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Insulin's Function in Health and Disease

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Abstract: *Insulin is a polypeptide hormone that is primarily released by cells in the pancreatic islets of Langerhans. The hormone may work in tandem with glucagon to control blood sugar levels; glucagon has catabolic properties while insulin has anabolic ones. Insulin controls blood glucose levels and causes the liver, muscles, and adipose tissue to store glucose, which causes total weight gain. Insulin plays a crucial role in the initiation and development of many chronic diseases because it modulates a variety of physiological processes.*

Other techniques are based on the exogenous infusion of glucose or insulin, or both, either under steady-state (the insulin suppression test) or under dynamic conditions (the insulin tolerance test, intravenous glucose-tolerance test with minimal model analysis, and constant infusion of glucose with model analysis). Homeostatic model assessment uses fasting plasma glucose and insulin concentrations to derive indices of insulin sensitivity and secretion from a mathematical model.

Keywords: glucose, homeostasis, control, illness, and insulin

I. INTRODUCTION

Insulin was given a name before it was really found. Oskar Minkowski and Joseph von Mering made this observation in 1889 in Germany, sparking the idea that the pancreas may be producing some unidentified molecule that regulates metabolism (1). They found that total pancreatectomy in experimental animals causes the development of severe diabetes mellitus. The case supporting the theory grew stronger over time: It also involved the discovery and clarification of the physiology of internal or endocrine secretions, discoveries of the association between diabetes and damage to the islets of Langerhans, a pancreatic cellular system. By the first decade of the 20th century, it was widely believed that the pancreas' "internal secretion" regulates the metabolism of carbohydrates.(2)In the past, it has been believed that insulin has no effect on the central nervous system (eNS). However, recent research has shown that insulin and its receptors are present in the eNS and has established the physiological, behavioral, and developmental effects of central insulin on the eNS. There is proof that CSF insulin concentrations alter eating habits and body weight, that plasma insulin accesses the cerebrospinal fluid (eSF) rather quickly, and that insulin may function as an eNS neuromodulator. The current review emphasizes recent literature and concentrates on significant unresolved issues and questions about insulin in the CNS. These articles contain references to prior works, but typically only the most recent(3)In addition to its role in diabetes, current research suggests that insulin has major physiological effects on a number of vital human organs, including the brain, heart, kidney, bone, skin, and hair follicles. Insulin promotes bone growth, reduces inflammation associated with osteoporosis, affects the central nervous system, and has pro- and anti-atherogenic effects in the vascular system (4).) Recent developments in insulin research have led to the development of insulin-signaling activators and targeted treatments for various ailments. Metformin, an insulin-receptor activator, has been shown in clinical and laboratory investigations to have kidney-protective characteristics.(5)Similar to how sulfonylurea increased insulin secretion by acting on pancreatic cells, it also increased insulin secretion.(6)A variety of choices are currently available for people with diabetes, including insulin mixes, concentrated insulins, and insulins with alternative administration methods. There are now rapid-acting, short-acting, intermediate-acting, and long-acting exogenous insulin’s available.(7)are not susceptible to measurement directly. Prior investigations into the kinetics of insulin typically examined how
quickly the hormone vanished following a pulse injection. The biological half-times of insulin have been estimated to be between 3 and 35 minutes.(8,9)The current research show that chronic hyperinsulinemia in humans can result in

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insulin resistance. After a 40-hour insulin infusion that raised plasma insulin levels to levels akin to those seen in insulin-resistant diseases like obesity.(10,11)

Insulin Injections:-

Insulin is a hormone that lowers the level of glucose (a type of sugar) in the blood by helping glucose enter the body's cells. Doctors use this hormone to treat diabetes when the body can't make enough insulin on its own. Although researchers are testing other ways to give insulin, it's only available now in a form that must be injected just under the skin. There are many types of injectable insulin, both short- and long-acting. Most people with diabetes take insulin injections based on their blood glucose levels, according to a plan that they've worked out with their doctor.

Fig:1. Insulin Injection

What are the symptoms of insulin not working properly?(30)

When insulin doesn't work the way it should, it can cause a wide range of symptoms. These symptoms can be severe and develop very quickly in type 1 diabetes.

On the other hand, the symptoms come on a lot more slowly in type 2 diabetes. It can take years for symptoms to develop. Often, people are diagnosed with type 2 diabetes before they notice any symptoms. Insulin resistance and prediabetes usually have no symptoms. Some people with prediabetes may have darkened skin in the armpit or on the back and sides of the neck, a condition called acanthosis nigricans. Many small skin growths called skin tags often appear in these same areas.

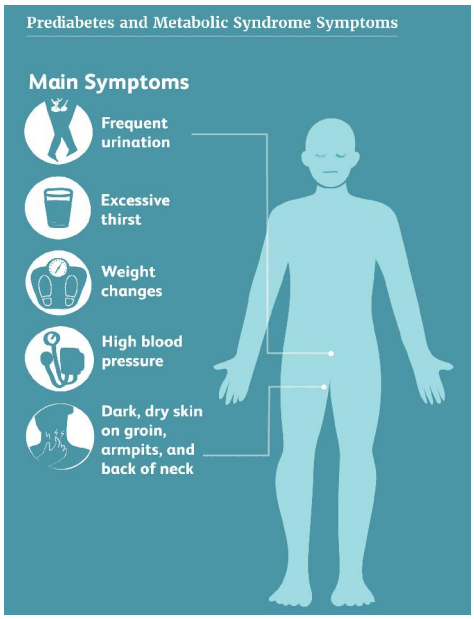

Fig: 2. Syndrom Symptoms

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When symptoms are present in either type 1 or type 2 diabetes, they can include:

- Extreme thirst
- Dry mouth
- Increased hunger
- Unintentional weight loss (type 1)
- blurry vision
- fatigue
- numbness and tingling in hands and feet (type 2)
- Slow-healing wounds
- More infections than usual
- Difficulty breathing or swallowing
- Weakness
- Muscle cramps
- Abnormal heartbeat
- Large weight gain in a short period of time
- Swelling of the arms, hands, feet, ankles, or lower legs

Another common sign of insulin resistance and prediabetes or diabetes is acanthosisnigricans, which are velvety hyper pigmented plaques (thickened skin) commonly found on the neck or in the armpits. It is one of the earliest telltale signs of high glucose levels.

Classification of Insulin

The 5 types of insulin are:-

- rapid-acting insulin.
- short-acting insulin.
- intermediate-acting insulin.
- mixed insulin.
- long-acting insulin. 25- 35 mU/1)

Regulation of Insulin Secretion:-

Understanding how insulin secretion is regulated requires knowledge of the physiology of insulin-producing cells. A peptide hormone called insulin is released by cells in the pancreas. One to two million pancreatic islets can be found in the human pancreas.(12)

The first stage in the metabolism of glucose is the phosphorylation of glucose by the enzyme glucokinase (GCK). Since insulin secretion is correlated with glucose phosphorylation by GCK, GCK gene failure or aberration causes a reduction in glucose-mediated insulin release, which in turn causes glucose intolerance or diabetes. While few studies have been reported in humans, research utilizing rodent models has contributed significantly to our understanding of insulin secretion.This variation could be explained by variations in the Km values of various isoforms of glucose transporters.(13)

Insulin signaling :-

Both internal and external tyrosine kinase domains make up the insulin receptor. Specific intracellular tyrosine residues are autophosphorylated when insulin binds to the extracellular region of the receptor, activating its kinaseactivity. A variety of scaffolding proteins, such as insulin receptor substrata (IRS) proteins, Cbl (casitas B-lineage lymphoma), or Cbl associated protein (CAP), can bind to intracellular receptor sites and get phosphorylated as a result of this autophosphorylation phase.(14,15).

Numerous preventative measures and multifactorial approaches employed by nephrologists, diabetologists, dieticians, and skilled diabetes specialists to provide a multidimensional care program slow the advancement of kidney illnesses in the treatment of diabetes and nephropathy. The kidneys should be protected from harm by using metformin's protective

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capabilities against a variety of renal illnesses, such as autophagy and AMP-activated protein kinase (AMPK) signaling pathways, according to recent studies.(16)Metformin also promotes hypoglycemia by lowering intestinal glucose absorption, enhancing glucose uptake through hepatic glycogenesis, and using peripheral tissues that improve insulin sensitivity. Sulfonylureas, a different sulfonylurea-receptor-binding medication, have an impact on pancreatic cells, increasing insulin secretion and perhaps causing hypoglycemia(27). Furthermore, metformin promotes hypoglycemia by lowering intestinal glucose absorption, enhancing glucose uptake through hepatic glycogenesis, and using peripheral tissues that improve insulin sensitivity.(18)

Physiological Roles of Insulin:

Insulin's primary function is to balance micronutrient levels during the fed state in order to control the body's energy supply (19). Transporting intracellular glucose to tissues and cells that depend on insulin, such as the liver, muscle, and adipose tissue, requires the hormone insulin. Any imbalance in exogenous energy sources causes the lipids stored in adipose tissue to break down, which ultimately speeds up insulin release. The key part that insulin plays in regulating a number of organ and tissue processes that are insulin-dependent is covered in the sections that follow.Although the specific method by which insulin controls hepatic function is yet unknown, it has been hypothesized that insulin affects the liver both directly and indirectly. Both in vitro and in vivo experimental models have shown that it can directly connect with hepatic insulin receptors and subsequently activate insulin signaling pathways in the liver(20).

Role of Insulin in the Regulation of Liver Function:-

Insulin acts to increase uptake of glucose in the liver, decreasing gluconeogenesis and promoting glycogen synthesis. Thus, the hyperglycemia in the presence of high doses of insulin cause excessive production and storage of glycogen in the liver.

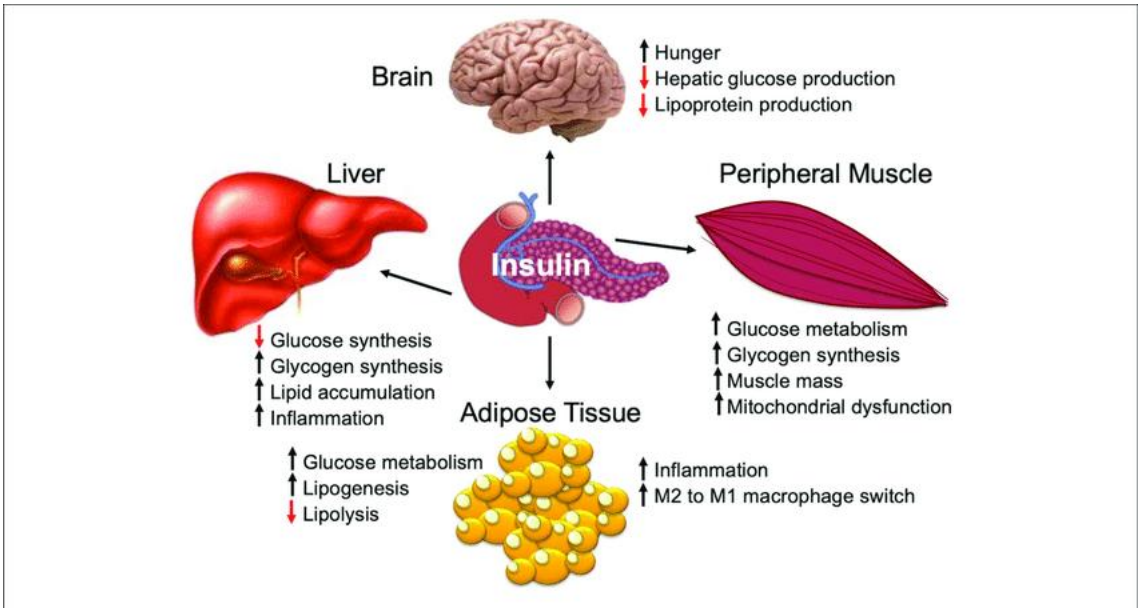

Fig: 3. Role Of Insulin in Liver Function

The key organ where insulin acts is the liver. The most vital of insulin's many crucial jobs is maintaining nutritional homeostasis, which involves turning extra glucose into fatty acids and precursor triglycerides (TAG) and creating glycogen from glucose.It has been shown that in a healthy person, insulin-driven gluconeogenesis in the liver, which also almost completely silences glycogenolysis, can reverse up to one-fifth of hyperinsulinemia. Gluconeogenesis is a process that insulin uses to make glucose for catabolic processes; it directly affects the liver but indirectly affects other tissues.(21)

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Role of Insulin in the Regulation of Skeletal Muscle Function:-

Skeletal muscle is no exception to the fact that insulin serves a number of crucial roles in every part of the body. One of the most active tissues in the human body, skeletal muscle accounts for around half of the body's weight and two-thirds of its protein.(22)This muscle is made up of bundles of highly organized muscle fibers (myofibers), each of which represents a single muscle cell and contains numerous myofibrils. Skeletal muscle uses around 70% of the glucose from whole-body glucose absorption, while the liver uses the remaining 30% through an insulin-dependent mechanism. Postprandial hyperglycemia stimulates insulin production from

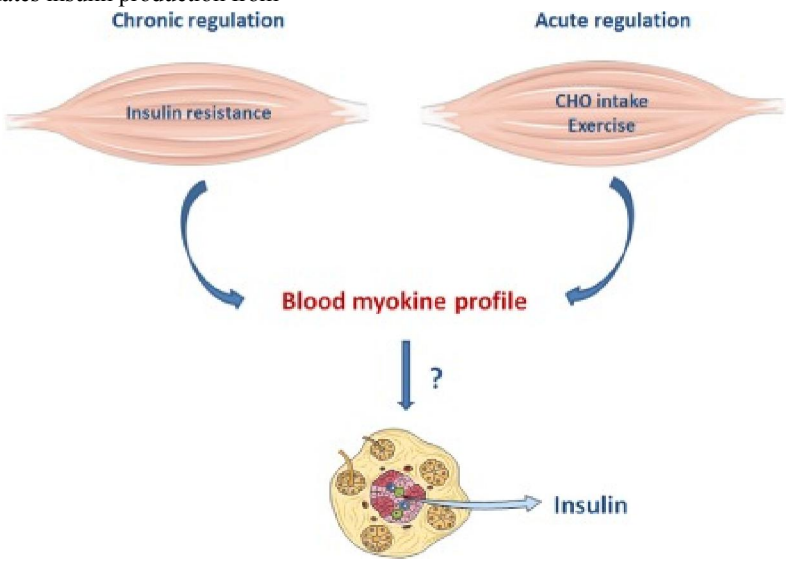

Fig: 4. Role of Skeletal Muscle Function

the pancreas, and a rise in plasma insulin concentration causes skeletal muscle to take in and use glucose. Poor muscle strength and function is connected with type 2 diabetes, according to epidemiological and experimental data.. Given that skeletal muscle is a significant venue for the disposal of glucose, quantitative reductions in muscle volume in type 2 diabetes patients may negatively impact overall glucose metabolism; as a result, insulin therapy may enhance ideal glucose goals.(23)

Major Physiological Roles:-

Brain:-

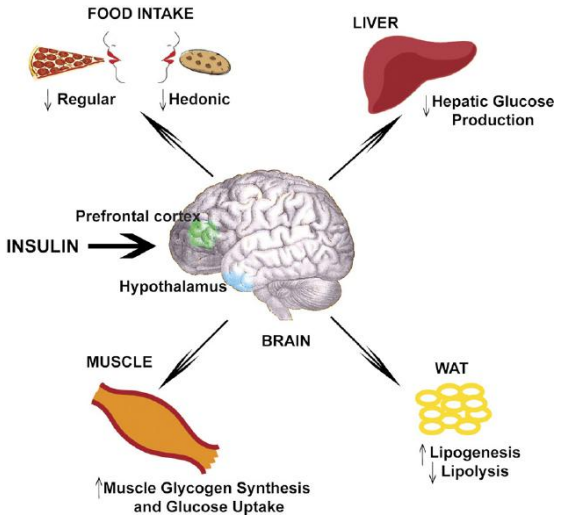

Fig:5. Major Physiological Roles Brain

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Because insulin has no effect on the brain's ability to absorb glucose, this organ was first thought to be insulin insensitive. The choroid plexus, pineal gland, and pituitary are just a few of the brain locations where insulin may boost glucose uptake, according to mounting data.(24)The exact mechanism causing these effects is unknown, but it has been hypothesized that the central nervous system's inherent gender differences may cause it to react differently to the acute insulin administration and subsequently regulate energy homeostasis and memory functions in a sex-dependent manner. In line with these findings, past research revealed that both obese men and women experience an equal impact on insulin transit into the brain. However, compared to men, women are more at risk of having dementia. Additionally, healthy subjects receiving acute and chronic (8 weeks, 160 IU per day) insulin intranasal treatment have shown improved cognitive functions.(25,26)

Kidney:-

The kidney's role in glucose metabolism. The kidney together with the liver is 1 of 2 body organs provided with gluconeogenesis capability and roughly contributes to 20% glycogen production in normal physiology. In the kidney, gluconeogenesis takes place in the cortical cells while the medullary cells metabolize glucose. It is relevant to observe that insulin inhibits while adrenaline stimulates glucose production in the kidney. Glucagon does not affect renal glucose production. Renal glucose metabolism supports glutamine extraction from tubular cells for the production of glutamic acid and ammonia (NH 3). It is an energy-based metabolic passage that plays a pivotal role in urine acid excretion (NH 4)

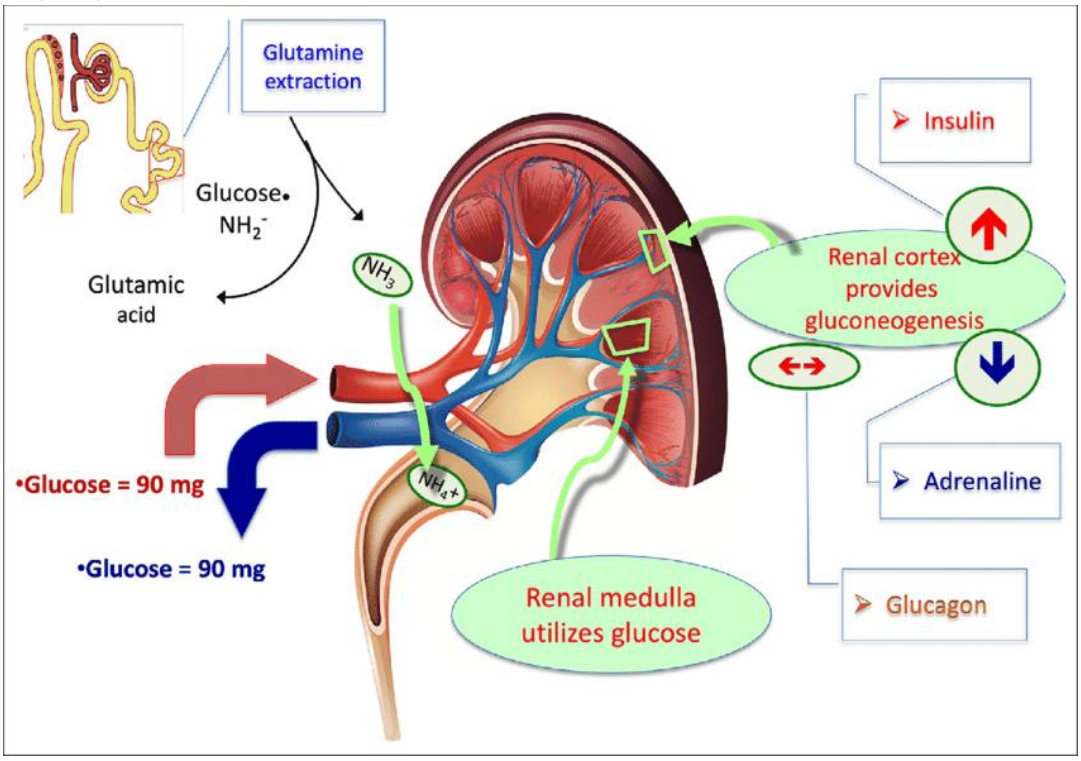

Fig: 6. Major Physiological Roles Kidney

The 1950s saw the first suggestions of insulin's effects on the kidney. Kidney homeostasis is one of the metabolic processes that insulin affects. Recent years have been a rise in studies into kidney IR's physiological significance. Renal epithelial cells in diabetic and insulin-resistant rat models showed reduced expression of IRs and phosphorylated IRs. A high-fat diet decreased

the expression of IRs in the kidney cortex of mice and type 1 diabetic rat models as well as type 2 diabetic people. Additionally, different IR deletions that targeted specific kidney epithelial cells in mice changed their systemic and renal metabolism. Angiotensin II (Ang-II), which interacts with angiotensin type 1 receptors in the renin-angiotens in system,

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mediates a variety of physiologic effects on many tissues, including renal tissues. Insulin resistance develops because Ang-II prevents PI3K signaling from being activated by insulin.(27)

Role of Insulin in Pathology:-

Insulin Deficiency:-

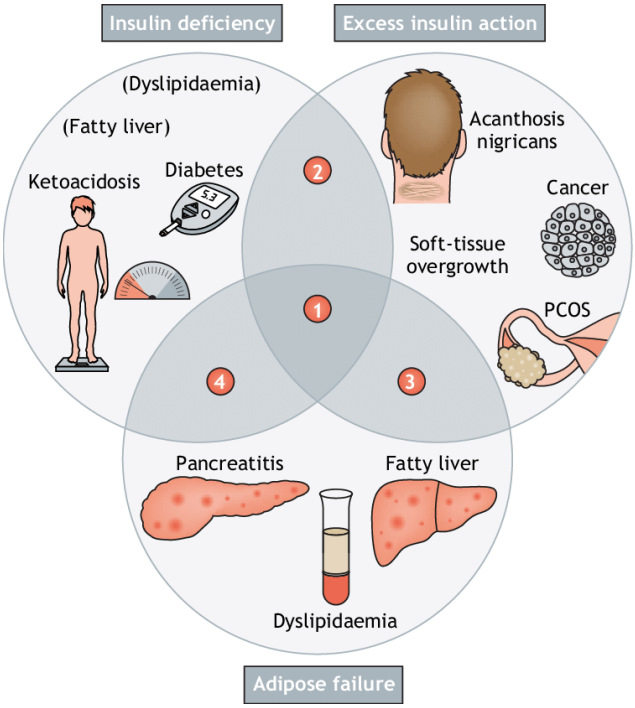

Fig: 7. Role of Insulin in Pathology Insulin Deficiency

The release of insulin and its functional control are both significantly influenced by nutrient availability. By increasing the excessive ROS production that hinders insulin action, a diet high in fatty foods has the potential to change the physiology of the mitochondria. It has been discovered that insulin-resistant people who are exercising in an aerobic state can simultaneously enhance mitochondrial biogenesis and efficiency. People over 30 with type 1 diabetes, which is characterized by a severe insulin shortage, share clinical and molecular characteristics with younger people, although the illness is commonly overlooked.Patients with obesity and insulin resistance should be prepared for their livers to overproduce glucose and accumulate lipids.As a result, insulin regulates both glucose and lipid metabolism via extrahepatic and intrahepatic routes, and both pathways interact to regulate insulin signaling. Direct hepatocyte insulin transmission is necessary for lipogenesis but not for inhibiting the synthesis of glucose.(28)

The Role of Insulin Signalling in Cancer:-

Systemic factors such as insulin activate the same signalling pathways as some of the most recurrent mutations in human cancer. The phosphoinositide 3-kinase (PI3K) signalling cascade, which is activated by insulin, regulates cellular metabolism and cell fate decisions, including cell survival and proliferation

There is growing evidence that receptor tyrosine kinases play a role in the development of cancer. Evidence suggests that Insulin receptors are over-expressed in cancer cells, especially those of the breast cancer. Increased insulin receptor expression is associated with shorter survival in breast cancers. Insulin receptors are frequently over-expressed and highly phosphorylated in breast tumors generated by diabetic mice.The receptor tyrosine kinase inhibitors (RTKIs) sunitinib, lapatinib and gefitinib have all been shown to reduce tumor size and inhibit cell proliferation in various types of cancer cells.

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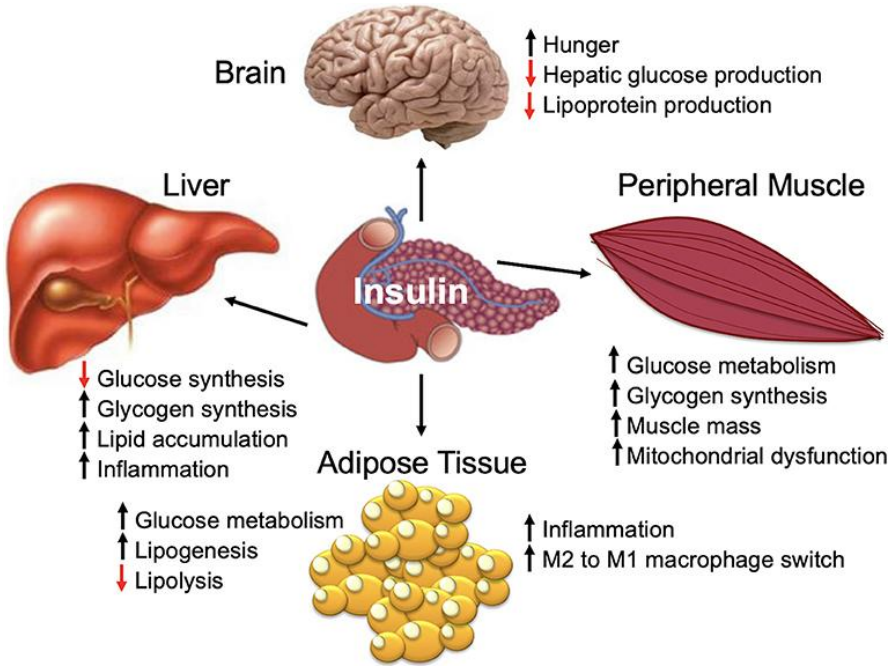

Fig: 8. The Role of Insulin Signalling in Cancer

Insulin signaling promotes cell division in tumors. Insulin can also bind to the insulin-like growth factor 1 (IGF1) receptor which consequently activates the mitogenic signaling pathways that promotes cellular growth and proliferation. Insulin-like growth factors (IGFs) are essential for growth and survival that suppress apoptosis and promote cell cycle progression, angiogenesis, and metastatic activities invarious cancers. The IGFs actions are mediated through the IGF-1 receptor that is involved in cell transformation induced by tumour

Hyperinsulinemia:-

The amount of insulin in the blood is higher than what's considered healthy. On its own, hyperinsulinemia isn't diabetes. But hyperinsulinemia often is associated with type 2 diabetes. Insulin is a hormone that the pancreas makes.

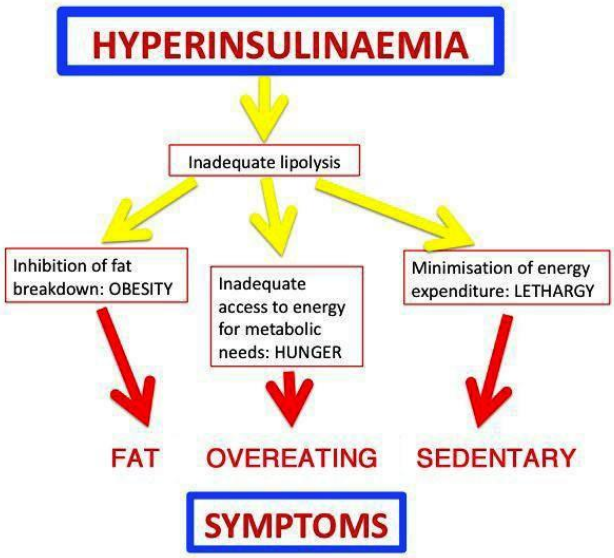

Fig: 9. Hyperinsulinemia

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Hyperinsulinemia (hi-pur-in-suh-lih-NEE-me-uh) is a condition in which there is more insulin in the blood than is normal. Hyperinsulinemia is not diabetes on its own. But type 2 diabetes and hyperinsulinemia frequently go hand in hand. A hormone produced by the pancreas is insulin. It aids in blood sugar regulation.

Although there is frequently no obvious sign of hyperinsulinemia, symptoms can include:

- Weight gain.
- Cravings for sugar.
- Intense hunger.
- Feeling frequently hungry.
- Difficulty concentrating.
- Feeling anxious or panicky.
- Lacking focus or motivation.
- Fatigue.

Weight gain:-

When a person takes insulin as a treatment for diabetes, they may gain weight. This is because their body begins absorbing glucose again and converting any excess into fat. If treatment does not manage diabetes well, and blood glucose levels are too high, this weight gain can occur.

Fig: 9. Weight gain

Type 2 diabetes, obesity, chronic inflammation, hypertriglyceridemia, and Alzheimer's disease are all directly impacted by hyperinsulinemia.According to a study, even at low glucose levels, higher dietary fatty acids enhance intestinal enterocyte incretin secretion, further raising GSIS. As a result, fatty acids are crucial in the development of diabetic hyperinsulinemia. Damaged myocardial insulin signaling, abnormal mitochondrial function, endoplasmic reticulum stress, impaired calcium homeostasis, abnormal coronary microcirculation, activation of the sympathetic nervous system, activation of the renin-angiotensin-aldosterone system, and maladaptive immune responses are characteristics of the diabetic cardiomyopathy found in hyperinsulinemic states. These pathophysiological changes result in oxidative stress, fibrosis, and hypertension(29)

II. CONCLUSIONS

Clinical practice has advanced our knowledge of diabetes in several significant ways in recent years. Our understanding of insulin has grown over time, and it is now obvious how crucial a function it plays in the control and secretion of insulin in the human body. We covered the function of insulin in several physiological systems in this post. We also extended the horizon of insulin by shedding light on how this hormone affects the energy balance of a number of significant body organs. However, there is still a lot we don't know about insulin, particularly with regard to hyperinsulinemia. These regions serve as an important ideal road map for future study since they are critical to insulin control, secretion, and the chronic disorders connected to insulin.

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