity, insulin resistance (IR) together with numerous circulating plasma factors contribute in a vicious cycle ultimately leading to progression of type 2 diabetes mellitus (T2DM) and increasing its prevalence ***(Tanabe et al., 2017)***.

The association of obesity and T2DM is believed to be through biologically active molecules known as adipokines. Adipokines might have a pathophysiological role in IR and β-cell dysfunction which highlights the etiology for T2DM ***(Neville et al., 2016; Tanabe et al., 2017)***. Unravelling newly identified adipokines massively increases, however the molecular mechanisms by which adipokines affect the pathogenesis of T2DM are not well elucidated.

Secreted frizzled-related protein 5 (Sfrp5) is a recently identified anti-inflammatory adipokine ***(Ouchi et al., 2010)***. The circulating Sfrp5 level has been extensively studied in field of cancer, but interestingly some animal studies revealed its involvement in obesity , glucose metabolism ***(Rulifson et al., 2014; Vincent and Postovit, 2017)*** and β-cell proliferation ***(Rebuffat et al., 2013)***. However, limited human studies reported contradictory data about Sfrp5 in obesity, T2DM and its association with β-cell function and IR.

Wnt1 inducible signaling pathway protein 1 (WISP1), is another recently validated adipokine and a downstream target of Wnt signaling pathway ***(Murahovschi et al., 2015)***.The circulating WISP1 level has been studied in several fields including cancer ***(Zuo et al., 2010)*** and atherosclerosis ***(Mill et al., 2012; Qi et al., 2016)***. Being a target of Wnt1 in Wnt signaling pathways, it has been linked to metabolic disturbances ***(Zhong***