International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 1370-1379 www.ijprajournal.com ISSN: 2456-4494

Insulin Resistance Of Body Cells And Its Impact On Different Body Systems

Abhishek* And Raj Kumar Shirumalla
Department Of Pharmacology,SGTUniversity,Gurugram(Haryana) – 122505, India

Submitted: 15-10-2022 Accepted: 31-10-2022

ABSTRACT
The mostcommon metabolic disorderthat affects the body's response towards insulin is diabetes mellitus.It is of two types – Type-1and 2. Type-2 diabetes Mellitus (T2DM)occurs chiefly due totwo factors: failure of insulin-sensitive tissues to respond effectively to insulin and poor insulin production by pancreatic β-cells. Since activity and release ofinsulinare critical for metabolism, the molecular mechanisms involved in insulin production, glucose homeostasis, and recognition are all closely regulated.Type-2 diabetes affects almost 90 to 95%of the diabetic population and is linked to reduced insulin secretion by pancreatic β-cells and insulin resistance in body cells. T2DM is triggered and progressed by metabolic abnormalities like obesity, insulin resistance, hyperinsulinemia, ordyslipidemia.The fundamental elements of T2DM, and the interaction of different body cells in insulin metabolism that contribute to insulin resistance or T2DM, are discussed in this review.

KEYWORDS: Hyperinsulinemia; Insulin resistance; Pancreatic β-cell;Pathophysiology;T2DM.

I. INTRODUCTION

Diabetes is a diverse metabolic illness defined by high blood glucose levels caused by either the body's inability to detectinsulin effectively or a lack of insulin production, or both**[1].**The National Institutes of Health describe diabetes as "a chronic condition in which the body cannot manage blood sugar levels." Diabetes is linked to several risk factors, including vascular damage, heart disease, nephropathy, retinopathy, and organ failure. It can lead to complications associated with multiple organ systems**[2].**Insulin, a hormone produced by the pancreas, promotes Glucose to absorb into the cells for use as energy. India has an approximate 77 million diabetics(as of October 2018, India's population accounted for around 17.5 percent of the world total), making it the world's second-largest diabetic population behind China.According to the International Diabetes, the number will rise to 134 million by 2045.Glucose is the body's primary energy source, particularly for the brain's routine operations. Increased blood glucose levels may be a consequence of lack of insulin, IR (insulin resistance), or a combination of both. InT1 Diabetes Mellitus, autoreactive T-lymphocytes attack insulin-secreting pancreatic β-cells, losing the cellsthat produce insulin. In T2DM, which affects 90 to 95% of diabetic patients and insulin resistance, pancreatic β-cells produce and secrete less insulin in response to high blood sugar levels, causing hyperglycemia. The T2DM pathophysiology is furthercomplicated by the interaction of hereditary and lifestyle variables**[3].**

The etiology of this disorder is complicated. It begins with the loss of the ability of body cells to respond normally to insulin, thereby disturbing the glucose homeostasis progressing to hyperglycemia. It can further includedamage of pancreatic β-cells, resulting in inadequate insulin releaseand worsening hyperglycemia. Insulin resistance in diabetes is caused by decreased insulin activity on targeted tissues like adipose tissue, liver, or skeletal muscle.Insulin's usual impact on carbohydrate metabolism is hypoglycemia; on lipids, it increases lipogenesis and lowers lipolysis by promoting biosynthesis of cholesterol; and on proteins, it favors inhibiting the protein synthesis catabolism. Hyperglycemia may be caused by insulin dysregulation in the metabolism of carbohydrates, proteins, and lipids**[4].**

TYPES OF DIABETES MELLITUS

T1DM

Only 5 to 10percentof personsare affected by T1DM, with 80–90% of adolescent children**[5].**T1DM, also calledJuvenile diabetes, arise when the insulin-secreting pancreatic β-cells are eliminated by circulating antibodies and the immune system's autoreactive T-cells, resulting in a

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 1370-1379 www.ijprajournal.com ISSN: 2456-4494

lifelong need for an external supply of insulin. The HLA family includes insulin, HLA-DRB1, HLA-DQB1, HLA-DQA1 genes, tyrosine phosphatase, protein, or glutamic acid decarboxylase (GAD) isoforms**[6].**It is essential for the immune system to be able to distinguish between the body's ownprotein and those produced by invadingmicroorganisms so that they can be spotted and eliminated. The variations of genes linked to T1DM, tyrosine phosphatase, protein, 2′-5′-oligoadenylate synthetase, insulin, interleukin-1, interleukin 2 receptor subunit alpha, HNF homeobox A, cytotoxic T-lymphocyte,CeC motif chemokine receptor-associated protein, primary histocompatibility complex class II DQbeta, andforkhead box P3leads to changes in insulin production. Environmental factors, including stress or viral infection, are recognized to have a role in etiology**[7].**

T2DM

Type-2DM, often known as adult-onset diabetes, appearsat the next stage of life affects 90-95 percent of the diabetic population **[8].**If both parents have diabetes, the chance of developing Type 2 Diabetes is roughly 60% by the age of 60. Older individuals commonly have concomitant comorbidities and use many medications, adversely impacting glucose metabolism .Relative insulin shortage caused by β-cell dysfunction is a significant contributor to the development of T2DM, which often co-exists with insulin resistance. Even though T2DM accounts for most diabetes cases (80%), it is still an ill-defined condition with no clear diagnostic criteria. **[9].**

Patients were subtyped into moderate or severe types of T2DM, with a prevalence of insulin resistance or insulinogenic, using clustering techniques based on age at diagnosis, HbA1c, HOMA, BMI, estimations of insulin resistance, and β-cell function, and glutamic acid decarboxylase autoantibodies. Over time, one kind might transform into another. Obesity, energy-dense 'western' diets, advanced age, and a sedentary lifestyle are major risk factors for T2DM, which has seen a four-fold rise in cases over the previous four decades. These risk factors may trigger both insulin resistance and β-cell failure. There are several medication classes available to treat T2DM, but none of them has been demonstrated to significantly alter the steady loss in β-cell function over time **[10].**

PANCREATIC B-CELL FUNCTION IN DIABETIC MELLITUS

Neuropeptides make up a complicated network in the human body, and hormones are produced primarily by the pancreas, brain, gut, liver, muscle tissue, and adipose tissueto keep blood glucose levels in balance. The pancreas is a vital component in this network, acting as a glucose sensor; the β-cell's job is to manage glucose levels by adjusting the quantity of insulin released into the circulation. Mitochondria play a crucial function in this process. The clinical manifestations of Type 1Diabetes Mellitus and Type 2 Diabetes Mellitus are linked to a reduction in the function of pancreatic β-cell as well as a decrease in the mass of β-cell. T1DM and T2DM, according to this "accelerator theory," are fundamentally the same condition characterized by the pace of pancreatic β-cell death and the accelerators that induce β-cell loss. Insulin resistance, high intrinsic rate, apoptosis,and autoimmune are examples of these accelerators. In order to sustain body metabolism, these accelerators work in different ways in different people **[11].**The accelerators are linked, and collectively they mediate the death of pancreatic β-cells. Insulin resistance is thought to cause apoptosis by releasing pro-inflammatory mediators, leading to the production of β-cell antigens and an autoimmune assault on pancreatic cells in genetically predisposed people **[12].**

THE CURRENT STATE OF KNOWLEDGE ON THE ROLES OF INSULIN RECEPTORS (IRS) IN THE BRAIN

For glucose transportation, neurons do not need insulin; the brain was thought to be a non-insulin targeting organ until the brain discovered IRsover 30 years ago.I am found in distinct locations such as the pyriform cortex, olfactory bulb, amygdala, hippocampus, and hypothalamus, as demonstrated byinsulin receptors mRNAunique regional expression with in situ hybridization and insulin binding with autoradiography.The cerebellum and choroid plexus had the most significant quantities of IRs mRNA expression. Surprisingly, the cerebellum exhibits substantial amounts of IRs mRNA but relatively modest levels of protein, possibly owing to the receptor's fast protein turnover rate **[13].**

Furthermore, a key distinction between brain and peripheral IRs is that brain IRs are not required as the significant and direct regulator of glucose transport and metabolism **[14].** Instead, the functions of brain IRs are dictated by the brain area in which they are found. The majority of data

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 1370-1379 www.ijprajournal.com ISSN: 2456-4494

suggest that brain IRs signaling is involved in central control of body energy homeostasis, aging-related neurodegeneration, cognition and modulation of synaptic plasticity, and central regulation of body energy homeostasis **[15].**

B-CELL DYSFUNCTION MECHANISMS

β-cell death has long been connected to β-cell dysfunction **[16]**.In type 2 diabetes, β-cell dysfunction manifests itself as a gradual decline from near-absent first-phase glucose-induced insulin secretion to impaired second-phase insulin secretion,glucose potentiation, disproportionate hyperproinsulinemia, as well as steady-state insulin secretion or impaired basal. Clinical illness and fasting hyperglycemia patients have concluded the method and exhibit all of these characteristics. The surprising outcome is that hyperglycemia compensates for the impaired glucose potentiation and second-phase defect, allowing nonglucose secretagogues to produce an insulin response that is entirely normal in magnitude and timing at the intermediate stages of final β-cell failure (fasting plasma glucose 200 mg/dl). Secretin, Glucagon-like peptide 1, tolbutamide, the β-adrenergic agonist isoproterenol, arginine, and other amino acids are all part of this reaction. The effect of glycemic potentiation was fairly comparable for all of these stimuli in a limited number of previous experiments. As a result, the deficiency is linked to an islet mechanism that is directly tied to the distinctive way Glucose governs insulin production, based on the lack of evidence to the contrary **[17].**

INSULIN RECEPTORS

Insulin affects metabolism, cell development, and differentiation in various ways. I am found in almost all mammalian cells, and they all react to insulin. A and B are the two isoforms of the IRs. Alternative splicing produces the latter, which has an extra exon encoding 11 amino acids. Because it exhibits similar affinities for IGF-II andinsulin, IRs-A stands out. The signaling features of the two isoforms seem to vary somewhat, with IRs-A being stronger than IRs-B in terms of metabolic effects and increasing synthesis of glycogen. Because liver cells are exposed to the high insulin concentrations of the portal vein, the lowered potency of IRs-B, the main isoform in the adult liver, is supposed to restrict hepatocyte sensitivity to insulin, in our perspective**[18].**

Insulin receptor with another tyrosine kinase (s) interactions

During memory formation and learning, the IRs interact with other tyrosine protein kinases in addition to their substrates and downstream signaling molecules. For example, the rat hippocampus synaptic membrane fractions bind to the non-receptor tyrosine kinase pp60 c-src protein. After a one-day training program, the interaction between these two proteins is found to be drastically diminished. The decrease, on the other hand, looks to be just transitory. The binding of pp60 c-src to IRs reverted to control levels as the training sessions progressed. Changes in the interplay between pp60c-src andIRs seem to be involved in the processing of relatively short-term memory **[19].**

Insulin-like growth factor-1 (IGF-1)

Although IGF-1signaling is critical for early brain development, its function in the aging brain is unknown. While decreased IGF1 signaling has long been thought to play a causal role in the aging process, correlation does not indicate causation. Lowering IGF1 signaling with age may mitigate the consequences of aging. More research is needed to fully understand the function and IGF-1 implications signaling in the aging brain **[20].**

Insulin Receptor Isoforms Role & Related Metabolic Complications in T2 Diabetes

Insulin receptor splicing is an animal-specific mechanism that is critical for insulin signaling and IGF selectivity. As a result, a high level of insulin receptor isoform expression is associated with a decrease in insulin metabolic signaling and an increase in IGF signaling, both of which are important for fetal growth development. Increased isoforms IRs-B expression, on the other hand, is associated with the dominance of insulin's metabolic activities in adulthood. Dysregulation of this system, which leads to an increase in IRs-A isoforms in adulthood, might have a role in various disorders **[21].**TheIRsA isoform is then overexpressed in various cancers, including thyroid, muscle, ovarian, lung, and colon cancers **[22].**

Insulin Resistance(IR) and IRA/IRB ratio

Insulin resistance is associated with an increase in the ratio of IRA/IRB in many insulins target tissues. On the other hand, other researchers have observed no significant differences in the ratio of IRA/IRB in several insulin resistance models**[23].**Various studies have shown a reduction

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 1370-1379 www.ijprajournal.com ISSN: 2456-4494

in the IR-A/IR-B ratio in skeletal muscle and adipocytes from diabetes individuals, whereas others have found no change **[24].**Huang et al. discovered an elevated IRA/IRB ratio in the muscle and liver of instantaneously obese diabetic rhesus monkeys, indicating that hyperinsulinemia might influence the alternative splicing of IR messenger RNA promoting insulin resistance **[25].**

Polymorphisms in the insulin receptor substrate and T2DM

In transfected cells of L6skeletal muscle cells and insulin-responsive biological type frequently used for investigations on insulin action, a substantial reduction in the interaction of thep85 subunit of PI3K to the Arg972 insulin receptor substrate-1(IRS-1)variant was also found**[26].**In Cos-7 cells, however, Arg972 IRS-1 expression variation causes a modest, but not a considerable, reduction in PI3K p85 subunit coupling to the Arg972 IRS-1 variants**[27].**

Other causes may account for the apparent gap, in addition to the clear variations in cell types employed as expression vectors for human insulin receptors and either wild-type insulin receptor substrate-1or the Arg972 insulin receptor substrate-1mutant were transiently co-transfected with Cos-7 cells.Likely, the effects of the Arg972 IRS-1 variation on PI3K interaction were disguised by changes in transfection efficiencies and recombinant protein production levels across trials.**[28].**

INSULIN RESISTANCE (IR) AND ITS MECHANISM ON DIFFERENT TISSUES

IR is referred to asthe reduction of insulin-responsive cells to insulin.A significantly impaired response to blood sugar levels by circulating insulin is referred to as IR (insulin resistance)**[29].**IR, often known as insulin deficiency, is divided into three categories: (1) reduced insulin production by β-cells; (2) insulin antagonists in the plasma, either because ofnon-hormonal substances orcounter-regulatory hormones that inhibitsignaling or IR; and (3) decreased insulin responsiveness in target tissues**[30].**The interaction of other substances such as IGF-1 andgrowth hormone influences insulin activity. Glucagon, glucocorticoids, and catecholamines suppress the insulin response during fasting to avoid insulin-induced hypoglycemia. This regulation is influenced by the insulin/glucagon ratio, which regulates the phosphorylation level of downstream enzymes in regulatory signaling pathways. Glucocorticoids stimulate muscle catabolism, whereas catecholamines enhance glycogenolysis and lipolysis;as a result, increased release of these hormones might be the cause of IR. Insulin resistance in the organs generally occurs before systemic IR, resulting in T2DM. The liver, adipose tissue, and skeletal muscle are 3 primary extra-pancreatic insulin-sensitive organs thatperform essential roles in the procedures. **[31].**

Skeletal Muscle

The glucose transporter GLUT4, hexokinase, and glycogen synthase are the major rate-limiting elements in glycogen production and glucose absorption.Trans-Golgi network (TGN), GLUT4, and endosomal recycling compartmenttranslocate from intracellular compartments to the plasma membrane when insulin binds to the insulin receptor in muscle cells. Extra-pancreatic factors such as skeletal muscle insulin resistance are essential in the progress of type-2 diabetes mellitus. Insulin stimulates muscle glycogen production by boosting the intake of Glucose from circulation in normal conditions. This mechanism enables Glucose to be absorbed and lowers its level in the blood **[32].**Any impairment in the upstream or downstream signaling pathway and mutations that lower insulin receptor or GLUT4 expression would limit glucose uptake into the muscle, leading to hyperglycemia**[33].**Insulin interaction with the insulin receptor'sβ-subunit causes the β-subunit to be phosphorylated on several tyrosine residues, allowing insulin-mediated signaling.As previously indicated, mutations in essential downstream signaling pathway proteins including IRS-2 or IRS-1 and PI3K (phosphoinositide 3-kinase) decrease insulin action on the muscle. In addition to mutations or poor epigenetic control, environmental variables may influence glucose absorption by muscle. Physical exercise improves glucose consumption by increasing blood flow into skeletal muscle cells **[34].**

Adipose Tissue

Anti-lipolysis impairment is almost always found to be substantially less severe than glucose disposal impairment in the same participants in studies that report it. Data from cell models orisolated cells enable a more direct evaluation of adipocyte anti-lipolysis responses to insulin since insulin signaling in the brain may alter in vivo adipose tissue lipolysis. Despite reduced insulin-stimulated glucose transport, data from adipose tissue andcell models from animal models

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 1370-1379 www.ijprajournal.com ISSN: 2456-4494

demonstrate that insulin-mediated regulation of lipolysis is essentially unchanged in insulin resistance, particularly at higher insulin doses. Indeed, in certain in vitro models of insulin resistance, the most noticeable alteration in lipolysis is the basal rate of lipolysis rather than the insulin response. These findings show that insulin-stimulated glucose transport is more severely hampered than anti-lipolysis reactions in insulin resistance. Furthermore, in vitro investigations show that nuclear exclusion of FOXO1 and insulin-stimulated protein synthesis, two key Akt-regulated activities, are unaffected in insulin-resistant adipocytes **[35].**

Adipose tissues were previously assumed to be the primary energy storage and supply. Still, it has since been shown that they are actively engaged in communication with other tissues, making them an active endocrine organ. As a result, it has been decided that adipose tissues are the principal endocrine organs capable of producing a range of adipose-derived mediators that regulate insulin sensitivity andenergy metabolism. Adipokines andFFAs are the most prominent adipose-derived mediators. TNF-, Leptin,IL-6, TIMP-1 (tissue inhibitor of metalloproteinases), monocyte chemotactic protein, adiponectin, andRBP-4 (retinol-binding protein) are only a few of the pro-inflammatory mediators found in adipokines (MCP1). In obesity and lipodystrophy, adipose tissue bulk becomes aberrant, resulting in the growth of insulin receptors in peripheral tissues. Adipokines are developing biomarkers for insulin resistance and sensitivity because, in adipose tissues, they reflect persistent low-grade inflammation. Systemic IR may occur when leptin and adiponectin levels are out of equilibrium. **[36].**

INSULIN RESISTANCE IN MULTIPLE SYSTEMS, A SIGNIFICANT ELEMENT OF DIABETES

T2DM is associated with resistance of insulin in the body, and it's considered to have the most influence in particular insulin "target tissues," such as muscle, adipocytes, and liver. Insulin resistance in muscle is commonly blamed for T2DM**[37].**Dysfunction of the insulin receptor is deadly in humans and animals soon after birth, as predicted, due to severe hyperglycemia and other poorly understood developmental abnormalities **[38].**The onset ofT2 diabetes is associated with multisystem insulin resistance, either by increasing compensatory mechanisms or by competing substantially with insulin production.The disruption of insulin receptors in pancreatic β-cells indicates an unanticipated function for insulin signaling during insulin production, even though the latter option is often overlooked. Glucose-stimulated insulin production is decreased in β-cells without insulin receptors, and glucose intolerance increases with age, yet diabetes does not arise .Insulin resistance in β-cells, as well as hepatic/muscle tissue, may be a key factor in type 2 diabetes. Insulin receptor disruption in distinct tissues emphasizes the interconnected nature of insulin-regulated metabolism**[39].**

Table 1. T2DM affects biochemical indicators, and the muscular, digestive, circulatory system

	Biochemical markers	Decreased or Impaired	Increased	References
		Circulating H2, APO-capacity AIs to bind lipids and HDI.	Hoeft, MPO, proteinase-3, illness, homocysteine, homocysteine, VEGF-A resistant, SONG, MGO, EPO, AGEs, GrB, TG, ox-LDL, FFAs and soLDL	**[40]**
Circulatory system	ECs	NOS, Enos, superoxide dismutase, catalase, mitochondrial membrane potential, mIR-126, mIR-2Ba, and mIR-LetZa.	Apoptosis, NF-kB1, EMPs, ROS, IL-B, ICAM-1	**[41]**
	CAPOs cells	VEGFR-1 expression	Apoptosis, VEGFR-2	**[42]**

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 1370-1379 www.ijprajournal.com ISSN: 2456-4494

			expression,	
Digestive system				
	Pancreatic Beta - cells	result synthesis, PDX-1 expression	insoluble IAPP induction, proteasomal dysfunction, mitochondrial dysfunction, ROS generation, Apoptosis caspase-3 expression, ER stress.	**[43]**
Muscular system	Skeletal muscle Cells Liver	GLUT-4 expression mIR-206	Toll statin expression, GRO-a, MCP-1, IL-8 IL-15, and NF-kB1 STAT3, NF-kB1, Steatosis	**[44]**

IMMUNE SYSTEM

Adaptive (or acquired) and innate immunity are the two basic components of the immune system. B cells, which generate T cells or antibodies divided into cytotoxic CD8+ and CD4+ helper cells, are responsible for adaptive immunity. The defective immunological responses in diabetes patients have been explored extensively in the literature **[45].**

Innate Immunity

The complement systems serve as an initial line of defense against invading microbes. It works via three distinct but interrelated pathways: lectin, alternative, or classical **[46].** Ilyas et al. discovered that under high Glucose, the interaction of high-mannose-containing glycoproteins with Type lectin proteins is significantly reduced in a dose-dependent manner.DC-SIGN-related protein, adhesion molecule-3-grabbingnon-integrin, and dendritic cell-specific intercellularMannose-binding lectin (MBL) are carbohydrate-binding proteins**[47].** Decreased MBL binding in the context of high sugar levels reduces lectin pathway activity significantly but does not affect alternative or classical pathway activity.Despite this, Barkai et al. found no significant variations in the MBL or classical pathway activity among T2DM patients and healthy people **[48].**

Macrophages

Macrophages are pro-inflammatory early in wound healing to clear debris or pathogens, but later in the healing process, they rectify inflammation and improve tissue repair. They are essential immune cells that play a role in T2DM-related atherosclerosis pathogenesis at all phases **[49].**

Khanna et al. discovered that in diabetic mouse wounds, poor macrophage phagocytosis of injured cells (efferocytosis) leads to increased wound healing, persistent chronic inflammation, and apoptotic cell load **[50].**According to Westwell-Roper et al., M1 cells also release pro-inflammatory cytokines.In T2DM, excessive macrophage phagocytosis of apoptotic beta-cells causes lysosomal permeabilization,inflammasome activation,reactive oxygen speciesproduction,and the release of the pro-inflammatory cytokines **[51].**

Neutrophils: Neutrophils are an essential part of innate immunity and a most common type of leukocyte. They use antimicrobial peptides, lysosomal enzymes, and ROS productionto phagocytose and destroy invading bacteria. Neutrophils from T2DM patients, but not healthy people, get activated and produce more reactive oxygen species (ROS)**[52].**

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 1370-1379 www.ijprajournal.com ISSN: 2456-4494

Table 2. T2DM's impact on the immune system

Adaptive immunity		References
Cellular immunity (T-Cells)	Th1 cells are elevated, Pathogen-specific Th17 cells are decreased, and expression of perforin, CD107a, and GrB is also reduced.	**[53]**
Humoral immunity (B cells)	Abs fail to activate complement, Abs become glycated, isotype switching is defective, Ab production is defective, and germinal centers are reduced.	**[54]**
Innate immunity		
Innate lymphoid cells (ILCs)	Produce high levels of IFN-g and ILC1s are increased.	**[55]**

II. CONCLUSION

The value of knowledge in the field of glucose metabolism, diabetes, and insulinhas not diminished. Indeed, due to rapid globalization and the normalization of a sedentary lifestyle, and rising diabetes,obesity, and related comorbidities, a study in this area must continue to expand.The critical role of β-cell dysfunction and the impact of insulin resistance on different body systems are discussed in this article. It identifies the primary elements that impact β-cell function, modifying the disease's natural path. To increase systemic insulin resistance, hyperglycemia disrupts the normal operations of the skeletal muscles, liver, pancreatic beta cells, gastrointestinal tract, and circulatory system. Understanding the processes involved in each stage of T2DM development and problems is critical for preventing, controlling, treating, or reversing T2DM pathogenesis and its complications. We have progressed because of the expansion of our knowledge of the pathophysiology of Type 2 diabetes, aided in part by the boom in and continuous development of molecular methods. It lays the groundwork determining the disease's genetic cause and establishing novel treatments and preventative strategies for Type 2 diabetes.

REFERENCES

[1]. Kharroubi AT, Darwish HM. Diabetes mellitus: The epidemic of the century. World journal of diabetes. 2015 Jun 25;6(6):850.

[2]. Navuluri RB. Gender differences in the factors related to physical activity among adults with diabetes. Nursing & Health Sciences. 2000 Dec;2(4):191-9.

[3]. Akter K, Lanza EA, Martin SA, Myronyuk N, Rua M, Raffa RB. Diabetes mellitus and Alzheimer's disease: shared pathology and treatment?. British Journal of clinical pharmacology. 2011 Mar;71(3):365-76.

[4]. Care D. In the same tables, the sentence "The diagnosis of GDM is made when the plasma glucose level measured 3 h after the test is $140 mg/dL (7.8 mmol/L)" is incorrect. The corrected sentence is as follows: "The diagnosis of GDM is made when at least two of the following four plasma glucose levels (measured fasting, 1 h, 2 h, 3 h after the OGTT) are met or exceeded. Diabetes Care. 2014 Mar;37:887.

[5]. Dabelea D, Mayer-Davis EJ, Saydah S, Imperatore G, Linder B, Divers J, Bell R, Badaru A, Talton JW, Crume T, Liese AD. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. Jama. 2014 May 7;311(17):1778-86.

[6]. Maahs DM, West NA, Lawrence JM, Mayer-Davis EJ. Epidemiology of type 1 diabetes. Endocrinology and Metabolism Clinics. 2010 Sep 1;39(3):481-97.

[7]. Vermeulen I, Weets I, Asanghanwa M, Ruige J, Van Gaal L, Mathieu C,

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 1370-1379 www.ijprajournal.com ISSN: 2456-4494

Keymeulen B, Lampasona V, Wenzlau JM, Hutton JC, Pipeleers DG. Contribution of antibodies against IA-2β and zinc transporter 8 to the classification of diabetes diagnosed under 40 years of age. Diabetes Care. 2011 Aug 1;34(8):1760-5.

[8]. Bhatti JS, Bhatti GK, Reddy PH. Mitochondrial dysfunction and oxidative stress in metabolic disorders—A step towards mitochondria-based therapeutic strategies. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2017 May 1;1863(5):1066-77.

[9]. Ounnapiruk L, Wirojratana V, Meehatchai N, Turtle S. Effectiveness of a behavior modification program for older people with uncontrolled type 2 diabetes. Nursing & Health Sciences. 2014 Jun;16(2):216-23.

[10]. Eizirik DL, Pasquali L, Cnop M. Pancreatic β-cells in type 1 and type 2 diabetes mellitus: different pathways to failure. Nature Reviews Endocrinology. 2020 Jul;16(7):349-62.

[11]. Tamarai K, Bhatti JS, Reddy PH. Molecular and cellular bases of diabetes: focus on type 2 diabetes mouse model-TallyHo. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2019 Sep 1;1865(9):2276-84

[12]. Wilkin TJ. The accelerator hypothesis: a review of the evidence for insulin resistance as the basis for type I as well as type II diabetes. International Journal of obesity. 2009 Jul;33(7):716-26.

[13]. Small SA, Gandy S. Sorting through the cell biology of Alzheimer's disease: intracellular pathways to pathogenesis. Neuron. 2006 Oct 5;52(1):15-31.

[14]. Van der Heide LP, Ramakers GM, Smidt MP. Insulin signaling in the central nervous system: learning to survive. Progress in neurobiology. 2006 Jul 1;79(4):205-21.

[15]. Zhao WQ, Townsend M. Insulin resistance, and amyloidogenesis as a common molecular foundation for type 2 diabetes and Alzheimer's disease. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2009 May 1;1792(5):482-96.

[16]. Christensen AA, Gannon M. The beta-cell in type 2 diabetes. Current diabetes reports. 2019 Sep;19(9):1-8.

[17]. Porte Jr D, Kahn SE. beta-cell dysfunction and failure in type 2 diabetes: potential mechanisms. Diabetes. 2001 Feb 1;50(suppl_1):S160.

[18]. Haeusler RA, McGraw TE, Accili D. Biochemical and cellular properties of insulin receptor signaling. Nature reviews Molecular cell biology. 2018 Jan;19(1):31-44.

[19]. Zhao WQ, Alkon DL. Role of insulin and insulin receptor in learning and memory. Molecular and cellular endocrinology. 2001 May 25;177(1-2):125-34.

[20]. Wrigley S, Arafa D, Tropea D. Insulin-like growth factor 1: at the crossroads of brain development and aging. Frontiers in cellular neuroscience. 2017 Feb 1;11:14

[21]. Escribano O, Beneit N, Rubio-Longás C, López-Pastor AR, Gómez-Hernández A. The role of insulin receptor isoforms in diabetes and its metabolic and vascular complications. Journal of diabetes research. 2017 Oct 19;2017.

[22]. Vella V, Milluzzo A, Scalisi NM, Vigneri P, Sciacca L. Insulin receptor isoforms in cancer. International journal of molecular sciences. 2018 Nov;19(11):3615.

[23]. Bosco D, Fava A, Plastino M, Montalcini T, Pujia A. Possible implications of insulin resistance and glucose metabolism in Alzheimer's disease pathogenesis. Journal of cellular and molecular medicine. 2011 Sep;15(9):1807-21

[24]. Belfiore A, Frasca F. IGF and insulin receptor signaling in breast cancer. Journal of mammary gland biology and neoplasia. 2008 Dec;13(4):381-406.

[25]. Escribano O, Beneit N, Rubio-Longás C, López-Pastor AR, Gómez-Hernández A. The role of insulin receptor isoforms in diabetes and its metabolic and vascular complications. Journal of diabetes research. 2017 Oct 19;2017.

[26]. Sesti G. Insulin receptor substrate polymorphisms and type 2 diabetes mellitus. Pharmacogenomics. 2000 Aug 1;1(3):343-57.

[27]. Hribal ML, Federici M, Porzio O, Lauro D, Borboni P, Accili D, Lauro R, Sesti G. The Gly→ Arg972 amino acid polymorphism in insulin receptor substrate-1 affects glucose metabolism in

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 1370-1379 www.ijprajournal.com ISSN: 2456-4494

skeletal muscle cells. The Journal of Clinical Endocrinology & Metabolism. 2000 May 1;85(5):2004-13.

[28]. Turban S, Hajduch E. Protein kinase C isoforms: mediators of reactive lipid metabolites in the development of insulin resistance. FEBS letters. 2011 Jan 21;585(2):269-74.

[29]. Czech MP. Insulin action and resistance in obesity and type 2 diabetes. Nature medicine. 2017 Jul;23(7):804-14.

[30]. Pearson T, Wattis JA, King JR, MacDonald IA, Mazzatti DJ. The effects of insulin resistance on individual tissues: an application of a mathematical model of metabolism in humans. Bulletin of mathematical biology. 2016 Jun;78(6):1189-217.

[31]. Wilcox G. Insulin and insulin resistance. Clinical biochemist reviews. 2005 May;26(2):19.

[32]. Satoh T. Molecular mechanisms for regulating insulin-stimulated glucose uptake by small guanosine triphosphatases in skeletal muscle and adipocytes. International Journal of molecular sciences. 2014 Oct;15(10):18677-92.

[33]. Abdul-Ghani MA, DeFronzo RA. Pathogenesis of insulin resistance in skeletal muscle. Journal of Biomedicine and Biotechnology. 2010 Oct;2010.

[34]. Wu H, Ballantyne CM. Skeletal muscle inflammation and insulin resistance in obesity. The Journal of clinical investigation. 2017 Jan 3;127(1):43-54.

[35]. Fazakerley DJ, Krycer JR, Kearney AL, Hocking SL, James DE. Muscle and adipose tissue insulin resistance: malady without mechanism?. Journal of Lipid Research. 2019 Oct 1;60(10):1720-32.

[36]. Rehman K, Akash MS. Mechanisms of inflammatory responses and development of insulin resistance: how are they interlinked?. Journal of biomedical science. 2016 Dec;23(1):1-8.

[37]. Cline GW, Petersen KF, Krssak M, Shen J, Hundal RS, Trajanoski Z, Inzucchi S, Dresner A, Rothman DL, Shulman GI. Impaired glucose transport is a cause of decreased insulin-stimulated muscle glycogen synthesis in type 2 diabetes. New England Journal of Medicine. 1999 Jul 22;341(4):240-6.

[38]. Accili D, Drago J, Lee EJ, Johnson MD, Cool MH, Salvatore P, Asico LD, José PA, Taylor SI, Westphal H. Early neonatal death in mice homozygous for a null allele of the insulin receptor gene. Nature genetics. 1996 Jan;12(1):106-9.

[39]. Bouzakri K, Roques M, Gual P, Espinosa S, Guebre-Egziabher F, Riou JP, Laville M, Le Marchand-Brussel Y, Tanti JF, Vidal H. Reduced activation of phosphatidylinositol-3 kinase and increased serine 636 phosphorylation of insulin receptor substrate-1 in primary culture of skeletal muscle cells from patients with type 2 diabetes. Diabetes. 2003 Jun 1;52(6):1319-25.

[40]. Naseer M, Bibi F, H Alqahtani M, G Chaudhary A, I Azhar E, A Kamal M, Yasir M. Role of gut microbiota in obesity, type 2 diabetes, and Alzheimer's disease. CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders). 2014 Mar 1;13(2):305-11.

[41]. Wang J, Kuusisto J, Vänttinen M, Kuulasmaa T, Lindström J, Tuomilehto J, Uusitupa M, Laakso M. Variants of transcription factor 7-like 2 (TCF7L2) gene predict conversion to type 2 diabetes in the Finnish Diabetes Prevention Study and are associated with impaired glucose regulation and impaired insulin secretion. Diabetologia. 2007 Jun;50(6):1192-200.

[42]. Daryabor G, Atashzar MR, Kabelitz D, Meri S, Kalantar K. The effects of type 2 diabetes mellitus on organ metabolism and the immune system. Frontiers in immunology. 2020 Jul 22;11:1582.

[43]. Onyango IG, Khan SM. Oxidative stress, mitochondrial dysfunction, and stress signaling in Alzheimer's disease. Current Alzheimer Research. 2006 Sep 1;3(4):339-49.

[44]. Kouidhi S, Berrhouma R, Rouissi K, Jarboui S, Clerget-Froidevaux MS, Seugnet I, Bchir F, Demeneix B, Guissouma H, Elgaaied AB. Human subcutaneous adipose tissue Glut 4 mRNA expression in obesity and type 2 diabetes. Acta Diabetologia. 2013 Apr;50(2):227-32.

[45]. Rubinstein MR, Genaro AM, Wald MR. Differential effect of hyperglycemia on the immune response in an experimental model of diabetes in BALB/cByJ and C57Bl/6J mice: participation of oxidative

stress. Clinical & Experimental Immunology. 2013 Mar;171(3):319-29.

[46]. Ricklin D, Hajishengallis G, Yang K, Lambris JD. Complement: a key system for immune surveillance and homeostasis. Nature immunology. 2010 Sep;11(9):785-97.

[47]. Ilyas R, Wallis R, Soilleux EJ, Townsend P, Zehnder D, Tan BK, Sim RB, Lehnert H, Randeva HS, Mitchell DA. High Glucose disrupts oligosaccharide recognition function via competitive inhibition: a potential mechanism for immune dysregulation in diabetes mellitus. Immunobiology. 2011 Jan 1;216(1-2):126-31.

[48]. Barkai LJ, Sister E, Csuka D, Prohászka Z, Pilely K, Garred P, Hosszúfalusi N. Decreased ficolin-3-mediated complement lectin pathway activation and alternative pathway amplification during bacterial infections in patients with type 2 diabetes mellitus. Frontiers in Immunology. 2019:509.

[49]. GilardiniMontani MS, Falcinelli L, Santarelli R, Granato M, Romeo MA, Cecere N, Gonnella R, D'Orazi G, Faggioni A, Cirone M. KSHV infection skews macrophage polarisation towards M2-like/TAM and activates Ire1 α-XBP1 axis up-regulating pro-tumorigenic cytokine release and PD-L1 expression. British Journal of Cancer. 2020 Jul;123(2):298-306.

[50]. Khanna S, Biswas S, Shang Y, Collard E, Azad A, Kauh C, Bhasker V, Gordillo GM, Sen CK, Roy S. Macrophage dysfunction impairs resolution of inflammation in the wounds of diabetic mice. PloS one. 2010 Mar 4;5(3):e9539.

[51]. Westwell-Roper CY, Ehses JA, Verchere CB. Resident macrophages mediate islet amyloid polypeptide–induced islet IL-1β production and β-cell dysfunction. Diabetes. 2014 May 1;63(5):1698-711.

[52]. Mayadas TN, Cullere X, Lowell CA. The multifaceted functions of neutrophils. Annual Review of Pathology: Mechanisms of Disease. 2014 Jan 24;9:181-218.

[53]. Kumar NP, Sridhar R, Banurekha VV, Nair D, Jawahar MS, Nutman TB, Babu S. Expansion of pathogen-specific mono-and multifunctional Th1 and Th17 cells in multi-focal tuberculous lymphadenitis. PLoS One. 2013 Feb 25;8(2):e57123.

[54]. Hess C, Winkler A, Lorenz AK, Holecska V, Blanchard V, Eiglmeier S, Schoen AL, Bitterling J, Stoehr AD, Petzold D, Schommartz T. T cell-independent B cell activation induces immunosuppressive sialylated IgG antibodies. The Journal of clinical investigation. 2013 Sep 3;123(9):3788-96.

[55]. Simoni Y, Newell EW. Toward meaningful definitions of innate-lymphoid-cell subsets. Immunity. 2017 May 16;46(5):760-1.