Insulin Dynamic Pattern Among Type 2 Diabetic Patients With And Without Nephropathy

Thesis

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Introduction

Worldwide, diabetic nephropathy is now the most common cause of entry to renal replacement therapy (RRT) programmes. However, the proportion of new entrant to RRT with diabetes has risen steadily in the last 20 years ***(Marshall, 2004).***

About 20-30% of patients with type 1 or type 2 diabetes develop evidence of nephropathy, but in type 2 diabetes, a considerably smaller fraction of those progress to end stage renal disease (ESRD). However, because of the much greater prevalence of the type 2 diabetes, such patients constitute over half of those diabetic patients currently starting on dialysis ***(American Diabetes Association, 2004).***

Endogenous insulin has circulatory half-life of 3-5 minutes. It is catabolized chiefly by insulinase enzyme in liver, kidney and placenta. Approximately 50% of insulin is removed in a single pass through the liver ***(Umesh et al., 2001).***

A 30- 40% reduction of insulin clearance in patients with overt diabetic nephropathy compared with diabetic patients without nephropathy was recorded. Paradoxically, in spite of higher circulating insulin levels, both the peak metabolic effect and the overall metabolic activity of insulin were diminished in patients with overt diabetic nephropathy when compared with diabetic patients without renal impairment ***(Ravel et al., 2001).***

Aim of the work

The aim of the work is to study the insulin dynamic pattern in relation to a standard meal among type 2 diabetic patients with and without nephropathy (microalbuminuria and macroalbuminuria).

Insulin

Insulin is a polypeptide hormone produced by the β- cells of the islets of Langerhans-clusters of cells that are embedded in the exocrine portion of the pancreas. The islets of Langerhans make up only about one to two percent of the total cells of the pancreas. Insulin is the most important hormone coordinating the use of fuels by tissues. Its metabolic effects are anabolic, favoring, for example, synthesis of glycogen, triacylglycerols, and protein ***(Bowen, 2004).***

Structure of insulin:

Insulin is composed of 51 amino acids arranged in two polypeptide chains, which are linked together by two disulfide bridges (fig. 1) ***(Kasper et al., 2004).***

Synthesis of insulin:

The biosynthesis involves two inactive precursors (fig. 2), preproinsulin and proinsulin, which are sequentially cleaved to form the active hormone plus the C-peptide. (C-peptide is essential for proper insulin folding). Also, because of its longer half-life in the plasma, the C-peptide is a good indicator of insulin production and secretion in early diabetes ***(Kasper et al., 2004).***

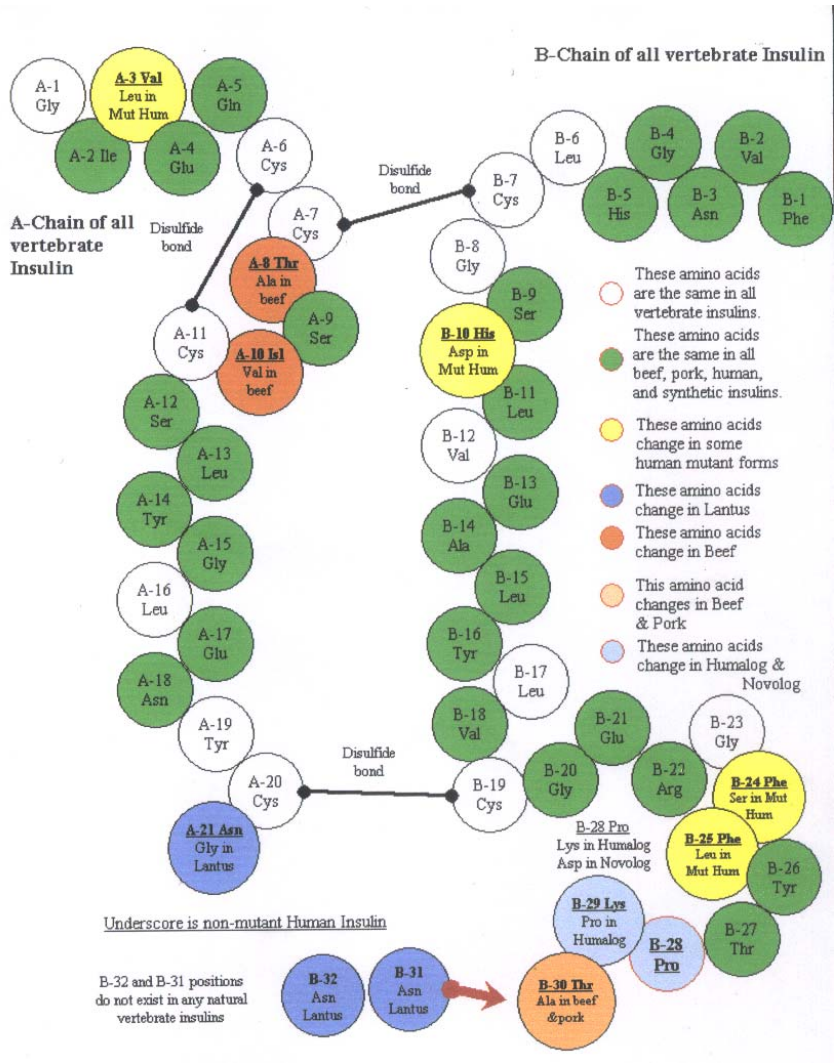

Fig. (1): Structure of insulin ***(Champe et al., 2005).***

Processing of insulin within the beta cell

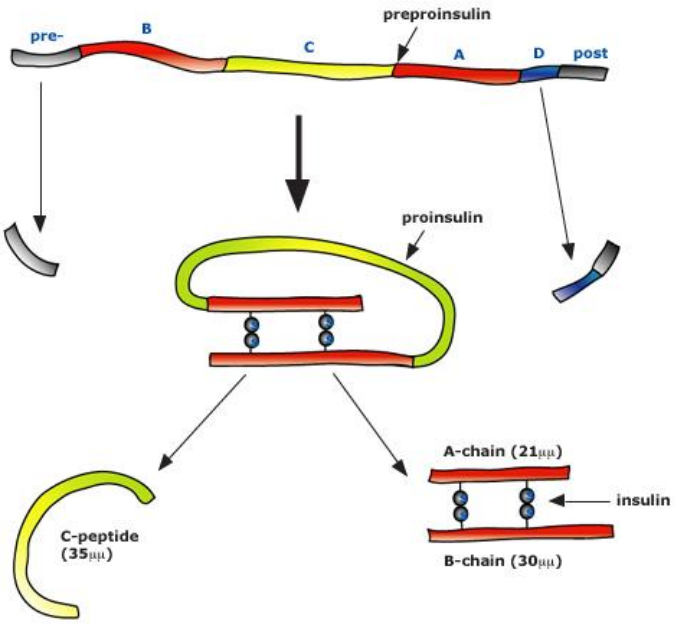

Fig. (2): Insulin is synthesized as preproinsulin in the ribosomes of the rough endoplasmic reticulum. The preproinsulin is then cleaved to proinsulin, which is transported to the Golgi apparatus where it is packaged into secretory granules located close to the cell membrane. Most of the proinsulin is cleaved into equimolar amounts of insulin and C peptide in the secretory granules ***(Champe et al., 2005).***

Regulation of insulin secretion:

(1) ***Stimulation of insulin secretion***:

Insulin secretion by the β-cells of the islets of Langerhans of the pancreas is closely coordinated with the release of glucagon by pancreatic α-cells. The relative amounts of insulin and glucagon released by the pancreas are regulated so that the rate of hepatic glucose production is kept equal to the use of glucose by peripheral tissues ***(Ganong, 2003).***

Factors affecting insulin secretion:

1- **Glucose:** The β-cells are the most important glucose sensing cells in the body. Like the liver, β-cells have glucokinase activity, and thus can phosphorylate glucose in amounts proportional to its actual concentration in the blood. Ingestion of glucose or a carbohydrate rich meal leads to a rise in blood glucose, which is a signal for increased insulin secretion as well as decreased glucagon synthesis and release. Glucose is the most important stimulus for insulin secretion ***(Chakraborty, 2006)*.**

Glucose transporter 2 (GLUT 2):

GLUT 2 is a glucose transporter that transports intracellular glucose and galactose across the basolateral membrane of cells including hepatocytes, pancreatic β – cells, renal tubular cells and intestinal epithelial cells ***(Brown, 2000).***

GLUT 2 has a very low affinity for glucose and seems to act as a transporter only when plasma glucose levels are

relatively high, as postprandially, so that diffusion of glucose across these cells increases as glucose levels rise. The low affinity of GLUT 2 for glucose reduces hepatic uptake of glucose during the basal state or during fasting ***(Kahn, 1992)*.**

2- **Amino acids:** Ingestion of protein causes a transient rise in plasma amino acid levels, which in turn, induces the immediate secretion of insulin. Elevated plasma arginine is a particularly potent stimulus for insulin synthesis and secretion ***(Chakraborty, 2006)*.**

3- **Gastrointestinal hormones:** The intestinal peptide secretin, as well as other gastrointestinal hormones e.g: gastric inhibitory polypeptide (GIP), stimulate insulin secretion. These hormones are released after the ingestion of food. They cause an anticipatory rise in insulin levels in the portal vein before there is an actual rise in blood glucose. This may account for the fact that the same amount of glucose given orally induce a much greater secretion of insulin than if given intravenously ***(Costanzo, 2004).***

Also, glucagon like peptide-1 (GLP-1) which is a gut derived incretin hormone produced in L cells, predominantly present in the ileum and the colon. Immunoreactive GLP-1 has been found throughout the entire small intestine, and co-localization of GLP-1 and GIP in mid-small intestine double staining cells have been described ***(Holst, 2004).***

The GLP-1 receptor is a G protein-coupled receptor ***(Thorens and Widmann, 1996)***, expressed by the B-cells, and possibly also by α-cells, endothelial cells, the peripheral nervous system, heart, kidney lungs and gastrointestinal tract. Both GLP-1 and GIP are rapidly metabolized by enzymatic degradation by the enzyme dipeptidyl peptidase (DPP-4) and cleared by the kidneys ***(Orskov et al., 1993).***

Physiological effects of GLP-1 on the β-cells:

The direct effect of GLP-1 on the β-cells is strictly glucose dependent and is exerted through interaction with the GLP-1 receptor located on the cell membrane of the β-cells ***(Holst and Gromada, 2004)*.**

Activation of the receptor entails numerous events including a rise in the intracellular concentration of cAMP, altered ion channel activity, handling of intracellular calcium and enhanced exocytosis of insulin containing granules ***(Holz, 2004).***

Physiological effects of GLP-1 on glucagon secretion:

GLP-1 inhibits the secretion of glucagon ***(Orskov et al., 1988)***, but the mechanism is not fully understood, and may be a consequence of several factors. The ability of GLP-1 to lower plasma glucose is preserved in type 1 diabetic patients without residual β-cell function. ***Creutzfeldt et al., 1996;*** indicated that a paracrine inhibitory

effect of insulin or other β-cell products is not involved. Surprisingly GLP-1 stimulates glucagon secretion in isolated rat pancreatic α-cells ***(Ding et al., 1997)***, making a direct inhibitory effect on the α-cells unlikely, but GLP-1 has been shown to stimulate the secretion of somatostatin, which in turn may inhibit glucagon secretion ***(Orskov et al., 1988).*** An important notion is that in vivo, the inhibitory effect of GLP-1 on glucagon secretion false away at glucose levels just below fasting levels, so that the normal counter regulatory glucagon secretion at hypoglycaemic levels is preserved, thus administration of GLP-1 is unlikely to be associated with an increased risk of hypoglycaemia ***(Nauk et al., 2002).***

(2) ***Inhibition of insulin secretion***: The synthesis and release of insulin are decreased during periods of stress (for example: fever or infection). These effects are mediated primarily by epinephrine which has a direct effect on energy metabolism, causing a rapid mobilization of energy yielding fuels, including glucose from the liver (produced by glycogenolysis or gluconeogenesis) and fatty acids from adipose tissue, thus in emergency situations, the sympathetic nervous system largely replaces the plasma glucose concentration as the controlling influence over β-cell secretion ***(Ganong, 2003).***

Insulin destruction by the kidneys:

The kidneys are the major site of insulin clearance from the systemic circulation, removing approximately 50% of peripheral insulin. In addition, the kidneys remove 50% of circulating proinsulin and 70% of c-peptide by glomerular filtration. Insulin analogs are also cleared by kidney. Glomerular clearance of insulin may occur both by nonspecific diffusion and by specific receptor- mediated transport. After entering the tubule lumen, more than 99% of the filtered insulin is reabsorbed by proximal tubule cells, primarily by endocytosis. Relatively little insulin is ultimately excreted in urine ***(Duckworth et al., 1998)*.**

Metabolic effects of insulin:

(1) Effects on carbohydrate metabolism: The effects of insulin on glucose metabolism are most prominent in three tissues: liver, muscle, and adipose. In the liver, insulin decreases the production of glucose by inhibiting gluconeogenesis and the breakdown of glycogen. In the muscle and liver, insulin increases glycogen synthesis. In the muscle and adipose tissue, insulin increases glucose uptake by increasing the number of glucose transporters in the cell membrane. The intravenous administration of insulin thus causes immediate decrease in the concentration of blood glucose ***(Costanzo, 2004).***

(2) Effects on lipid metabolism:

a- ***Decreased triacylglycerol degradation***: insulin decreases the level of circulating fatty acids by inhibiting the activity of hormone sensitive lipase in adipose tissue. Insulin probably acts by promoting the dephosphorylation and, hence, inactivation of the enzyme ***(Champe et al., 2005).***

b- ***Increased triacylglycerol synthesis***: Insulin increases the transport and metabolism of glucose into adipocytes, providing the substrate glycerol 3-phosphate for triacylglycerol synthesis. Insulin also increases the lipoprotein lipase activity of adipose tissue by increasing the enzyme synthesis, thus providing fatty acids for esterification ***(Bowen, 2004).***

(3) Effects on protein synthesis: In most tissues, insulin stimulates the entry of amino acids into cells, and protein synthesis ***(Champe et al., 2005).***

Role of hyperinsulinaemia in cancers:

Hyperinsulinaemia in breast cancer:

Insulin has been proposed as the potential mediating factor for the increase risk of breast cancer among obese postmenopausal women. Because obesity is associated with hyperinsulinaemia and insulin resistance. Insulin is a mitogenic agent that also has direct effects on the development of breast cancer pathogenesis ***(Calle and Kaaks, 2004).***

Hyperinsulinaemia in prostate cancer:

Insulin levels have been examined in relation to prostate cancer risk. A case control study conducted in china found a 2.6 fold higher risk of prostate cancer comparing the top with the bottom tertiles of fasting plasma insulin ***(Hsing et al., 2001).***

Also in that study, higher fasting plasma glucose was positively and higher insulin sensitivity was inversely related to prostate cancer risk ***(Hsing et al., 2003).***

One study found that increased serum insulin was associated with increased risk of prostate cancer recurrence ***(Lehrer et al., 2002).***

Hyperinsulinaemia in pancreatic cancer:

Insulin and insulin growth factor-I (IGF-I) axis function an integrated fashion to promote cell growth and survival. IGF-I and IGF-I receptors are highly expressed in pancreatic cancer cell lines, and initiation of intracellular signaling leading to increase in proliferation, invasion and expressions of mediators of angiogenesis and a decrease in apoptosis in pancreatic tumour cell lines ***(Stoeltzing et al., 2003).***

Hyperinsulinaemia in colon cancer:

Hyperinsulinaemia has been hypothesized to be an underlying factor linking obesity, physical inactivity, type 2

diabetes mellitus as risk factor for colon neoplasia ***(Giovannucci, 1995).***

Insulin has growth promoting properties and increases free insulin-like growth factor (IGF-I) levels. Studies of circulating IGF-I in relation to risk of colon cancer or adenoma have generally found modest increases in the risk of cancer or adenoma ***(Giovannucci, 2003).***

Hyperinsulinaemia, hypertension and progressive renal disease:

Obesity, especially the visceral type, is associated with peripheral resistance to insulin actions and hyperinsulinaemia, which predisposes to development of diabetes. A common genetic predisposition to insulin resistance and hypertension and the coexistence of these two disorders predisposes to premature atherosclerosis. A constellation of metabolic and cardiovascular derangements, which also includes dyslipid-aemia, dysglycaemia, endothelial dysfunction, fibrinolytic and inflammatory abnormalities, left ventricular hypertrophy, microalbuminuria, and increased oxidative stress, is referred to as the cardiometabolic syndrome ***(Fadi et al., 2004).***

Mechanism of insulin action:

Insulin binds to specific, high affinity receptors in the cell membrane of most tissues, including liver, muscle, and adipose tissue. This is the first step in a cascade of reactions