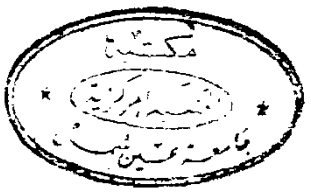
EFFECT OF SALT CONTENT OF DIET ON CARBOHYDRATE METABOLISM

Thesis

Submitted for the Partial Fulfilment

of the Master Degree of General Medicine



By

MEDHAT NAGI GHALI

(M.B., B.Ch.)

Supervised by

Prof. Dr. ADEL SHAKER

Professor of Internal Medicine

Faculty of Medicine, Ain Shams University

Prof. Dr. SAMIR MOHAMED SADEK

Professor of Internal Medicine

Faculty of Medicine, Ain Shams University

Assit. Prof. Dr. HASSAN EL-SAYED SOLIMAN

Assistant Professor of Internal Medicine

Faculty of Medicine, Ain Shams University

1987

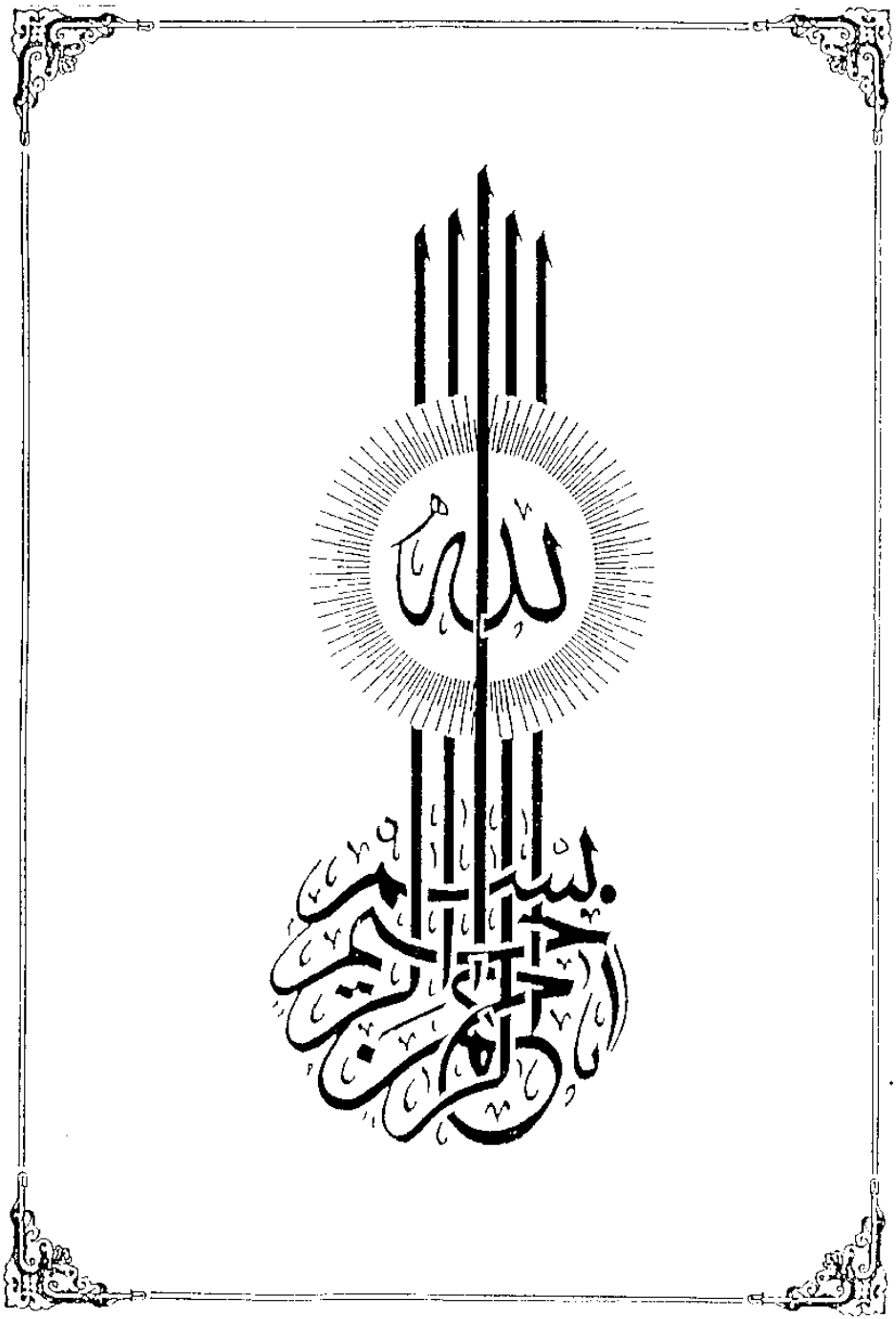
ACKNOWLEDGEMENT

I would like to express my sincere thanks and deepest gratitude to: Professor Dr. ADEL SHAKER, Professor of Internal Medicine, Ain Shams University, who offered me the encouragement, the generous support and many useful criticisms and suggestions throughout this study. His precious guidance and continued supervision which were kindly given are beyond acknoledgement.

I wish to express my deepest gratitude to Professor Dr. SAMIR MOHAMED SADEK, Professor of Internal Medicine, Ain Shams University, for his cordial support and kind help during this study.

I am deeply greatful to Assistant Professor Dr. HASSAN SOLIMAN, Assistant Professor of Internal Medicine, Ain Shams University, who offered much of his time and experience for providig me with advice, suggestions and planning of this work and for kind supervision.

My deep gratitude to Mr. MAGDI ABBAS and all staff and members in Department of Endocrinology, Ain Shams University, for their kind help in fulfilling the practical part of this work.



CONTENTS

INTRODUCTION & AIM OF WORK

INTRODUCTION AND AIM OF WORK

The size and duration of the increase in plasma glucose concentration after the consumption of standardised meals of various food rich in carbohydrates vary considerably in both normal adults *(Jenkins et al., 1981)* and diabetics *(Huttunen et al., 1982)*.

These differences may result from the effects on the rate of gastric emptying, digestion and absorption and on the chemical nature of the constituent monosaccharides. Viscous dietary fibre *(Jenkins et al., 1978)*, protein in food *(Anderson and Levine, 1981)*, the type of starch *(Goddard and Young, 1984)* and physical form of the food, raw or cooked, whole or ground *(Snow and O'Dea, 1981)*, may all affect postprandial plasma glucose concentrations.

Recently, The amount of salt content of diet was found to be important as regards its effect on the glycaemic response *(Thorbun et al., 1986)*.

Aim of Work

The aim of the present thesis is to compare the level of blood glucose and serum insulin after consumption of standardised carbohydrate diet, with and without addition of slat.

REVIEW OF LITERATURE

CHAPTER I
CHEMISTRY OF INSULIN

CHEMISTRY OF INSULIN

Historical Perspective

Langerhans identified the islets in 1860's but did not understand their function, nor did Von Mering and Minkowski, who demonstrated in 1889 that pancreatectomy produced diabetes. The link between the islets and diabetes was suggested by *De Mayer, 1909* and by *Sharpey-Schaffer, 1917* but it was Banting and Best who proved this association in 1921. After ligation of the pancreatic duct in dogs, which resulted in atrophy of exocrine pancreas, these investigators used acid-ethanol to extract from the remaining tissues an islet cell factor that had potent hypoglycaemic activity. The factor was named "Insulin" *(Granner, 1985)*.

Insulin was the first protein proved to have hormonal action, first protein crystallized, the first protein sequenced, the first protein synthetized by chemical techniques. The first protein shown to be synthesized as a large precursor molecule, and first protein prepared for commercial use by recombinant DNA technology *(Granner et al., 1985)*.

Chemistry

Insulin is a small protein whose sequence was determined in early 1950 by Sanger and his colleagues *(Ryle et al., 1955)*.

Insulin is a polypeptide consisting of 2 chains, A and B, linked by 2 interchain disulphide bridges that connect A_7 and B_7 and A_{20} to B_{19}.

A third interchain disulphide bridge connects residues 6 to 11 of the A chain. The location of these 3 disulphide bridges is invarient, and the A

and B chains have 21 and 30 aminoacids, respectively, in most species. Insulin has molecular weight 5734 *(Granner, 1985)*. The covalent structure of human insulin is illustrated in Fig. (1-1).

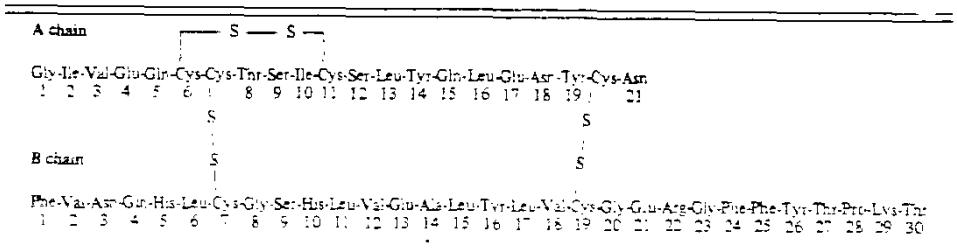


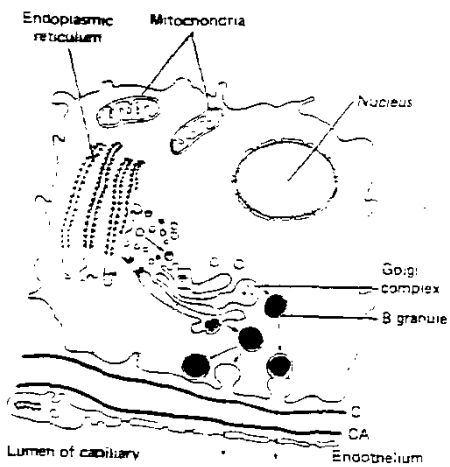
Fig. (1-1): Covalent structure of human insulin (Ganong WE: Review of medical physiology, 12th ed. Lange, 1985).

Biosynthesis

Insulin is synthesised in endoplasmic reticulum of B cells (Fig. 1-2). It is then transported to the Golgi complex, where it is packaged in membrane bound granules. These granules move to the cell wall by process that appears to involve microtubules, and their membranes fuse with the membrane of the cell, expelling the insulin to the exterior by exocytosis. The insulin then crosses the basal laminas of B cell and a neighbouring capillary and the fenestrated endothelium of the capillary to reach the blood stream.

Like other polypeptide hormones and related proteins that enter the endoplasmic reticulum, insulin is synthesized as part of large preprohormone. The gene for insulin is located on chromosome 11 in humans *(Owerbach et al., 1980)*.

Preproinsulin has a 23-aminoacid leader sequence removed as it enters the endoplasmic reticulum. The remainder of molecule is then folded to make proinsulin. The peptide segment connecting the A and B chains is normally detached in the granules before secretion. Without the connection, the proper folding of the molecule for formation of disulphide bridges would be difficult. The polypeptide that remains in addition to insulin after the connection is served is called connecting peptide (C-peptide). It contains 31 amino acid residues and has 10% of biologic activity of insulin. It enters the blood stream along with insulin when the granule contents are extruded by exocytosis. It can be measured by radioimmunoassay, and its level provides an index of B-cell function in patient receiving exogenous insulin *(Ganong, 1985).*



(Fig. 1-2) Schematic representation of insulin biosynthesis and secretion. Insulin is synthesized in the rough endoplasmic reticulum and translocated in the Golgi apparatus, where the B granules are formed. The granules fuse to the cell membranes, insulin is released by exocytosis, and the hormone passes through the basal lamina of the B-cell (C) and the basal lamina (CA) plus the fenestrated endothelium of nearby capillary to enter the blood stream.

Regulation of Insulin Secretion

The human pancreas secretes 40-50 units of insulin daily, which represents about 15-20% of hormone stored in the glands.

Insulin secretion is an energy requiring process that involves the microtubule-microfilament system in the B cells of islets.

The mechanism of action of different insulin secretagogues has not been clearly established.

1. Glucose

Is the prime stimulus and is the most important physiologic regulator of insulin secretion. The threshold concentration for secretion is fasting plasma level (80-100 mg/dl), and maximal response is obtained at glucose level between 300 and 500 mg/dl. Glucose in releasing insulin when given orally is much more effective than when given by IVI, hence, various gastrointestinal hormones including secretin, cholecystokinin, glucagon and gastrin have been implicated in insulin release but gastric inhibitory polypeptide (GIP) is now thought to play a major role in this process. Two different mechanisms have been proposed to explain how glucose regulates insulin secretion. One suggests that glucose combine with membrane, possibly located on the B cell membrane, that activates the release mechanism. The second hypothesis suggests that the intracellular metabolites or rate of metabolite flux through a pathway such as pentose phosphorus shunt, the citric acid pathway, or glycolytic pathway is involved.

2. Amino Acids, Fatty Acids and Ketone Bodies

High protein meals stimulate insulin release, and arginine, lysine, and leucine are potent insulin secretagogues.

Whether these aminoacids act in absence of glucose is unclear (leucine may).

Physiologic concentrations of short and long chain fatty acids and ketone bodies are weak secretagogues in most species.

3. Hormonal Factors

Numerous hormones affect insulin release. Alpha adrenergic agonists, principally epinephrine, inhibit insulin release even when this process has been stimulated by glucose. Beta adrenergic agonists stimulate release probably by increasing c-AMP.

4. Intracellular Mediators of Secretion

Oxygen consumption and ATP utilization increase as glucose stimulates insulin release. This is associated with a K-induced depolarization of membrane that results in the rapid entry of Ca^{+2} via voltage dependent agent.

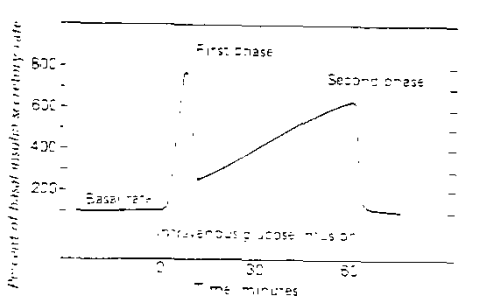
Replacement of extracellular Na^{+} with another monovalent cation blunts the effects of glucose and other secretagogues; Na+ may regulate the intracellular concentration of Ca^{+2} through a cotransport system (Granner, 1985).

5. Neural Regulation of Insulin

Is important in vivo. The vagus, through acetyl choline release, stimulates insulin secretion, while sympathetic discharge predominantly inhibits it. It is very likely that other neurotransmitters, such as somatostatin, dopamine, serotonin, and vip also have effects. Recently, there has been considerable interest in central regulation of insulin by hypothalamus, with the ventrolateral nucleus controlling vagal drive to the islets and ventromedial nucleus stimulating sympathetic innervation.

Secretion of insulin occurs in two phases: a fast first phase that begins within 1 minute and lasts 5-10 minutes, probably from secretion of already formed granules situated near the cell surface. If the stimulus is sustained there is slower second phase of secretion, in which much of insulin is newly synthesized.

In vivo, insulin secretion is controlled by a finely integrated combination of metabolic, hormonal and neural mechanisms, for first there is "cephalic" phase due to vagal stimulation. This is followed by release of gut hormones and absorptions of glucose, which together cause steady rise in insulin level to peak in 45 - 66 minutes *(Alberti and Hockaday, 1985).*



(Fig. 1-3): The biphasic pattern of insulin release in response to an increased plasma glucose concentration

Stimulators and Inhibitors of Insulin Secretion (Table 1-1)

Stimulators	Mechanism	Glucose required
1. Glucose	? Glucoreceptor ? metabolites ± Ca^{+} shift	
2. Glucagon		+
3. Gut hormone (GIP)		+
4. B-adrenergic agents	C-AMP	+
5. Prostaglandins		+
6. Leucine	?membrane effect ?metabolites	-
7. Other a.a.	?	+
8. Fatty acids	?	-
9. Ketone bodies	?	-
10. Acetyl choline vagal stimulation	? Ca^{+2} shift	-

Inhibitors	Mechanism	Glucose required
1. α adrenergic agent	C-AMP	-
2. Sympathetic nerve stim.		
3. Dopamine	?Ca^{+2} shifts	-
4. Serotonin	?Ca^{+2}	-
5. Somatostatin	?	