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Insulin Resistance: A Getting route to Metabolic Dysfunction and Cancer: A review

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ABSTRACT

The impaired reaction of insulin target organs to normal insulin concentrations is known as insulin resistance. One of the main pathologic characteristics of several metabolic illnesses, including type 2 diabetes mellitus, is the process. What causes insulin resistance specifically? No one actually knows, but many valid explanations have been put out. In addition to summarizing the function of insulin in glucose metabolism in the traditional metabolic organs, this review will list the mechanisms (inflammatory response, end-of-retinoid stress, ectopic lipids in the liver, and skeletal muscle) that have been proposed to explain insulin resistance. The other one makes suggestions for possible treatment approaches for the inflammation linked to insulin resistance. The other suggests that medicine may be used to treat any insulin resistance. the failure of adipose tissue to store energy may be the primary cause of insulin resistance. Since there is currently no gold standard test for insulin resistance, it is challenging to define the condition clinically. However, the metabolic effects of insulin resistance, as outlined by the metabolic syndrome and insulin resistance syndrome, are a clinical sign of insulin resistance. Gaining a better understanding of the effects of insulin resistance and the syndromes that arise from it is the aim of this work. Insulin resistance, which can lead to cancer and a host of other hormone-related problems, is caused by DNA damage.

KEYWORDS : Insulin resistance , polycystic ovary syndrome, genetic , cancer, DNA Damage, and Obesity.

INTRODUCTION

When the liver, adipose tissue, and muscle cease responding to increased insulin levels in response to a decrease in blood glucose, a physiological condition known as insulin resistance develops. Among other modern illnesses, it is also thought to be the cause of metabolic syndrome, which includes atherosclerosis, type 2 diabetes, and nonalcoholic fatty liver disease (NAFLD). Increased plasma glucose levels outside the body are one of the primary clinical indicators of type 2 diabetes (T2DM), and they appear before insulin resistance. In prediabetic hyperinsulinemia, insulin levels increase to ensure adequate availability for normal activity, but they are not significantly impacted by a persistent condition of β-cell failure that progresses to diabetes by hyperbolic therapy. Several theories are commonly accepted as credible, despite the fact that the precise cause of insulin resistance is unknown. In addition to discussing several possible causes of insulin resistance, such as the ectopic accumulation of lipids in the liver and skeletal muscle, this article emphasizes the function of insulin in the metabolism of glucose in metabolic tissues, including the adipose,

liver, and skeletal muscle. Furthermore, we propose future therapy approaches that particularly target ectopic fat deposition in the liver and enhance the energy used by the skeletal muscles in order to address fat-induced insulin resistance[1].

The three primary body parts that show insulin resistance are skeletal muscle, the liver, and adipose tissue. The body's tissues lose their sensitivity to insulin signals when they consume too many calories over time. Up to 70% of the glucose utilized by the circulation can be made up of skeletal muscle using the hyperinsulemic-euglycemic clamp. Reduced muscle tissue absorption of glucose is a direct consequence of muscular insulin resistance. Glucose is transported by muscle to the liver, where it is converted into DNL. An increase in glucose substrate also contributes to hepatic insulin resistance. Insulin resistance is increased throughout the body when DNL rates are higher. Moreover, they raise plasma triglycerides and create an environment of excess energy substrate, which results in ectopic fat deposition in and around [2].

Insulin-Receptor

Insulin begins to function when it attaches to its receptor, which is found on the cell membrane of the target cell. The two β-subunits and the two extracellular α-subunits of the heterotetrameric protein INSR are joined by disulfide bonds. The α- and β-subunits are produced from a single precursor via proteolytic cleavage. Alternative splicing of the INSR mRNA results in the production of two different isoforms: isoform A (INSR-A) and isoform B (INSR-B). The carboxy-terminal (C-terminal) portion of the α-subunit of INSR-B has a 12-amino-acid sequence, whereas INSR-A does not. These isoforms also alter the site of expression. The primary sites of INSR-A expression are hematopoietic cells, tumor cells, the central nervous system, especially the brain, and embryonic and fetal tissues. The highest levels of INSR-B expression are found in the liver and insulin-targeted tissues, including muscle, adipose tissue, and the kidneys. INSR-A predominantly mediates mitogenic effects, whereas INSR-B primarily mediates metabolic effects [3]. There is also the hybrid receptor. In this case, the heterotetramer is formed by the α/β dimers of insulin-like growth factor-1 receptor (IGF-1R) and INSR. Compared to insulin-like growth factors-1 (IGF-1) and II (IGF-2), insulin has a reduced affinity for binding to the hybrid receptor [4].

Substrates for Insulin Receptors:

When insulin binds to the α-subunit of INSR, it changes its conformation. This conformational shift activates phosphotyrosine-binding proteins by autophosphorylating tyrosine residues and activating tyrosine kinase in the β-subunit [5]. Among the substrates of INSR are proteins belonging to the insulin receptor substrate (IRS) family. These proteins are referred to as IRS-1 through IRS-6. Humans exhibit significant IRS-1 and IRS-2 expressions. PTP-1B, GRB-10, GRB receptor-bound protein-2 (GRB-2), Shc-transforming protein (Shc), and SH2B adapter protein-2 (SH2B2) are additional insulin receptor substrates [6]. Two significant signaling pathways are activated upon phosphorylation of these substrates: the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathway and the mitogen-activated protein kinase (MAPK) pathway. Shc phosphorylation promotes the Ras-MAPK

system, whereas IRS protein phosphorylation mostly activates the PI3K/AKT pathway [7].

Insulin Signaling Pathways Inside Cells:

Among the several physiological functions that insulin controls is the tyrosine kinase insulin receptor (INSR). Enzymes that regulate growth and metabolism are activated when the substrates of the insulin signaling pathways phosphorylate due to active INSR. Insulin resistance can result from disruptions in many signaling pathways.

1. 1. The signaling pathway between PI3K and AKT: The IRS protein is activated when insulin binds to the INSR and becomes autophosphorylated. AKT/mTOR-network (also known as PKB—protein kinase B—mammalian target of rapamycin complex) signaling is initiated after IRS-induced PI3K activation. Phosphatidylinositol 4,5-bisphosphate (PIP2) phosphorylates atypical protein kinase C (aPKC) and AKT, which phosphorylates phosphatidylinositol 3,4,5-triphosphate (PIP3). AKT participates in several biological functions. Active AKT phosphorylates glycogen synthase kinase, deactivating it and preventing the activity of ATP-citrate lyase and other enzymes, which stops the synthesis of fatty acids and glycogen. By deactivating the mammalian target of rapamycin complex 1, AKT activation phosphorylation promotes protein synthesis. AKT mediates cell survival by inhibiting the proapoptotic pathway. Sterol regulatory binding proteins (SREBPs) are also activated by it; these proteins enter the nucleus and aid in the transcription of genes related to the production of fatty acids and cholesterol. When AKT regulates the cell cycle and the flow of glucose transporters from the intracellular space to the plasma membrane, muscle and fat cells are able to absorb more glucose from the blood [8,9].

2. **The Pathway of MAPK Signaling:**

Another important insulin signaling pathway is MAPK signaling. Its activation is independent of the PI3K/AKT signaling pathway [10]. Adaptor molecules with SH2 domains, such as growth factor receptor-bound protein 2 (Grb2) and Src homology (Shc), occupy the docking sites of activated INSR and IRS proteins. The MAPK pathway is started by IRS-1's interaction with Grb2 [11]. The son-of-sevenless (SOS) Ras guanine nucleotide exchanger factor (GEF) is linked to Grb2. Guanosine diphosphate, an inactive GDP-bound form of Ras that is bound to SOS, is the source of Ras-GTP, an active GTP-bound form of RasActive Ras phosphorylates and activates the MAP kinases MEK1 and MEK2, which in turn activates cRaf. ERK1 and ERK2 are examples of extracellular signal-regulated kinases. Following this, translocated active ERKs are carried to the nucleus, where they phosphorylate and activate transcription factors, such as ELK1, to promote cell division and proliferation and the synthesis of new proteins [12].

INSULIN RESISTANCE MECHANISMS:

Issues with proximal insulin signaling are not commonly associated with IR in most kinds of type 2 diabetes mellitus. Only 2.4% of the total INSRs are needed for a complete physiological response in rat adipocyte insulin-binding assays. However, problems at the receptor or post-receptor level could cause insulin to lose its functionality while in circulation. It has been demonstrated that the

INSR gene contains over 60 mutations. A heterozygous mutant condition associated with type A INSR decreases the tyrosine phosphorylation of the β subunit when it binds to insulin. Anomalies in the generation of anti-INSR antibodies can also cause this. reduced tyrosine phosphorylation of IRS1 was associated with reduced INSR activity in hyperinsulinemic ob/ob mice [13]. For all known physiological activities, insulin binds to the insulin receptor (INSR) on the plasma membrane of the target cell. The INSR receptor tyrosine kinase is a heterotetrameric complex made up of two membrane-spanning β subunits with tyrosine kinase domains each and two extracellular α subunits that bind insulin. The B isoform of INSR is the primary isoform expressed in differentiated muscle, liver, and WAT. It is thought to mediate the majority of insulin's metabolic effects since it is far more selective for insulin. The A isoform, which is formed when exon 11 is spliced, is particularly valuable because of its high affinity for IGF-2 and is often produced during fetal development. Despite having two insulin binding sites, the INSR exhibits negative cooperativity. According to the knowledge currently available, one INSR is bound to and triggered by one insulin molecule at healthy concentrations. The β subunit-induced conformational change unlocks the cis-autoinhibition of the kinase activation loop, allowing Tyr and Tyr to be transphosphorylated in that order. The recruitment of INSR substrates requires the β subunit to be tyrosine phosphorylated on residues in the juxtamembrane area, such as Tyr, after tris-phosphorylation. Signaling events following INSR activation can be classified into two main functional groups: mitogenic signals and metabolic signals. The main source of mitogenic signals is the mitogen-activated protein kinase (MAPK) pathway, a signaling axis that many receptor tyrosine kinases share. It has been looked into in great detail. The opposite is true for the IGF-1 receptor: metabolic processes can be initiated with lower insulin concentrations than mitogenic reactions [14].

Certain Organs and Tissues Have Insulin Resistance:

Insulin stimulates the absorption of glucose by skeletal muscle, a mechanism that is critical to glucose metabolism. Up to 80% of the glucose absorbed by the postprandial blood circulation is absorbed by this tissue. The main abnormality in type 2 diabetes is thus muscle insulin resistance, which may impact metabolism across the body. Insulin resistance in skeletal muscle leads to obesity in animal models when GLUT4 or insulin receptor tyrosine kinase (IRTK) is deleted. Research indicates that anomalies in the insulin signaling system are the source of the reduced glucose transport [15]. Additionally, there are indications that abnormalities in proximal insulin signaling may be the cause of IR in skeletal muscle Impaired activation of PI3K, IRS-1, AKT, and insulin receptor tyrosine kinase may be the root cause of these issues. The discovery that obese people and insulin-resistant animals have lower levels of active IRTK tyrosine kinase in their skeletal muscles lends credence to this idea. Additionally, it was demonstrated that PI3K's IRS-1-associated activity and IRS-1 tyrosine phosphorylation were reduced in insulin-resistant skeletal muscle. An additional study confirmed that insulin-resistant muscle has higher protein breakdown as a result of disruptions in insulin signaling pathways. In db/db mice, an animal model of insulin resistance used in the study, the primary

proteolytic systems, caspase-3 and the proteasome, were activated and there was enhanced protein degradation. Further studies revealed that muscle deterioration is caused by insulin resistance. A mechanism that preventsProtein is broken down by a process that inhibits PI3K/AKT, whose activation starts caspase-3 and the ubiquitin-proteasome proteolytic pathway [16].

Resistance to Insulin in Skeletal Muscle:

Muscular IR may have several effects on the body's general metabolism because skeletal muscle is necessary for insulin-stimulated glucose consumption [17]. In the skeletal muscle of patients with diabetes and obesity, early research showed decreased surface INSR content and decreased purified receptor activity. IR in skeletal muscle has been linked in numerous studies to inadequate GLUT4 protein translocation. Furthermore, IR in skeletal muscle may also result from abnormalities in proximal insulin signaling, specifically in the actions of IRTK, IRS1, PI3K, and AKT. The decreased skeletal muscle activity in obese/diabetic mice[18] lends credence to this. Randle et al. (1963) suggested that a decrease in glucose intake brought on by an increase in fatty acid oxidation causes lipid-induced IR in skeletal muscle. Increases in fatty acid oxidation lead to a decrease in glucose absorption and a buildup of intramyocellular glucose and G6P [19]. The part played by the glucose-fatty acid cycle in lipid-induced IR has been questioned by a number of models. For instance, animals who have double deletions in pyruvate dehydrogenase kinase 2/4 (Pdk2/4) show inflexible glucose oxidation, which suggests that their glucose-fatty acid cycle is inefficient[20].

Furthermore, IR in skeletal muscle may also result from abnormalities in proximal insulin signaling, specifically in the actions of IRTK, IRS1, PI3K, and AKT. The decreased skeletal muscle activity in obese/diabetic mice[18] lends credence to this. Randle et al. (1963) suggested that a decrease in glucose intake brought on by an increase in fatty acid oxidation causes lipid-induced IR in skeletal muscle. Increases in fatty acid oxidation lead to a decrease in glucose absorption and a buildup of intramyocellular glucose and G6P [19]. The part played by the glucose-fatty acid cycle in lipid-induced IR has been questioned by a number of models. For instance, animals who have double deletions in pyruvate dehydrogenase kinase 2/4 (Pdk2/4) show inflexible glucose oxidation. Our muscles weaken and our body's capacity to regulate blood sugar levels declines with age. Skeletal muscle GLUT4 expression and glucose metabolism are reduced in the elderly. This leads to pathological alterations, including reduced insulin sensitivity, aberrant insulin signaling pathways, and reduced insulin-stimulated AKT activity. Numerous pathophysiological alterations are seen in aging skeletal muscle, including oxidative stress, endoplasmic reticulum stress, mitochondrial dysfunction, intramyocellular lipid accumulation, inflammation, autophagy, sarcopenia, and a diminished non-classical axis of the renin-angiotensin system. Even chronic diseases may raise the risk of insulin resistance in skeletal muscle, which would then lead to insulin resistance, aging skeletal muscle is an independent risk factor for insulin resistance [22].

Insulin resistance in polycystic ovary syndrome:

A growing body of research suggests that PCOS and the IR it causes are genetically predisposed. It also implies that intrauterine development limitations or exposure to androgen during critical growth phases may have contributed to

the prenatal origins of PCOS. Although the post-binding issue in insulin receptor signaling is widely recognized, PCOS is a complex and poorly understood condition [23].Impaired insulin action in several target organs, as seen by basal compensatory hypoinsulinemia and a diminished insulin response to glucose excess, is the pathophysiology of insulin resistance (IR) in PCOS. The majority of organ systems and tissues may be impacted by PCOS. Insulin regulates nutrition availability and demand differently in different tissues. One important aspect of PCOS pathophysiology is the production of Hi by tissue IR. In women with PCOS, insulin resistance (IR) specifically and reciprocally impacts metabolic or mitotic pathways in both non-traditional insulin target tissues (ovary and pituitary gland) and classical insulin target tissues (liver, skeletal muscle, and adipose tissue). Furthermore, excess testosterone, inflammatory cytokines, and fat accumulation are additional systemic variables that contribute to the IR process of peripheral tissues [24]. Insulin sensitivity and systemic glucose metabolism are significantly influenced by adipose tissue. PCOS-afflicted women had systemic fat accumulation and significantly greater subcutaneous fat cell volume compared to body mass index (BMI)-matched control women; visceral fat volume was only raised in PCOS phenotypic A patients [25]. Whole-body IR is significantly correlated with increases in visceral adipose tissue volume, in particular [26]. Adipose tissue exposed to infrared light exhibits decreased glucose uptake, fat formation, and a marked inhibition of lipid breakdown. Fatty acid overconsumption exacerbates skeletal muscle and hepatic insulin resistance and causes lipid accumulation [27]. Epigenetic modifications, such as DNA methylation, histone status, and miRNA expression, control insulin resistance in women with PCOS. Regardless of whether they have IR or not, a study found 79 genes with differential methylation in women with PCOS [28], and hypermethylation of the LAMIN gene promoter was linked to IR in PCOS [29]. Small non-coding RNAs known as microRNAs (miRNAs) are involved in the post-transcriptional control of gene expression. miRNAs are crucial genes involved in the regulation of androgen production, inflammation, adipogenesis, and signaling because they are regulators of gene expression. Women with PCOS and healthy women exhibit significantly different levels of miRNA expression [30]. Research has demonstrated that the PI3K/Akt-GLUT4 signaling pathway is impacted by microRNAs released into the bloodstream by adipose tissue macrophages and adipocyte exosomes. The ovary's insulin-sensitive pathway contains Mir-155-5p and related PCOS target genes, and Mir-222 also has a positive correlation with blood insulin levels, indicating that these genes may be used as PCOS biomarkers [31].

Diagnosis:

- Lipopystrophy (acquired, localized, or generalized): Loss of fat tissue brought on by hereditary or acquired factors, which may result in the ectopic deposition of fat in the liver or muscle.
- Polycystic ovarian syndrome (PCOS).
- Obesity: Overweight is defined as having a BMI of 25 to 29.9; class I obesity is defined as having a BMI of 30 to 34.9; class II obesity is defined as having a BMI of 35.0 to 39.9; and class III obesity is defined as having a BMI of 40.

• Hypertension: The most recent ACC/AHA criteria for diagnosing hypertension include a diastolic pressure of at least 80 mm Hg or a systolic pressure of at least 130 mm Hg.

• Hypertriglyceridemia: High triglyceride concentrations (above or equivalent to 150 mg/dL).

- Type 1 diabetes
- Type 2 diabetes

• Other types of glucose intolerance, such as gestational diabetes, impaired glucose tolerance, and impaired fasting glucose[32].

The pathophysiological understanding:

Skeletal muscle, the liver, and adipose tissue are the three main locations of insulin resistance. An ongoing excess of calories causes the body's tissues to become less sensitive to insulin signals. Up to 70% of the glucose utilized by the circulation can be made up of skeletal muscle using the hyperinsulinemic-euglycemic clamp. Reduced muscle tissue absorption of glucose is a direct consequence of muscular insulin resistance. Glucose is transported through muscle in the liver, where de novo lipogenesis (DNL) takes place. Insulin resistance also develops in the liver as a result of an increase in glucose substrateIncreased plasma triglycerides, insulin resistance, and ectopic lipid deposition in and around internal organs are all consequences of higher DNL rates, which provide an environment of excess energy substrate [33].

Severe insulin resistance diseases exhibit a wide range of clinical symptoms in addition to various metabolic traits. By spotting commonalities, clinicians might be better equipped to spot insulin resistance situations. Acanthosis nigricans, a velvety, hyperpigmented thickening of the skin, is another common cutaneous indication of severe insulin resistance, in addition to skin tags. Evidence suggests that elevated levels of circulating insulin interact with the IGF-1 receptor on keratinocytes and dermal fibroblasts, albeit the exact pathophysiology is still understood. Hyperandrogenism and ovarian dysfunction are also common in women. Clinical signs in affected females typically include hirsutism, polycystic ovaries, irregular menstruation, and oligomenorrhea. The pathophysiology of ovarian hyperandrogenism and polycystic ovarian syndrome is linked to the gonadotropin-insulin connection, or hyperinsulinemia. Severe insulin resistance is now known as Acanthosis nigricans, hyperandrogenism, and insulin resistance, or HAIR-AN, and as a subphenotype of polycystic ovarian syndrome. Other clinical features linked to some severe insulin resistance syndromes include hypertriglyceridemia, dyslipidemia, nonalcoholic fatty liver disease, abnormal adipose topography, abnormal musculature, abnormal adipose tissue loss, acromegaloid symptoms, and other growth abnormalities [34].

Genetic factors:

Genetic errors pertaining to substance metabolism, aberrant insulin structure, and other pertinent genetic disorders can be linked to impairment of the intracellular insulin signaling system and insulin-related illnesses [35].

Insulin Resistance-Associated Genetic Loci:

Genes linked to several loci linked to the development of insulin resistance are good biological candidates for association with insulin sensitivity measurements. One of the first genetic variations to be reliably linked to a lower risk of Type 2 diabetes was the proliferator-activated receptor gamma (PPARγ)

variant Pro12Ala [36]. These days, PPARy agonists are used to treat type 2 diabetes (T2D). Energy and fatty acid metabolism-related genes are transcriptionally regulated by a nuclear receptor known as PPARγ. comprehensive investigation of correlation on a population in Europe [37].

An essential part of the insulin signaling system, IRS1 (insulin receptor substrate 1) starts the activation of PI3K in response to insulin. In a European population, insulin resistance and hyperinsulinemia have been linked to the C allele at rs2943641 next to IRS1. The risk allele was linked to lower baseline levels of IRS1 protein and lower PI3K activity following insulin infusion, according to functional investigations, suggesting a causal role for the variation in disease risk. Additionally, lower HDL cholesterol, higher triglycerides, a lower body fat percentage, and insulin resistance have all been linked to the SNP rs2943650, which is next to IRS1. The glucokinase regulator (GCKR) gene, also called the glucokinase regulatory protein (GKRP) gene, binds to glucokinase and prevents it from doing its job. The liver's capacity to remove glucose is regulated by this essential enzyme [38].

Common Metabolic Syndrome Genetic Variation:

Two main methods have been used to search for genetic determinants in the metabolic syndrome: either the disease as a whole or as two parts, or correlations between the separate components of the syndrome have been investigated. Many putative genes were linked to different metabolic syndrome traits through linkage and candidate gene association studies prior to GWAS, but many of these findings were not verified. The majority of genome-wide association studies (GWAS) conducted to date have looked at associations between variants and the various components of the metabolic syndrome because there are many loci linked to type 2 diabetes, 157 loci linked to lipids, more than 90 loci linked to hypertension, and at least 56 loci consistently linked to obesity [39]. Even if the definition of metabolic syndrome employed in each of these GWAS may have contributed to some of the slight overlap, it's interesting to note that many of the genes discovered are linked to lipid characteristics. Variants ZNF259, APOB, LPL, APOA5, CETP, and GCKR have previously been linked to triglycerides, high-density lipoprotein cholesterol, or low-density lipoprotein cholesterol. There is currently insufficient information to identify a pathway or pathways that connect the various components of the condition. using a different method to determine whether the different components are connected by similar metabolic pathways Data from 1193 twin men from the Vietnam Era Twin Study of Aging were analyzed using a new methodology. To determine whether the various components of the metabolic syndrome were linked by shared metabolic pathways, measurements of adiposity (waist circumference and body mass index), blood pressure, insulin resistance (fasting insulin and glucose), and lipids (high-density lipoprotein cholesterol and triglycerides) were employed. Results show that, in addition to insulin resistance, there are common genetic impacts on lipids, blood pressure, and obesity [40].

The Insulin Gene Mutations:

Recessive or dominant mutations in the insulin gene can cause damage to the insulin protein. For instance, dominant mutations that break three disulfide bonds result in the broken secondary structure seen in mature insulin. These

misfolded proteins lead to endoplasmic reticulum stress and pancreatic β-cell apoptosis. Non-functional insulin is produced by recessive mutations in the insulin gene. Patients with the same mutation and those with different mutations have been observed to have different clinical characteristics [41]. Receptor affinity is decreased by 500 times when leucine (ValA3 → Leu) is substituted for a conserved valine in the A chain. This replacement is seen in Wakuama's therapeutic version of insulin [42]. Additionally, PheB24 → Ser (discovered in insulin Los Angeles) and PheB25 → Leu (found in insulin Chicago) are examples of known B chain alterations that have been found [43]. Both insulin bioactivity and the hormone's binding affinity to INSR are markedly reduced by these changes. HisB10→Asp is another mutation that has been demonstrated to increase hormone activity via increased routes. This mutation, however, is identified as proinsulin and linked to hyperproinsulinemia brought on by abnormal protein trafficking [44]. Insulin resistance and pancreatic β-cell dysfunction brought on by genetic factors Inherited insulin resistance problems in humans severe human insulin resistance (SIR) diseases. These disorders are distinguished by high amounts of circulating insulin to overcome insulin resistance and the symptoms that follow, including the skin lesion acanthosis nigricans. Other physical and biochemical traits can be used to identify certain illnesses. Diabetes frequently coexists with chronic complications including ketoacidosis. Because INSR mutations result in receptors with up to 25% of normal insulin binding activity, patients typically live past one year of age, unlike those with leprechaunism. 22 Patients who have Type A syndrome, a milder form of insulin receptor malfunction, live into adulthood with insulin resistance, acanthosis nigricans, and hyperandrogenism in females, which includes hirsutism, irregular menstruation, and masculinization. Mutant insulin receptors can act in a dominant negative manner by generating hybrids with wild-type receptors and suppressing their function in some situations where inheritance occurs in an autosomal dominant pattern [45]. People with Rabson-Mendenhall syndrome can be distinguished from those with Donohue syndrome by their abnormal teeth, fingernails, and thick, rapidly growing scalp hair. Ketoacidosis is one of the chronic problems that commonly takes with diabetes. Because their receptors may have up to 25% of normal insulin binding capacity, people with INSR mutations usually live longer than a year, unlike those with leprechaunism. 22 A lesser form of insulin receptor dysfunction can result in type A syndrome, which causes patients to have insulin resistance, acanthosis nigricans, and hyperandrogenism in females, including hirsutism, menstrual disruption, and masculinization, until adulthood. Mutant insulin receptors can exhibit dominant negative behavior, adhering to an autosomal dominant pattern of inheritance, when they hybridize with wild-type receptors and inhibit their activity [46].

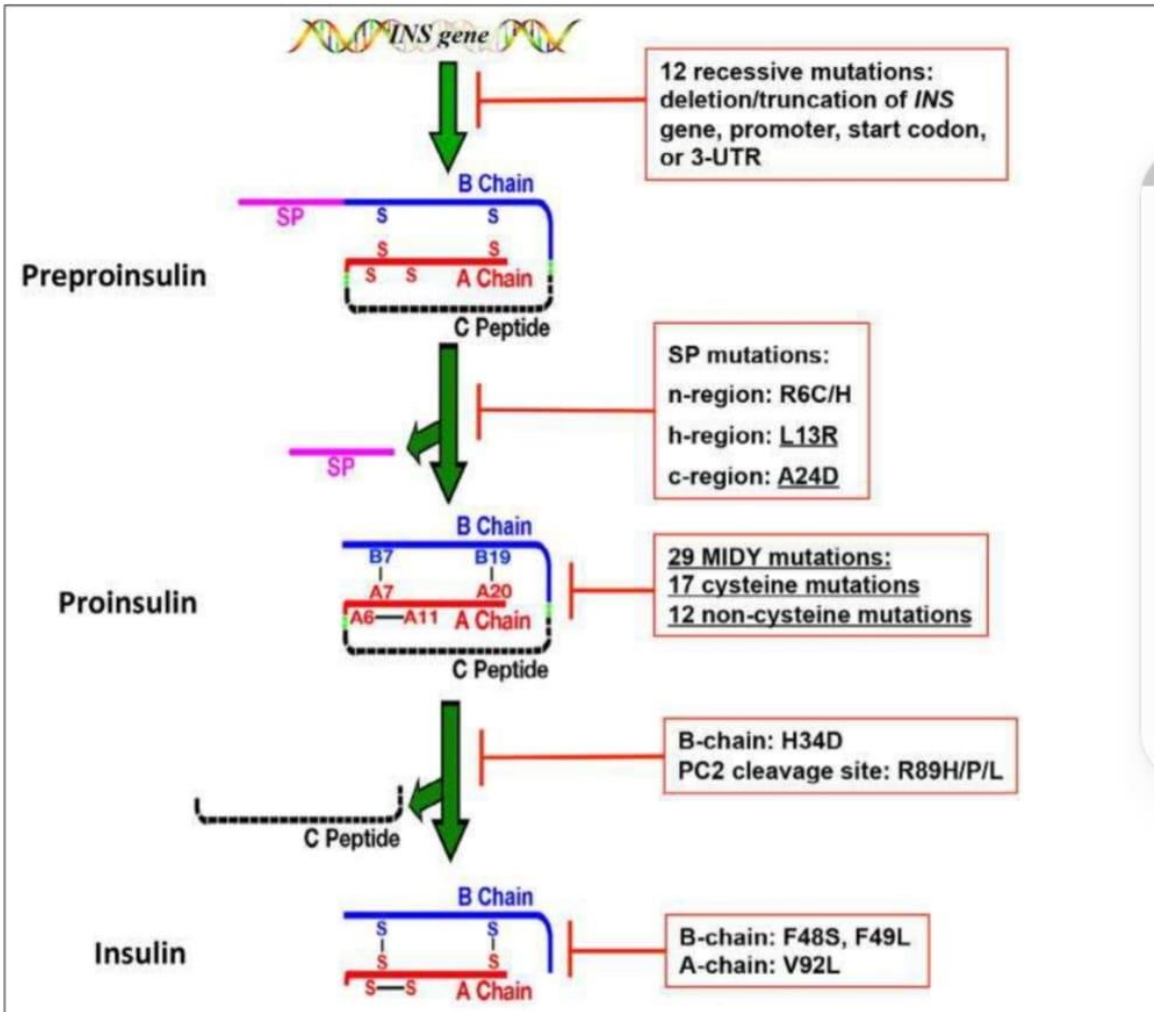

Fig.1 : The impact of mutations in the INS gene on the primary stages of insulin production. The coding sequence encoding every functional domain of the preproinsulin molecule, such as signal peptide (SP, pink), insulin B-chain (blue), C-peptide (black), and insulin A-chain (red), as well as the proteolytic cleavage sites of signal peptidase (SPase) and prohormone convertases (PC1/3 and PC2, green), have been found to contain INS-gene mutations. Every significant step of insulin production is impacted by the mutations. Due to either INS gene deletion or truncation, failure of insulin translation initiation, or instability of insulin mRNA, twelve recessive mutations in the untranslated regions cause an over 80% reduction in insulin output. Preproinsulin translocation into the ER is faulty when SP mutations occur in the n-region (R6C/H) or h-region (L13R). The cleavage of SP is hindered by the mutation at the A24D location. The majority of INS-gene mutations impact proinsulin folding in the endoplasmic reticulum (ER), which hinders the synthesis of three native disulfide linkages that have been evolutionarily conserved: B7-A7, B19-A20, and A6-A11. Proinsulin's ability to be sorted into the controlled secretory route is impacted by H34D. Proinsulin processing is hampered by non-cysteine mutations at the PC2 cleavage site (R89H/P/L). The way that insulin binds to the insulin receptor is impacted by mutations in the A-chain (V92L) and B-chain (F48S and F49L). The highlighted mutations are all responsible for Mutant INS-gene-induced Diabetes of Youth (MIDY). (Liu, et al.,2015)

Problems with the Insulin Gene:

Autosomal dominant mutations in the insulin gene disrupt three disulfides and bonds in mature insulin, affecting the secondary structure of the insulin protein. The β-cell pancreatic islets of Langerhans disintegrate and the endoplasmic

reticulum is stressed due to the disrupted secondary structure of insulin. Reduced hormone synthesis or altered insulin protein function are the results of autosomal recessive mutations. When leucine is substituted for conserved valine in the A chain (ValA3→Leu), a therapeutic form of insulin known as insulin Wakayama is created. This mutation reduces the receptor's capacity to bind insulin by a factor of 500. Insulin's bioactivity is considerably decreased by mutations in the B chains PheB24→Ser (insulin Los Angeles) and PheB25→Leu (insulin Chicago) [48].

Insulin Resistance Factors and Certain Cancers:

There is a connection between IR and metabolic disorders. The result is frequently cardiovascular disease, type 2 diabetes, hypertension, and a number of other metabolic problems. Inflammation, dyslipidemia, hyperinsulinemia, and hyperglycemia are some of the consequences of IR. Cancer patients frequently exhibit metabolic abnormalities linked to IR, which lowers overall survival and increases recurrence rates [49]. A meta-analysis revealed that significant IR was seen in cancer patients. This finding is noteworthy because it suggests that the metabolic dysfunction linked to cancer may be significantly influenced by insulin resistance (IR). This metabolic imbalance raises the chance of cancer death and recurrence. Several epidemiological studies have identified the risks for malignancies such as endometrial, lung, hepatocellular, pancreatic, colorectal, breast, and liver cancers [50]. Obesity has been linked to the development of tumors because of potential changes in hormones and metabolism. Insulin resistance and elevated levels of circulating insulin are prevalent traits in obese individuals. By inhibiting IGF binding proteins, which raises the availability of free insulin-like growth factors, hyperinsulinemia itself encourages carcinogenesis and the proliferation and development of tumor cells. The AKT signaling pathway may be involved in the carcinogenesis produced by insulin and IGF. Studies have indicated that an elevated body mass index (BMI) in overweight people is linked to a higher risk of cardiovascular disease and DNA damage from oxidative stress. generally, hormones, inflammation, telomere length loss, and insufficient DNA repair [51].

Mechanisms of Insulin Resistance and Cancer : Numerous genetic and environmental factors may have an impact on the onset of IR. Mutations in the genes that encode insulin, IGF, or IGFR, as well as in the insulin postreceptor signaling pathway, are examples of genetic variations. Insulin resistance (IR) may be brought on by environmental factors such age, drugs, illnesses, obesity, and overweight [52]. The connection between IR and cancer is influenced by a variety of cellular and molecular processes. Furthermore, there is growing evidence that elevated insulin, in conjunction with IGF1 and IGF2, is crucial for the development and progression of cancer in patients who are insulin-resistant.419 Insulin, IGF1, and IGF2 are the three ligands that specifically attach to the IGF-IR and INSR receptors to activate the insulin receptor substrates. This leads to the activation of the PI3K/Akt/mTOR, PI3K/Akt/FoxO, or Ras/MAPK/(ERK-1/2) pathways, which are critical for the growth of cancer cells and the advancement of cancer. Second, via deactivating GSK3β through the PI3K/Akt signaling pathway, these events promote oncogenic β-catenin signaling, which has been linked to chemoresistance and cancer stemness [53]. Moreover, insulin and IGF1 suppress the synthesis of sex-hormone binding

globulin (SHBG) while increasing the ovarian production of sex steroids, which can both promote cellular proliferation and decrease apoptosis in the endometrial and breast epithelium. Furthermore, since ROS reduces DNA's ability to produce mutation and carcinogenesis, it may be the reason why IR patients have a higher chance of developing cancer. The relationship between IR and various malignancies will become more complex as additional unique biological processes linking IR to cancer are discovered. There might be a novel approach to preventing cancer and related issues with the use of innovative diagnostic and therapeutic techniques[18]. There are two known splice variant isoforms of INSR: the INSR-A isoform, which is expressed in some tumors (like mammary cancers), has a high affinity for binding IGF-II, and the INSR-B isoform is primarily involved in controlling glucose uptake and metabolism through metabolic response signals. Because of these cellular mechanisms, INSR expression and/or activity anomalies can lead to the development of many metabolic and neoplastic illnesses. Obesity, type 2 diabetes, the metabolic syndrome, and polycystic ovarian syndrome are among the common dysmetabolic disorders linked to abnormalities in the INSR signaling system [54].

DNA oxidative damage and obesity:

Numerous studies have demonstrated the connection between insulin resistance, high body mass index, impaired insulin signaling, and pro-inflammatory cytokines. Reduced insulin signalling and associated mitochondrial dysfunction are the outcomes of high intracellular ROS and oxidative stress levels in adipocytes. The eventual result of this is insulin resistance. Obesity-related oxidative stress and inflammation can worsen DNA damage, increase the likelihood of mutations, and impede DNA repair processes. Increased consumption of fatty acids and glucose, which stimulates the NOX4 enzyme and causes adipocytes to produce more ROS, is a hallmark of early-stage obesity. ROS are produced in immune cells by NOX2, which is mediated by intracellular cytokines and is brought on by chronic inflammation [55]. Patients with type 2 diabetes have higher levels of 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG), a biomarker of oxidative DNA damage, in their urine samples [51].Repairing damage to nuclear and mitochondrial DNA, as well as damage from free radicals, is crucial under normal circumstances. However, elevated insulin levels cause free radical activity and DNA damage buildup when the antioxidant system is overworked in obesity and type 2 diabetes [56].

IGFs and insulin:

The effect of insulin and IGFs on the development of cancer has been the subject of several investigations. Examining the role of insulin throughout the development and progression of cancer is intriguing. Exams revealed a higher incidence of obese diabetic individuals with hyperinsulinemia. Additionally, there is a discernible increase in the global population of diabetics being treated with insulin or its analogue. Human studies have demonstrated that the risk of dying from cancer is increased in those with hyperinsulinemia, high IGF-1 levels, or both. It is believed that insulin is an oncogenic factor because of its high correlation with the onset of cancer. Clinical data has connected IR to cancer, although the precise mechanisms behind this reliance remain unclear. There is growing evidence that circumstances such as hyperinsulinemia, aberrant insulin levels, and insulin-mediated signaling can lead to the development and metastasis of cancer [57]. Hyperinsulinemia can be classified into two categories: endogenous and exogenous. Endogenous hyperinsulinemia is caused by decreased hepatic clearance and increased insulin synthesis as a compensatory strategy. This kind of hyperinsulinemia can be caused by metabolic syndrome, obesity, prediabetes, type 2 diabetes, and other hereditary and/or environmental factors. Exogenous hyperinsulinemia occurs when artificial insulin or its analogs are subcutaneously administered into diabetic patients. Research findings from both in vitro and in vivo studies suggested that hyperinsulinemia could be triggered to start and spread cancer [58,59].

Etiologic treatment approaches:

therapy with leptin. In the United States, the only medication explicitly recommended for the treatment of lipodystrophy is methyleptin, an analogue of leptin. Meteleptin therapy decreased appetite and favored metabolic profiles compatible with lowering or even stopping antidiabetic medications in a number of prospective, albeit small and uncontrolled, investigations with widespread lipodystrophy. Nonalcoholic steatohepatitis also got better. Methyleptin users had a decrease in fasting glucose levels as a result of enhanced insulin secretion, hepatic glucose synthesis, and peripheral glucose clearance. Triglyceride levels started to drop a few weeks later, and they had dropped by 60% after a year. Metreleptin has also shown some promise when taken off-label in young individuals with partial lipodystrophy. However, the FDA has prohibited the use of metreleptin for lipodystrophies other than complete lipodystrophy because of the potential for the development of anti-leptin neutralizing antibodies. Although T cell lymphoma has been seen in patients with acquired lipodystrophy receiving metreleptin, it is still unknown whether these occurrences were the result of a drug side effect or the normal course of the disease [60,61]. Tesamorelin, an analogue of growth hormone-releasing hormone (GHRH), has been approved by the FDA to treat metabolic issues associated with visceral fat accumulation in patients with HALS. Tesamorelin is injected under the skin once daily. Visceral fat decreased during therapy, according to several randomized therapeutic trials; however, quick reaccumulation was observed upon medication discontinuation. Care is recommended because tesamorelin may exacerbate glucose intolerance by raising IGF-1 levels [62]. drugs that suppress the immunological system. Historically, treating type B insulin resistance has been difficult, and varying degrees of immunosuppression have

been employed with varying degrees of success Malek et al., (63). outlined how seven individuals with type B insulin resistance experienced remission after taking a combination of rituximab, cyclophosphamide, and pulse steroids. However, immunosuppressive medication was discontinued after around eight months, and the extent of insulin resistance remained unknown. The success may be attributed to additional strategies aimed at removing the troublesome antibody. Furthermore, different levels of efficacy have been documented in the use of plasmapheresis, cyclosporin A, azathioprine, and intravenous immunoglobulins [64].

CONCLUSION

The biology, clinical manifestations, and possible therapeutic approaches of a number of severe insulin resistance diseases have been covered in this review. Research on these uncommon conditions has historically led to new developments in the field of diabetes and has given us valuable knowledge about the physiology and mechanism of action of insulin.

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