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Study of Hyperglycemia Control in Type 2 Diabetes

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Abstract

Diabetes Mellitus (DM) is a metabolic syndrome with multiple etiological factors including hereditary and ecological factors leading to hyperglycemia. Hypoglycemia can be a limiting factor for management and a barrier to achieving optimal glycemic control in persons with insulin-treated type 2 diabetes. Even modest hypoglycemia can have a negative impact on a person's quality of life, and anxiety of hypoglycemia can lead to under insulation. The prevalence and effects of hypoglycemia in people with type 2 diabetes, with an emphasis on those who use basal insulins, are explored in this article, along with preventative and management measures.

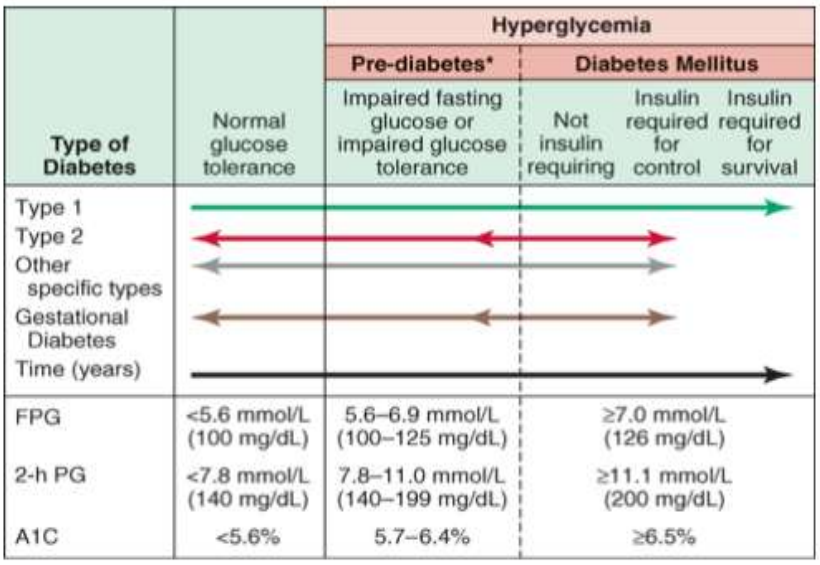
Keywords : Hypoglycemia;; Insulin biosynthesis; insulin secretion

Introduction

In Type 1, Constitutes only 5- 10% of all cases of diabetes. The disease begins before the age of 18 in approximately 75% cases (Michael, 2013). Type 1 Diabetes is usually autoimmune in origin with the destruction of Islets of Langerhans of pancreas.Autoantibodies are directed against several particles of Islet cells encompassing antibodies to Insulin, Glutamicacid decarboxylase, tyrosine phosphatase IA-2and IA- 2B (Edelstein, 1997). Clinical features include polydipsia, polyphagia, polyuria, rapid weight loss, hyperventilation, abrupt onset, insulin dependence and ketotic tendency (Edelstein, 1997).

Whereas in Type 2, Hyperglycemia resulting from Insulin resistance due to secretory defect of Insulin will cause a relative but not absolute Insulin deficiency. Patients in this case are

mostly obese with strong genetic predisposition and the risk increases with increasing age, obesity and physical inactivity. It is characterized by adult onset, with milder symptoms and rarely, when not treated properly, leads to ketoacidosis.



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

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PATHOPHYSIOLOGY OF TYPE 2 DIABETES MELLITUS AN OVERVIEW OF GLUCOSE HOMEOSTASIS

The balance among glucose production, peripheral glucose uptake and its utilization reflects Glucose Homeostasis .Although Insulin is the major controller of glucose metabolism, neural signals, metabolic inputs and other hormones (e.g. glucagon) also are involved. The organs that manage glucose and lipids interact by neural and humoral mechanisms with fat and muscle secreting adipokines, myokines, and metabolites that affect hepatic function. During fasting, low insulin increases glucose levels in blood by inducing hepatic gluconeogenesis and glycogenolysis and decreases uptake of glucose among insulin-sensitive organs (skeletal muscle and fat), thus mobilizing stored precursors as amino acids (proteolysis) and free fatty acids (lipolysis). When blood glucose or insulin levels are down, pancreatical alpha cells secrete Glucagon which stimulates glycogenolysis and gluconeogenesis in the liver and renal medulla. After a meal, the glucose load, rises Insulin and decreases Glucagon, reverses the

fore said processes. Insulin, being an anabolic hormone, promotes the synthesis of carbohydrate; fat and protein. Major portion of post-meal glucose is used by skeletal muscle, which is an effect of insulin-stimulated glucose uptake. Other tissues, most notably the brain, use glucose in an insulin independent fashion. Proteins secreted by skeletal myocytes (irisin), adipocytes (leptin, resistin, adiponectin, etc.), and bone also affect glucose homeostasis.

INSULIN BIOSYNTHESIS

Beta cells of the pancreatic islets produce Insulin .Initially, it is synthesized as a single-chain precursor polypeptide of 100 amino acids, Pre-pro insulin .Subsequently proteolytic cleavage removes the amino-terminal signal peptide forming Proinsulin. Proinsulin,an 86 amino acid structurally resembles insulin-like growth factors I and II, which weakly bind to the insulin receptor. Proinsulin is stored in Golgi complex. Here it is cleaved into a 31-residue fragment, the C peptide and the A (21 amino acids) and B (30 amino acids) chains of insulin, are generated which are connected by disulphide bonds (NCCLS, 1979) . Finally, the mature insulin molecule and C peptide are stored together and secreted together from secretory granules in the pancreatic beta cells.

C peptide is excreted more slowly than insulin. So it is a use full marker of insulin secretion and allows discrimination between endogenous and Exogenous insulin in the evaluation of hypoglycemia. Pancreatic beta cells always secrete islet amyloid polypeptide (IAPP) or amylin, a 37-amino acidpeptide, along with insulin. The physiological role of IAPP is not completely defined ,but it forms the major component of the amyloid fibrils deposited in the islets of patients with type 2 DM, and an analogue is sometimes used in the treatment of type1and type2 DM. Human insulin is synthesized by recombinant DNA technology.

Insulin biosynthesis is controlled at the levels both transcription and translation. Insulin content in β-cells is highly dynamic. In the presence of nutrients Insulin accumulates and decreases in response to nutrient deprivation. The quick response of β-cells to cellular signals is generally due to transcriptional regulation (OrciL, 1979).

INSULIN SECRETION

Glucose is the most important regulator of insulin secretion, although amino acids, ketones, various nutrients, gastrointestinal peptides, and neuro transmitters also affect insulin secretion. Insulin synthesis is stimulated by a glucose level >3.9mmol/L (70mg/dL), primarily by promoting protein translation and processing. Stimulation of insulin secretion by glucose begins with its transport into the β-cells through a facilitative glucose transporter .Phosphorylation of glucose by Glucokinase is the rate limiting step that regulates glucose-

mediated insulin secretion .Further steps of glycolysis generates ATP, which reduces the activity of an ATP-sensitive K+ channel.

This channel consists of two separate proteins: one is the binding site for certain oral hypoglycemic (e.g., sulfonylurea, meglitinides); the other is a K+channel protein (Kir6.2).Inhibition of this K+ channel stimulates β-cell membrane to depolarize which opens up voltage-dependent calcium channels(causing calcium influx) and promotes insulin secretion. Secretory profiles of insulin reveal a pulsatile pattern of hormone release. Small secretory bursts occur about every 10 minutes, combined with greater amplitude oscillations of about 80–150 min. In cretins are secreted by neuro endocrine cells of the gastrointestinal tract after food ingestion and they improve glucose influenced insulin secretion and suppress glucagon secretion. Glucagon-like peptide1 (GLP-1), released from L cells in the small intestine is the most potent in cretin. It induces insulin secretion only when the blood glucose level is above the fasting level. In cretin analogues are pharmacologic agents that increase the activity of endogenousGLP-1 enhanced insulin secretion.

INSULIN RESPONSE CURVE

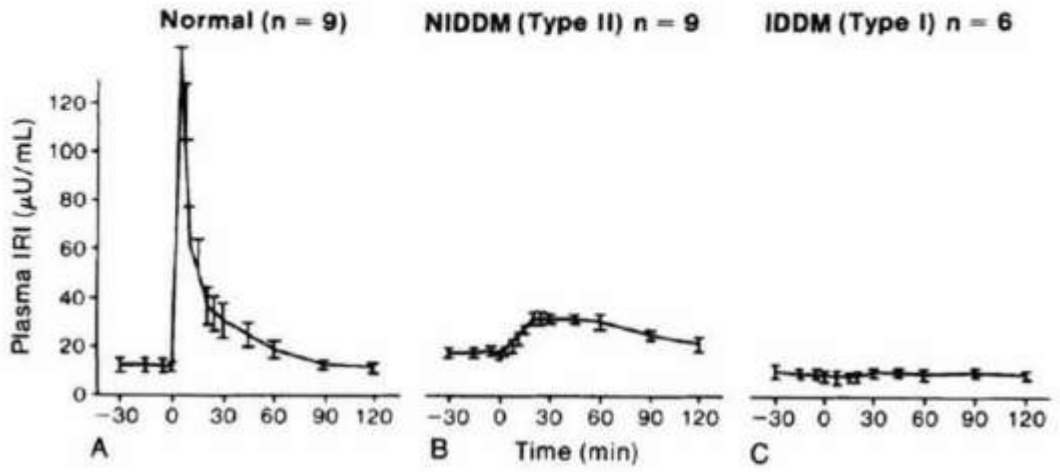
Insulin response occurs in two phases.

First phase insulin response: it occurs within the first ten minutes following a glucose injection. It is due to the release of stored insulin.

Second phase insulin response: begins just after the first-phase response has stopped. It is due to the continuing insulin synthesis and its release.In most type 2 Diabetes patients the second phase response is conserved while the first phase response and the normal pulsatile insulin secretion are lost (Boura-Halfin 2009). In type 1Diabetes patients there is very low or nil insulin response.

Plasma insulin response to glucose administration. An intravenous pulse of 20g Insulin was administered at time 0. The values in the curve before time 0 indicate baseline values.

Response of plasma insulin to glucose stimulation



INSULIN ACTION

After insulin secretion into the portal venous system, ~50% is cleared and by the liver. There remaining insulin enters the systemic circulation and binds to specific receptors on target sites. The molecular basis of Insulin action is still not completely clear (TaniguchiCM, 2006, RajpathakSN, 2009). On binding with the insulin receptor intrinsic tyrosine kinase activity is stimulated, leading to receptor auto phosphorylation and phosphorylation of intracellular 19 signaling molecules, such as insulin receptor substrates (IRS1, 2, 3&4; Shc &Gab-1). IRS and other adaptor proteins initiate a sequence of phosphorylation and Dephosphorylation reaction, causing the widespread metabolic and mitogenic effects of insulin. One of the cascades is the activation of the phosphatidyl inosito l-3′-kinase (PI-3-kinase).

Pathway leading to translocation of GLUT4 to the cell surface, resulting in glucose uptake by skeletal muscle and fat. Insulin activate so the r such signaling pathways inducing glycogen synthesis, protein synthesis, lipogenesis, and modification of various genes in insulin-responsive cells.

INSULIN LIKE GROWTH FACTORS

Two types of Insulin-like Growth Factors (IGF) are known. IGF 1 & 2are polypeptides related to Insulin structurally (Samani, 2007). The IGFs are found to be involved in cancer development as suggested by the accumulating recent evidences. (Hwa1999) IGF1 mediates growth hormone action and is a major controller of cell growth and differentiation. The function of IGF 2 is not clearly defined. They exert their actions by binding with specific IGF

1 and 2 receptors. The circulating concentration of IGFs is 1000 times that of Insulin still they are kept in active by binding with nearly six families of specific binding proteins (CombettesMM 2006). The role of IGFs in normal metabolism of carbohydrates is not understood but administration of exogenous IGF produces hypoglycemia. In adequate IGF1 causes dwarfism.

PATHOPHYSIOLOGY

Two main pathological defects have been identified (KahnCR, 1994.Sacks.Flier, 1992)

1. Insulin resistance–insulin's ability to act on peripheral tissues is reduced
2. β-cell dysfunction-pancreas cannot sufficiently produce insulin to match insulin resistance.

It's now clearly established that type 2 DM is a heterogeneous syndrome and there is no single cause for the incidence and progression of diabetes.

INSULIN RESISTANCE:

Defined as—a decreased biological response to normal concentrations of circulating Insulin (NCEP 2001). It is due to defective Insulin action. Insulin resistance can assume two spectra: Euglycemia (with high endogenous Insulin) and Hyperglycemic (despite large doses of exogenous Insulin)(Carr,2008) Insulin Resistance Syndrome (Metabolic syndrome/ syndrome X).

It s established if a person meets three or more of the following criteria. (Carr, 2008)

- Abdominal obesity (waist circumference> 35 inches in females or > 40 inches in males)
- TGL > 150 mg/dL
- HDL < 50mg/dL (females) or < 40mg/dL (males)
- Blood pressure ≥ 130/ 85mmHg
- Fasting plasma glucose ≥ 110mg/dL

LOSS OF β-CELL FUNCTION: Hyperglycemia over a period of time renders the β-cells unresponsive to its increase. This is termed glucotoxicity (zimmetPZ, 1988, stern 1991.kulkarni, 1999). The degree of unresponsiveness correlates with glucose concentration and duration of hyperglycemia. But reverting to euglycemia rapidly restores the defect. Increased serum fatty acid has also been found

to be involved in the β-cell failure (Kulkarni,1999) .Recent evidences suggest that insulin resistance could lead to alterations in the β-cell production of insulin ,type2 diabetes (knowler, 2002).

ENVIRONMENT

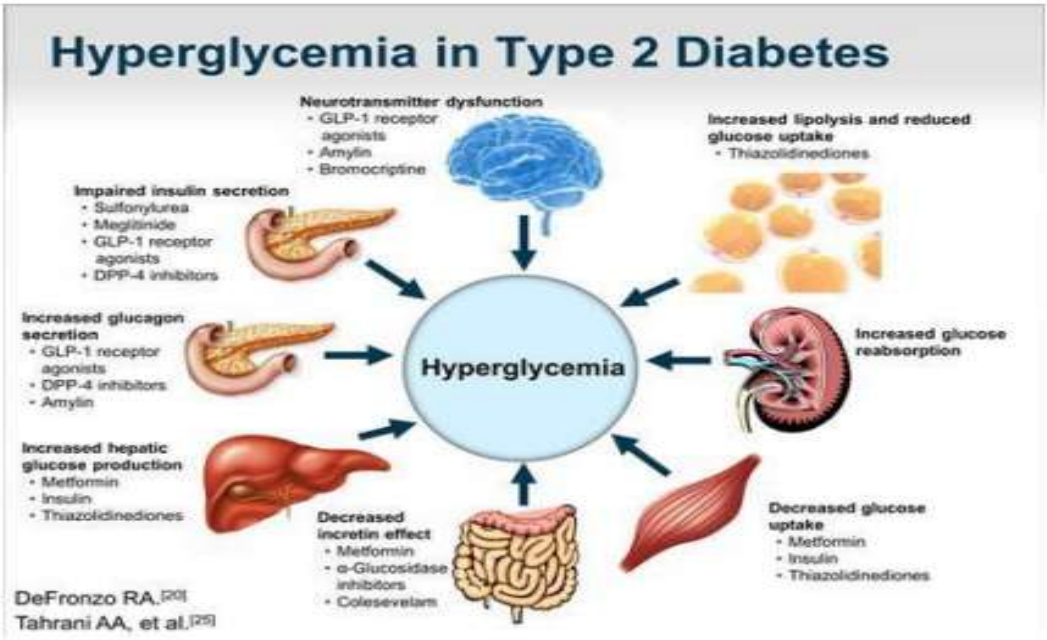
Diet and exercise are the most important environmental factors implicated in the pathogenesis of type 2 Diabetes. Besides the fact that 60- 80% of diabetic individuals are obese, Diabetes develops only in less than 15% of obese people. But almost all obese individuals are hyper insulinemic and have insulin resistance. In some randomized studies life-style changes (enhanced Physical activity) in subjects with IGT decreased the incidence of type2 diabetes (TuomilehtoJ.2001).

With every 500 kcal raise in energy expenditure in a day, a reduction of 6% in age adjustable risk for type 2 diabetes has been noticed (Burtis, 2012). This is because physical activity enhances the sensitivity of skeletal muscles and adipose tissue to insulin.

OMINOUS OCTET

The pathogenesis of type 2 diabetes has broadened from the triumvirate of β cell, muscle, and liver related defects (DeFronzo, 2009) to the ominous octet‖ described in the 2008 Banting Lecture (Mudhaffar, 2013) The most recent and important player in the pathogenesis of Type 2 Diabetes Mellitus is the brain. The brain and its seven accompaniments form the―Ominous Octet.The components and their mechanisms in the pathogenesis of type2 DM are Muscle- Decreased glucose uptake, Adipose tissue- Increased lipolysis, Pancreatic β-cells- Reduced Insulin production ,Liver- Increased glucose synthesis, Brain- Neurotransmitter dysfunction 25, Pancreatic α-cells- Increased glucagon production, Kidney- Increased glucose reabsorption, Intestine- Reduced in cretin effect.

It was demonstrated by Porte and colleagues that in rodents Insulin was a powerful appetite suppressant (Schwarttz, 2000.Hedley, 1999) . It is well established that obesity is frankly associated with type 2 DM (Attie,2003.DeFronzo,1988).Obese individuals, whether diabetic or non diabetic, are insulin resistant and hyper insulinemic. In spite of hyper insulinemia their food intake is increased. This indicates that the insulin resistance extends from peripheral tissues to brain as well.



CONCLUSION

This study examined the relationship between cardiovascular risk and type 2 diabetes through the evaluation of oxidative stress and total antioxidant capacity. It is found that insulin resistance is the culprit of hyperglycemia and dyslipidemia in type2 DM which in turn is responsible for the increased oxidative stress. This links type2 diabetics directly in to life-threatening complications of atherosclerosis.

The study there for suggests, the estimation of plasma antioxidants levels with other routine investigations may be useful in the prevention of the diabetic complications. Decreased TAC values could be considered as an early marker in the pathogenesis of complications of T2DM. Astute treatment could improve longevity and quality of life of the patient or can even revert some complications.

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