List of Contents

List of Tables

List of Figures

List of Abbreviation

Abbreviation

HLA	**Hummen leycocyt antigen**
GLUT	**Glucose transport**
DKA	**Diabetic ketoacidosis**
NKHHC	**Non kitotic hyperosmolar coma**
MODY	**Maturity-onset diabetes of the young**
CABA	**Coronary artery bypass graft**
BMI	**Body mass index**
ESRD	**End stage renal disease**
ACE	**Angiotenin-converting enzyme**
BUN	**Blood urea nitrogen**
NPO	**Nothing by mouth**
MI	**Myocardial infarction**
ABGs	**Arterial blood gases**
TCA	**Tricarboxylic acid**
ACTH	**Adrenocorticotrophic hormone**
IPTR	**International pancreas transplant Registry**
ECG	**Electro Cardiography**
EMG	**Electro Myography**

Introduction

Diabetes mellitus is a medical disorder characterized by persistent variable hyperglycemia (high blood sugar levels), resulting either from inadequate secretion of the hormone insulin, an inadequate response by the body's cells to insulin, or a combination of these factors **(Marks, 1999).**

The most common forms of diabetes are typeI, type II and gestational diabetes. Type I (10% of cases) is due to destruction of the islets of Langerhans, which produce insulin; it can only be treated with insulin injections. In type II (90% of cases) the main problem is decreased sensitivity of the body's cells to insulin, known as insulin resistance, although insulin production is often affected in the later stage. Usually treatment is with oral hypoglycemic drugs, as well as diet and exercise, or eventually with insulin injections. Gestational diabetes may develop during pregnancy and is similar to type II in its mechanism; it may affect fetal health and 40% of women with gestational diabetes develop type 2 diabetes later on in life **(Redondo,et al, 2001).**

Since the discovery of insulin 1921 diabetes has been considered as a treatable but chronic condition, and the main risks to health are its characteristic long-term complications. These include cardiovascular disease, chronic renal failure (it is the main cause for dialysis in developed world adults), retinal damage which can lead to blindness and is the most significant cause of adult blindness in the non-elderly in the developed world, nerve damage, erectile dysfunction (impotence), and gangrene with risk of amputation of toes, feet, and even **.**

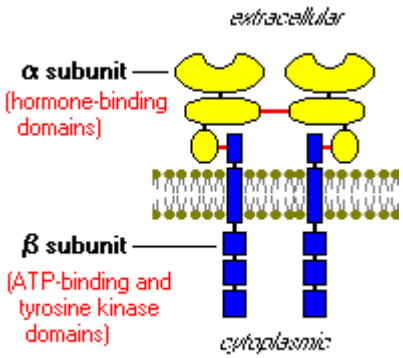
The complications are less common and less severe in people who have well-controlled blood sugar levels. In fact, the better the control, the lower the risk of complications. Hence patient education, understanding and participation is vital. Healthcare professionals who treat diabetes also address other health problems that may accelerate the deleterious effects of diabetes. These include smoking elevated cholesterol levels (control with diet, exercise or medication), obesity (even modest weight loss can be beneficial), high blood pressure, and lack of regular exercise **(Hirsch, et al, 1991).**

Transplantation of the pancreas or islet cell constitutes surgical treatment for patients with type I diabetes mellitus. Pancreatic transplantation is now an established procedure for the surgical treatment of diabetes mellitus. Islet cell transplantation has the potential to be the procedure of choice once it becomes more routine because of the minimal surgery involved.

Cadaveric donors provide whole pancreas grafts and islet cells, whereas living donors provide distal segments for transplantation. Auto-islet transplantation is the method of choice to treat endocrine deficiency following total pancreatectomy **(Gruessner, et al, 2002).**

Metabolic Effect of Insulin

Insulin is a key player in the control of intermediary metabolism. It has profound effects on both carbohydrate and lipid metabolism, and significant influences on protein and mineral metabolism **(Marks, 1999).**



Fig(1) Insulin receptors (Marks, 1999).

The Insulin Receptor and Mechanism of Action

Like the receptors for other protein hormones, the receptor for insulin is embedded in the plasma membrane. The insulin receptor is composed of two alpha subunits and two beta subunits linked by disulfide bonds. The alpha chains are entirely extracellular and house insulin binding domains, while the linked beta chains penetrate through the

plasma membrane. The insulin receptor is a tyrosine kinase. In other words, it functions as an enzyme that transfers phosphate groups from (ATP) to tyrosine residues on intracellular target proteins. Binding of insulin to the alpha subunits causes the beta subunits to phosphorylate themselves (autophosphorylation), thus activating the catalytic activity of the receptor. The activated receptor then phosphorylates a number of intracellular proteins, which in turn alters their activity, thereby generating a biological response. Several intracellular proteins have been identified as phosphorylation substrates for the insulin receptor, the best-studied of which is insulin receptor substrate-1 or (IRS-1). When (IRS-1) is activated by phosphorylation, a lot of things happen. Among other things, (IRS-1) serves as a type of docking center for recruitment and activation of other enzymes that ultimately mediate insulin's effects. A more detailed look at these processes is presented in the section on Insulin Signal Transduction **(Service, 1999).**

Insulin and Carbohydrate Metabolism

Glucose is liberated from dietary carbohydrate such as starch or sucrose by hydrolysis within the small intestine, and is then absorbed into the blood . Elevated

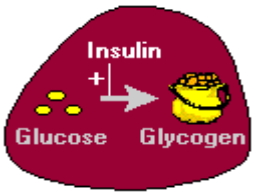
concentrations of glucose in blood stimulate release of insulin, and insulin acts on cells thoughout the body to stimulate uptake, utilization and storage of glucose. The effects of insulin on glucose metabolism vary depending on the target tissue. Two important effects are:

(1) Insulin facilitates entry of glucose into muscle, adipose and several other tissues. The only mechanism by which cells can take up glucose is by facilitated diffusion through a family of hexose transporters. In many tissues, muscle being a prime example , the major transporter used for uptake of glucose (called GLUT4) is made available in the plasma membrane through the action of insulin. In the absense of insulin, (GLUT4) glucose transporters are present in cytoplasmic vesicles, where they are useless for transporting glucose. Binding of insulin to receptors on such cells leads rapidly to fusion of those vesicles with the plasma membrane and insertion of the glucose transporters, thereby giving the cell an ability to efficiently take up glucose. When blood levels of insulin decrease and insulin receptors are no longer occupied, the glucose transporters are recycled back into the cytoplasm **(Ratner, et al, 2000).**

(2) Insulin stimulates the liver to store glucose in the form

of glycogen. A large fraction of glucose absorbed from the small intestine is immediately taken up by hepatocytes, which convert it into the storage polymer glycogen.Insulin has several effects in liver which stimulate glycogen synthesis. First, it activates the enzyme hexokinase, which phosphorylates glucose, trapping it within the cell. Coincidently, insulin acts to inhibit the activity of glucose-6-phosphatase. Insulin also activates several of the enzymes that are directly involved in glycogen synthesis, including phosphofructokinase and glycogen synthase. The net effect is clear: when the supply of glucose is abundant, insulin "tells" the liver to bank as much of it as possible for use later. A well-known effect of insulin is to decrease the concentration of glucose in blood, which should make sense considering the mechanisms described above. Another important consideration is that, as blood glucose concentrations fall, insulin secretion ceases. In the absense of insulin, a bulk of the cells in the body become unable to take up glucose, and begin a switch to using alternative fuels like fatty acids for energy. Neurons, however, require a constant supply of glucose, which in the short term, is provided from glycogen reserves. In the absense of insulin, glycogen synthesis in the liver ceases and enzymes responsible for breakdown of glycogen become active.

Glycogen breakdown is stimulated not only by the absense of insulin but by the presence of glucagon, which is secreted when blood glucose levels fall below the normal range **(Ratner, et al, 2000).**



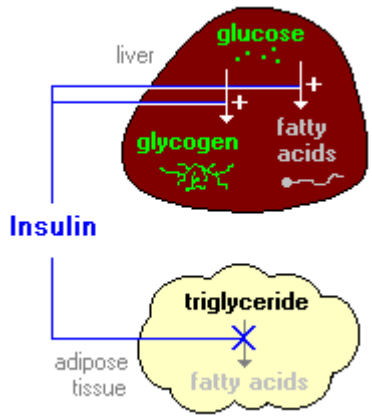
Fig(2) Insulin and glucagons(Ranter,et al,2000).

Insulin and Lipid Metabolism

The metabolic pathways for utilization of fats and carbohydrates are deeply and intricately intertwined. Considering insulin's profound effects on carbohydrate metabolism, it stands to reason that insulin also has important effects on lipid metabolism. Notable effects of insulin on lipid metabolism include the following:

(1) Insulin promotes synthesis of fatty acids in the liver. As discussed above, insulin is stimulatory to synthesis of glycogen in the liver. However, as glycogen accumulates to high levels (roughly 5% of liver mass), further synthesis is strongly suppressed.When the liver is saturated with

glycogen, any additional glucose taken up by hepatocytes is shunted into pathways leading to synthesis of fatty acids, which are exported from the liver as lipoproteins. The lipoproteins are ripped apart in the circulation, providing free fatty acids for use in other tissues, including adipocytes, which use them to synthesize triglyceride **(Segel, et al, 2002).**



Fig(3) synthesize of triglyceride (Segel, et al, 2002).

(2) Insulin inhibits breakdown of fat in adipose tissue by inhibiting the intracellular lipase that hydrolyzes triglycerides to release fatty acids.Insulin facilitates entry of glucose into adipocytes, and within those cells, glucose can be used to synthesize glycerol. This glycerol, along with the fatty acids delivered from the liver, are used to synthesize triglyceride within the adipocyte.

By these mechanisms, insulin is involved in further accumulation of triglyceride in fat cells.From a whole body perspective, insulin has a fat-sparing effect. Not only does it drive most cells to preferentially oxidize carbohydrates instead of fatty acids for energy, insulin indirectly stimulates accumulation of fat in adipose tissue **(Segel, et al, 2002).**

Other Notable Effects of Insulin

In addition to insulin's effect on entry of glucose into cells, it also stimulates the uptake of amino acids, again contributing to its overall anabolic effect. When insulin levels are low, as in the fasting state, the balance is pushed toward intracellular protein degradation. Insulin also increases the permiability of many cells to potassium, magnesium and phosphate ions. The effect on potassium is clinically important. Insulin activates sodium-potassium (ATPases) in many cells, causing a flux of potassium into cells. Under certain circumstances, injection of insulin can kill patients because of its ability to acutely suppress plasma potassium concentrations **(Segel, et al, 2002).**

Glucoregulatory Factors

Hormonal Glucoregulatory Factors

Hormones are the most important glucoregulatory factors, and the regulation of their secretion is complex. Glucose, specifically the plasma glucose concentration, is the most important determinant of the secretion of glucoregulatory hormones, including insulin, glucagon, epinephrine, growth hormone, and cortisol. Insulin, the dominant glucose-lowering hormone,suppresses enogenous glucose production and stimulates glucose utilization by insulin-sensitive tissues, thereby lowering the plasma glucose concentration. Insulin is secreted from beta cells of the pancreatic islets into the hepatic portal circulation and acts on the liver and peripheral tissues. It inhibits hepatic glycogenolysis and gluconeogenesis and, in concert with other factors (including hyperglycaemia hypoglucagonemia), converts the liver into an organ of net glucose uptake and fuel storage (glycogen and triglycerides). It also suppresses renal glucose production and stimulates glucose uptake, storage, and utilization by tissues such as muscle and fat. In the postabsorptive state, insulin regulates the plasma glucose concentration primarily by restraining hepatic glucose production. Higher levels, such as those

that occur after meals, are required to stimulate glucose utilization **(Rizza, et al, 1981).**

Conversely, decreased insulin secretion causes increased hepatic (and renal) glucose production and decreased glucose utilization by insulin-sensitive tissues such as muscle and thus tends to raise the plasma glucose concentration. Insulin is therefore both a glucose-lowering (regulatory) and a glucose-raising (counterregulatory) hormone. The rate of insulin secretion is regulated by a number of factors, the most important of which is glucose. A fall in the plasma glucose concentration has an immediate inhibitory effect on insulin secretion, thereby limiting a further fall in the plasma glucose level. Insulin is a potent and critical hormone. Either profound insulin deficiency or marked insulin excess can be lethal. But it is not the only glucoregulatory hormone **(Rizza & Gerich, 1979).**

Glucose-raising or glucose counterregulatory hormones include glucagon, epinephrine, growth hormone, and cortisol. In response to falling plasma glucose levels, glucagon is secreted from alpha cells of the pancreatic islets into the hepatic portal circulation and is believed to act exclusively on the liver under physiologic conditions .