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Study of The Effect of Bariatric Surgery on Serum Glucagon Like Peptide-1 Concentration and Insulin Resistance among Obese Type 2 Diabetic Patients

Thesis

Submitted for Partial Fulfillment of M.D Degree
In Internal Medicine

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Nesma Ali Ibrahim

List of Abbreviations

11β-HSD1	: 11β-hydroxysteroid dehydrogenase type 1
AMP	: Adenosine monophosphate
AMPK	: AMP-activated protein kinase
ASBS	: American Society for Bariatric Surgery
ASMBS	: American Society for Metabolic and Bariatric Surgery
ATMs	: Adipose tissue macrophages
ATP	: Adenosine triphosphate
BMI	: Body mass index
BPD	: Bilio–pancreatic diversion
CCK	: Cholecystokinin
CNS	: Central nervus system
COE	: Center of Excellence
CPT-1	: Carnitine palmitoyltransferase-1
CRP	: C-reactive protein
DJB	: Duodenal–jejunal bypass
DPP-4	: Dipeptidyl peptidase-4
ELISA	: Enzyme-Linked Immunosorbent Assay
ER	: Endoplasmic reticulum
ERK	: Extracellular signal-regulated kinase
FA	: Fatty acids
GIP	: Glucose- dependent insulinotropic peptide
GK	: Goto-Kakizaki
GLP-1	: Glucagon-like peptide-1
GLP-1R	: GLP-1 receptors
GLP-2	: Glucagon-like peptide-2
GLUT-4	: Glucose transporter-4
GPR	: G-proteincoupled receptor
GRPP	: Glicentin-related pancreatic polypeptide
GSK3	: Glycogen synthase kinase- 3
HDL-Chol	: High-density lipoprotein cholesterol
HGP	: Hepatic glucose production
HOMA-IR	: Homeostasis model assessment of insulin resistance
ICV	: Intracerebral ventricular

List of Abbreviations (Cont.)

IGT	: Impaired glucose tolerance
IKKβ	: Inhibitor of nuclear factor-κB (NF-κB) kinase-β
IL-6	: Interleukin-6
IR	: Insulin resistance
IRS	: Insulin receptor substrate
JNK	: JUN N-terminal kinase
LABS	: Longitudinal Assessment of Bariatric Surgery
LADA	: Latent autoimmune diabetes of adulthood
LAGB	: Laparoscopic adjustable gastric banding
LDL-Chol	: Low-density lipoprotein cholesterol
LEAD	: Liraglutide effect and action in diabetes
MAPK	: Mitogen-activated protein kinase
MEK	: ERK kinase
MetS	: Metabolic syndrome
MPGF	: Major proglucagon fragment
NEFA	: Non esterified fatty acids
NF-κB	: Nuclear factor-κB
NGT	: Normal glucose tolerance
NIH	: National Institutes of Health
PAI-1	: Plasminogen activator inhibitor-1
PAM	: Peptide amidating monooxygenase
PC	: Prohormone convertase
PDK1	: Phosphoinositide-dependent protein kinase- 1
PG	: Plasma glucose
PGC-1	: PPARγ coactivator 1
PI3K	: Phosphatidylinositol 3-kinase
PKA	: Protein kinase A
PKB	: Protein kinase B
PKC	: Protein Kinase C
PPARγ	: Peroxisome proliferator-activated receptor γ
PrG	: Proglucagon
PTB1B	: Protein Tyr phosphatase-1B
PTH	: Parathyroid hormone
PYY	: Peptide YY
RBP4	: Retinol-binding protein 4

List of Abbreviations (Cont.)

ROS	: Reactive oxygen species
RP	: Restrictive procedures
RYGB	: Roux-en-Y gastric bypass
SA-HRP	: Streptavidin-horseradish peroxidase
SG	: Sleeve gastrectomy
SOCS	: Suppressor of cytokine signalling
SOS	: Swedish Obesity Study
SRC	: Surgical Review Corporation
T2DM	: Type 2 diabetes mellitus
TLR4	: Toll-Like Receptor 4
TNFα	: Tumor necrosis factor α
VBG	: Vertical banded gastroplasty
WHO	: World Health Organization
WHR	: Waist to hip ratio

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INTRODUCTION

Type 2 diabetes mellitus is a complex metabolic disease characterized by insulin resistance and progressive failure of pancreatic beta cells, resulting in hyperglycemia ***(Kashyap and Defronzo, 2007)***. The increasing prevalence of obesity worldwide is accompanied by an explosion in the prevalence of type 2 diabetes; about 60% of all cases of diabetes are attributable to obesity ***(Yach et al., 2006)***.

Obesity, a potent risk factor for type 2 diabetes, contributes to its development by inducing insulin resistance and inflammation, which in turn impair glucose regulation ***(Mokdad et al., 2003)***. Fat deposits in the abdomen, muscles, and liver contribute to elevations of circulating free fatty acids and adipocyte-derived cytokines that mediate insulin resistance and inflammatory pathways ***(Itani et al., 2002)***.

Existing medical therapeutic strategies to achieve and maintain clinically significant weight loss remain limited. Surgical procedures for the treatment of obesity are, however, highly effective in achieving substantial and sustained weight loss, but they are technically demanding, costly and carry small but significant rates of morbidity and mortality ***(Carel et al., 2006)***.

Glycemic control in diabetic patients improves markedly within days of bariatric surgery, which suggests that the procedures alter the hormones that control insulin secretion ***(Rubino, 2006)***. The enteroinsular axis includes the gut hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). These hormones, also known as *incretins*, are secreted by intestinal L and K cells, respectively, in response to nutrients and directly enhance insulin secretion ***(Fetner et al., 2005)***.

Bariatric procedures were classified as restrictive, malabsorptive, or combined, reflecting the purported mechanism of weight loss ***(Rubino, 2006)***.

Restrictive procedures, such as laparoscopic adjustable gastric banding (LAGB) and vertical banded gastroplasty (VBG), greatly reduce the volume of the stomach to decrease food intake and induce early satiety. Malabsorptive procedures, such as biliopancreatic diversion (BPD), shorten the small intestine to decrease nutrient absorption. Combined procedures, such as the Roux-en-Y gastric bypass (RYGB), incorporate both restrictive and malabsorptive elements ***(Murphy and Bloom, 2006)***.

Both BPD and RYGB alter the secretion of orexigenic and anorexigenic gut peptides, which interact with appetitive centers in the arcuate nucleus of the hypothalamus to decrease

appetite. On average, bariatric surgery reduces body mass index by 10 to 15 kg/m^2 and weight by 30 to 50 kg ***(Bult et al., 2008)***.

Dramatic improvements in glycemic control have been observed in subjects with T2DM following bariatric surgery, and specifically the Roux-en-Y gastric bypass (RYGB) procedure ***(Schauer et al., 2003)***. In the early postoperative period following RYGB, many patients with T2DM discontinue all antidiabetic medication, and may achieve normal fasting plasma glucose concentrations even before substantial weight loss has occurred ***(Clements et al., 2004)***.

Bariatric surgery alters both insulin secretion and insulin sensitivity, thus improving glucose regulation ***(Kashyap et al., 2010)***.It has been postulated that the improvements in glycemic control, reduction in appetite, and subsequent weight loss following bypass surgery may be due to changes in circulating gut hormones ***(Rubino and Marescaux, 2004)***.

Glucagon-like peptide-1 is a potent insulin secretagogue that is secreted by the L cells of the distal ileum in response to ingested nutrients and is inactivated by the enzyme dipeptidyl peptidase IV (DPP-IV) ***(Holst, 2007)***.

By activating adenylate cyclase, GLP-1 acts on pancreatic islets to augment glucose-dependent insulin secretion. The subsequent increase in insulin levels within

islets inhibits glucagons secretion, possibly through direct activation of GLP-1 receptors on α cells ***(Flint et al., 2001)***. Glucagon-like peptide-1 also slows gastric emptying, which delays digestion and blunts postprandial glycemia, and acts on the central nervous system to induce satiety and decrease food intake. Finally, GLP-1 increases glycogenesis in hepatocytes and skeletal muscle and increases lipogenesis in adipocytes, which may improve insulin sensitivity ***(Luque et al., 2002)***.

AIM OF THE WORK

The aim of this study is to assess the effect of bariatric surgery on serum glucagon like peptide-1(GLP-1) concentration and insulin resistance among obese type 2 diabetic patients.