

# Molecular Insights of Diabetic Complications and Future Targets for Therapy

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## ABSTRACT

In Diabetes, hyperglycemia, insulin resistance, oxidative stress and inflammation are the known associates for the loss of  $\beta$  cell function. Indeed, number other factors influencing many other molecular mechanisms are involved in the progression of microvascular and macrovascular complications. This review focused on the putative mechanism such as polyol pathway, hexosamine pathway, PKC, AMPK and MAPK pathways; AGEs, GLP -1, GIP, DPP4, 11 $\beta$  HSD1, DGAT2, SGLT2, HSP, TXNIP and SCD; the role of cytokines, adipokines and growth factors; role of GPCRs and other receptors like SUR, HCA2 and MTR; the role of autophagy and epidemic factors involved in diabetes and associated complications.

**Key words:** Diabetes, Hyperglycemia, Insulin Resistance, Diabetic Complications, Molecular mechanisms.

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## INTRODUCTION

The high concentration of circulating glucose is a common dysfunction of microvasculature of various parts of the body, which arise diabetes and diabetic complications. Insulin resistance is a common phenomenon for hyperglycemia. The loss of intracellular signaling in response to insulin is defined as insulin resistance. The organs which depend on their glucose uptake through insulin are liver, adipose tissue, skeletal muscle and other organs of insulin dependence. If any impairment of glucose uptake develops insulin resistance due to impaired insulin signaling.<sup>[1]</sup>

The uncontrolled hyperglycemia and insulin resistance contributes to the progression of diabetic complications through numerous molecular mechanisms. Some of the mechanisms are polyol pathway, hexosamine pathway, protein kinase pathway, AMPK pathway, formation of advanced glycation end products (AGEs), chemokines,

adipokines, some of G protein coupled receptors (GPCRs), incretins and many metabolic enzymes involved in the formation and metabolism of glucose by several mechanisms (Figure 1). Hyperinsulinaemia is also one of the risk factor for diabetic complications along with these contributors. It acts by cellular uptake of amino acid and fatty acids by affecting the nutrient homeostasis and by stimulating glycolysis and  $N^+/K^+$  ATPase activity, inhibition of hepatic gluconeogenesis and glycogen synthesis at liver and muscle, lipid levels (Triglycerides) in liver and adipose tissue and by inhibiting DNA synthesis, gene expression and apoptosis.<sup>[2]</sup>

## MOLECULAR INSIGHTS OF DIABETIC COMPLICATIONS

### Polyol Pathway

Persistence hyperglycemia tends to increase the rate of glucose metabolism through polyol pathway upto 4 to 5% than normal conditions and is found to be more susceptible during diabetic complications.<sup>[3]</sup> The toxic aldehydes are reduced to inactive alcohols in presence of enzyme aldose reductase. The circulating glucose levels are gone beyond the normal, the glucose converted to sorbitol by aldose reductase and

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oxidized to fructose later by conserving the co-factor NADPH.<sup>[4]</sup> Due to conservation of NADPH, this was essential for production of reduced glutathione (GSH) intracellular antioxidant. Thereby polyol pathway increases the intracellular oxidative stress by disturbing the antioxidant system. The end product of polyol pathway i.e fructose such as triose phosphate, fructose 3-phosphate, 3-deoxyglucosone and methylglyoxal act as glycating agents and these intermediates accelerate the production of advanced glycation end products (AGEs).<sup>[5]</sup>

### Advance Glycation End Products (AGEs)

The Maillard reaction is a consequence of interaction between the free amino groups of proteins with heterogeneous sugar group by covalent attachment non-enzymatically. The posttranslational modifications of these glycated products are called advanced glycation end products and progressive factors of diabetes complications by modulating the insulin secretion and insulin signaling pathways.<sup>[6]</sup> They are formed as cross linking and non-cross linking AGEs involved in matrix cell interactions. The receptors of AGEs (RAGEs) transmits signals NADPH dependent oxidases, transforming growth factors, cytokines, proinflammatory cytokines, chemokines, NOS induced stress, vascular adhesion molecule 1 and MAP kinases. These predictive factors elevate the circulating soluble RAGE concentrations, plasma and urine AGE levels in diabetes mellitus.<sup>[7]</sup>

### Incretins

Incretins are released immediately after food induction from enteroendocrinal cells. Incretins can enhance the glucose induced insulin secretion and also promotes post prandial insulin production called as insulinotropic effect. They can inhibit the gastric emptying time; inhibit appetite, glucagon secretion and slow down the rate and production of endogenous glucose.<sup>[8]</sup> The major types of incretins involved in insulinotropic effect are GLP-1 and Glucose insulinotropic peptide (GIP). The GLP -1 elicited their action by binding to the specific receptor and triggers the intracellular cAMP and  $Ca^{2+}$  levels in pancreatic  $\beta$  cell. They can protect the  $\beta$  cells from apoptosis. They up regulate transcriptional factors, pancreatic duodenal homeobox -1 protein (PDX-1) to stimulate the cell proliferation. Thereby augment the insulin gene transcription and upregulates the Glucokinase and GLUT 2.<sup>[9]</sup>

In a similar pattern, GIP binding to the GIPR enhances the intracellular cAMP and  $Ca^{2+}$  in  $\beta$  cells of pancreas. They can be able to promote the cell

survival by stimulating the lipoprotein lipase activity and by modulating the synthesis of fatty acids and incorporating the fatty acids into triglycerides.

GIP achieves its insulinotropic effects by binding to its specific receptor (GIPR), which is positively coupled to increased intracellular cAMP and  $Ca^{2+}$  levels in  $\beta$  cells. In addition to being insulinotropic, GIP is involved in fat metabolism in adipocytes: it enhances insulin-stimulated incorporation of fatty acids into triglycerides, stimulates lipoprotein lipase activity, modulates fatty acid synthesis and promotes  $\beta$ -cell proliferation and cell survival.<sup>[10]</sup>

### Hexosamine Pathway

The key enzyme involved in the glucose transportation into the cell is hexosamine or glucokinase. High glucose load inside the cell initiate the process of glycolysis to form glucose 6 phosphate, fructose 6 phosphate. Immediately this fructose 6 phosphate gets converted to glutamine:fructose – phosphate aminotransferases and finally converted to urine diphosphate N acetyl glucosamine.<sup>[11]</sup> These residues bind to the serine and threonine of transcriptional factors and over modify the glucosamine by the process of phosphorylation and are often involved in pathological gene expression changes of transcriptional factors. There by enhances the expression of transforming growth factor and plasminogen activator inhibitor -1. The expression of glucokinase is controlled by the glucose 6 phosphate dehydrogenase (G6PDH) and changes in this rate limiting causes diabetes and development of diabetic complications.<sup>[12]</sup>

### Protein Kinase C (PKC)

The hyperglycemia activates the intracellular secondary messenger protein kinase. Glucose can directly activate the isoforms of PKC  $\alpha$ ,  $\beta$ 1,  $\beta$ 2 and  $\gamma$ . The activation was caused by glucose dependent and insulin dependent insulin secretion from the pancreatic  $\beta$  cells upon increased calcium ( $Ca^{+2}$ ) influx with inhibiting the ATP sensitive potassium ( $K^{+}$ ) channels.<sup>[13]</sup> The insulin resistance is caused by the translocation of PKC due to enhancement serine/ threonine kinase pathway thereby it tends to the phosphorylation of insulin receptor substrate 1 (IRS -1). The activation of signaling of IRS 2 might cause the increased proliferation of pancreatic  $\beta$  cells, phosphorylation of protein kinase B and inhibition of fork head –O transcriptional factor -1.<sup>[14]</sup> The AGEs and angiotensin II can also activates the PKC signaling.<sup>[15]</sup>

### AMP activated protein kinase (AMPK)

The metabolism of glucose and lipid are regulated by the AMPK. The activation of AMPK requires

phosphate for energy for metabolism. The activation is also observed in the skeletal muscle contraction and myocardial ischemia. The regulation of metabolism of glucose is by glucose transport and the cholesterol and triglycerides metabolism is by fatty acid oxidation. The insulin sensitivity of AMPK slows down the free fatty acid synthesis and enhances mitochondrial oxidation. The inactivated transcriptional and post translation inhibits the HMG Co A reductase, thereby inhibits the cholesterol synthesis by phosphorylation.<sup>[16]</sup>

### Mitogen-Activated Protein Kinases (MAPK)

MAPK triggers the cascade of intracellular mechanisms to initiate the stimulation of inflammatory cytokines and mediators of the cellular differentiation, apoptosis and inflammation of pancreatic  $\beta$  cells and are likely to be the key factor for the development of diabetic complications.<sup>[17]</sup>

### Diacylglycerol Acyltransferase (DGAT)

The DGAT existed in two forms are DGAT1 and DGAT 2. The key enzyme involved in the triglyceride synthesis was DGAT1 in a final reaction. It has identified homology to acyl Co A cholesterol acyltransferase genes. It is involved in the covalent binding of fatty acyl Co A with diacylglycerol.<sup>[18]</sup> Fatty acids induced deficiency of DGAT1 exacerbated insulin resistance in muscles and over expression of DGAT nullify the actions of fatty acids.

DGAT1 found to have elevated diacylglycerol in skeletal muscle and protect the pancreas from the insulin resistance. The mechanism is established that the insulin sensitivity might be due to activation of PKC activation via diacylglycerol and JNK 1. These responses are attributed to the alteration in serine phosphorylation of IPS -1, enhanced Akt activation and translocation of glucose 4 membrane. Along with the mechanisms, DGAT1 regulates the triglyceride synthesis and IMF formation by modulating the insulin signaling pathway, MAPK pathway and unsaturated fattyacids biosynthesis in type 2 diabetes mellitus.<sup>[19]</sup>

### Dipeptidyl-peptidase 4 (DPP4)

The process shedding is caused by the circulating DPP4 with their defected Cytoplasmic domain and transmembrane region. They are able to cleave the membrane of human adipocytes and smooth muscles through the association of matrix metalloproteases. The promoter genes of DPP4 contain respective sites for binding of various transcriptional factors such as NF $\kappa$ B, SP-1, EGFR, necrotic factors.<sup>[20]</sup> Enhanced expression of DPP4 is observed with all types of interferons when it stimulates STAT  $\alpha$  binding at the same region. The

binding motif of STAT1 is associated with interferon  $\gamma$  activated sequence (GAS) in chronic inflammatory conditions. Inhibition of DPP4 causes activation of anti apoptotic factors and suppression of pro apoptotic genes and activation of pro-survival genes in pancreatic  $\beta$  cells. The inhibition of DPP 4 enzymes acts by prolonging the activity of incretins GLP-1 and GIP and by this way DPP4 elicits regulation on glucose dependent insulin secretion and sensitivity.

### 11 $\beta$ -hydroxysteroid dehydrogenase type 1 (11 $\beta$ -HSD1)

Cortisol plays major role in metabolic pathways. Excessive cortisol levels stimulate the glucocorticoids signaling pathway on active tissues and have been involved in the metabolic syndromes such as diabetes and obesity. The regeneration and intracellular activity of cortisol is regulated by the enzyme 11 $\beta$ -HSD1. The enzyme enhances the production and levels of cortisol in liver and adipose tissue. It also enhances the cortisol by the conversion of inactive cortisol into active form and enhances the intracellular cortisol function to maintain the circulation levels. Both animal and clinical studies confirmed the role of 11 $\beta$ -HSD1 expression in adipose tissue during the obesity and other metabolic dysfunctions.<sup>[21]</sup>

### Stearoyl-CoA desaturase (SCD)

SCD is an enzyme that catalyzes the synthesis of substrates of triglycerides, cholesterol esters and phospholipids are monounsaturated fatty acids such as oleate and palmitoleate.<sup>[22]</sup> Leptin is a mediator of regulating energy homeostasis and targets the SCD1 gene in attributing to their insulin sensitizing action.<sup>[23]</sup> SCD1 has a property of increasing energy expenditure, maintained body adiposity and increased insulin sensitivity. SCD1 Down regulation enhances the Akt phosphorylation and reduced expression of glucose 6-

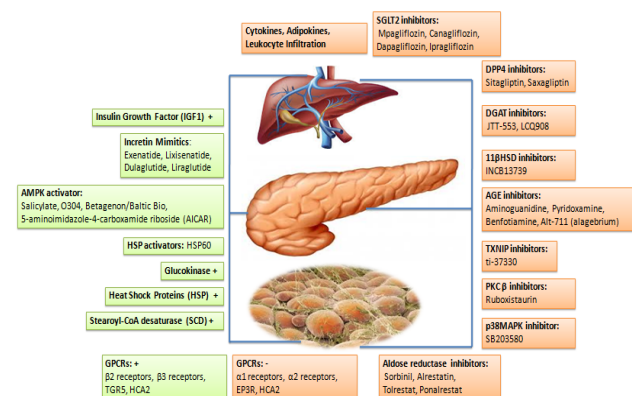


Figure 1: Molecular Mechanism in diabetes with possible targets for therapy.

phosphate and phosphoenolpyruvate carboxykinase. The deficiency of SCD1 also suppressed the expression of PTP – 1B. The mechanisms which are affected by SCD1 are tyrosine phosphorylation of insulin receptor IRS1 and IRS2. The phosphorylation of Akt and GLUT4 translocation might be due to the association of IRS with  $\alpha$ p85 sub unit of the phosphatidylinositol 3 kinase in skeletal muscle and adipose tissue.<sup>[24]</sup>

### Sodium Glucose co-Transporter 2 (SGLT -2)

The SGLT -2 is a transporter to regulate the blood glucose by reabsorbing the glucose from the kidney by glomerular filtrate. It transports the sodium and glucose to the cells through the basolateral membranes by sodium/potassium ATPase pumps using the sodium gradient. SGLT 2 creates malabsorption of glucose/galactose by inhibiting the intestinal absorption of glucose/galactose. The lipolysis and weight loss by the SGLT 2 might be due to the inhibition of SGLT 2 by shifting to the utilization of lipids instead of carbohydrates due to reduced glucose levels.<sup>[25]</sup> The inhibited glucose reabsorption in the kidney activates the hepatic glucose production to compensate the loss of glucose in urine and to tend to the condition glucosuria (glucose in urine). Hence, SGLT2 inhibitors promote the insulin sensitivity by inhibiting the renal glucose reabsorption and by reducing blood glucose levels.

### Cytokines and Adipokines

Cytokines are a complex group of molecules capable of triggering differential effects on cells depending on factors such as cell type, timing and the context of their expression. These molecules are able to share receptors and act synergistically to amplify their effects and therefore conceptually, it is likely that cytokines and their receptors could be difficult to target therapeutically given that their temporal expression may alter many times over the course of the development and progression of diabetes complications. IL-1 is a cytokine that is primarily released by immune cells but is also secreted by resident monocytes, macrophages, adipocytes and other cells at the sites of diabetic complications. The release of IL-1 also has a number of other effects on cells, including secretion of prostaglandins that affect vascular permeability via changes in local hemodynamics,<sup>[26]</sup> which may also be relevant for cells at sites of diabetic complications. IL-6 is a proinflammatory cytokine and an important mediator of cell proliferation, endothelial cell permeability and matrix overproduction. These adipokines include adiponectin, a 30-kDa circulating plasma protein.

Adiponectin modulates a number of metabolic processes; in particular those associated with glucose homeostasis and fatty acid catabolism and are found in relatively high concentrations within the circulation. Adiponectin circulates in multimeric forms and binds to two adiponectin receptors (AdipoR1 and AdipoR2) inducing signaling via stimulation of 5'-adenosine monophosphate activated protein (AMPK) and likely other intracellular pathways.<sup>[27]</sup>

White adipose tissue is the source of large quantities of adipokines such as IL-6 and TNF- $\alpha$  in diabetic patients.<sup>[28]</sup> Adipose tissue is highly secretory, releasing a number of factors that are modulated in response to hyperglycemia. These are thought to induce a number of effects both systemically and likely on surrounding tissues, which may be important to the development of diabetic complications.

### Growth Factors

Insulin is arguably the major growth factor associated with tissue growth and survival. Hyperinsulinemia has been associated with organ and tissue hypertrophy. In this context, hypertrophy and hyperplasia are most commonly seen at the major sites of peripheral insulin signaling such as the liver, skeletal muscle and adipose tissue. IGF-I and -II also bind to the insulin receptor<sup>[29]</sup> and are primarily produced by the liver in response to changes in growth hormone. Excesses of insulin caused by acute abundance of exogenously administered insulin or hyperinsulinemia alter IGF-I concentrations and enhance VEGF expression during ischemia. TGF- $\beta$ 1 is arguably the most potent inducer of tissue fibrosis and chronic administration of a neutralizing TGF- $\beta$ 1 antibody improves renal function and structure in models of type 1 and type 2 diabetes.<sup>[30]</sup> Connective tissue growth factor (CTGF), is also being considered as a pathogenic mediator of diabetic complications.<sup>[31]</sup> CTGF expression is mediated by a number of factors commonly expressed in diabetes including TGF- $\beta$ 1, hyperglycemia, or mechanical stretch. The VEGF family (VEGF A-D) stimulates cellular responses by binding to cell surface tyrosine kinase receptors, the most common of which is VEGFR-2 (KDR/Flk-1), that is known to mediate most of the known cellular responses to VEGF.

### Leukocyte infiltration

Phagocytic cells such as monocytes and macrophages are often the first infiltrating cells that arrive at sites of diabetic complications in response to chemotactic molecules, in particular CCL2, CX3CL1 and CCL5. Indeed, rodent studies have suggested a causal role of



monocytes and macrophages in the development of diabetic complications.<sup>[32]</sup>

### G-Protein Coupled Receptors (GPCRs)

The role of GPCRs is implicated in the  $\beta$  cell dysfunction, insulin resistance, obesity and type 2 diabetes progressions. The types of GPCRs involved in diabetes and induced complications are

**$\alpha 1$ -adrenoceptors:** The metabolic abnormalities of  $\alpha 1$  adrenoceptors due to polymorphism of Arg347Cys, physiological dysfunctions and metabolic effects associated with activation of these receptors in liver, muscle and adipose tissue. But its activation indirectly influences the glucose metabolism in brain, heart and other tissues.

**$\alpha 2$ -adrenoceptors:** They are present majorly in pancreas, adipose tissue and adrenal glands.  $\alpha 2A$  adrenoceptors are present in both  $\alpha$  and  $\beta$  cells of pancreas and their stimulation causes increased glucagon secretion from cells and insulin secretion from  $\beta$  cells. These receptors are involved in lipolysis in adipose tissue; hence the agonists may decrease the availability of glycerol for hepatic gluconeogenesis.<sup>[33]</sup> The  $\alpha 2A$  adrenoceptors antagonists are improves the insulin sensitivity and glucose tolerance. There was also a predisposing  $\alpha 2A$  adrenoceptors genetic association with type 2 diabetes.

**$\beta 2$ -Adrenoceptor:**  $\beta 2$  Adrenoceptors activation stimulate the glucose uptake by numerous mechanisms. Indirect mechanism induces vasodilation by increasing the insulin secretion from pancreatic  $\beta$  cells and direct stimulation causes insulin stimulated glucose uptake in skeletal muscle.<sup>[34]</sup> A significant increase in glucose levels were also observed with stimulation of  $\beta 2$  Adrenoceptors due to glycogenolysis. An increased glucose uptake causes activation of G protein receptor kinase, activation of mTORC2 due to stimulation of cAMP. The translocation of GLUT4 activates the  $\beta 2$  Adrenoceptors but does not involved in the AKt or AS160 translocation as like as insulin.<sup>[35]</sup>

**$\beta 3$ -adrenoceptors:** They influences the  $\beta 2$  adrenoceptors acts as agonists for lipolysis and production of heat in brown fat and it was evidenced by improving the glucose tolerance and ameliorating the insulin resistance.<sup>[36]</sup>

**CB1R:** The physiological activity of CB1R observed in metabolic tissues and in both white and brown adipocytes, where they enhance the fatty acid synthesis followed by reduction in lipolysis. Excessive stimulation of CB1R expression showed marked activation of inflammasomes, apoptosis in macrophages and finally causes loss of  $\beta$  cell function.<sup>[37]</sup>

**EP3R:** The ligand for the EP3R is prostaglandin E2 of arachidonic acid pathway. The pancreatic cells are abundant with eicosapentaenoic acid, which are precursors of prostaglandin E3. They improve the insulin secretion of glucose dependent, reduce production of IL-1 $\beta$ , improved glucose tolerance and enhanced  $\beta$  cell function. The EP3R blockage is a valuable therapy for the treatment of diabetes.<sup>[38]</sup>

**TGR 5:** The TGR 5 presents in the pancreatic  $\alpha$  cell. The bile acids contains Takeda G protein receptor 5 (TGR 5) with had a role in regulation of glucose homeostasis. They have the activity of inhibition of ATP dependent potassium channels and activation of higher intracellular calcium and promote glucose stimulated insulin secretion. These events activate the intestinal L cells and activate the GLP – 1 biosynthesis and secretion to control the glucose.<sup>[39]</sup>

### Sulphonyl Urea Receptors (SUR)

SUR belongs to the GPCRs, which act as targets for the oral antihyperglycemic agents, they act by stimulating the insulin release from the pancreatic  $\beta$  cells. The higher glucose load in the  $\beta$  cells works for the source of ATP and it binds to the  $K_{ATP}$  channels and make it close. The intracellular levels of the ATP and ADP facilitate either opening or closing of Kir6.x potassium channels. This closure initiates the opening of voltage dependent calcium channels to increase the membrane potential which triggers the insulin release by exocytosis. The blockage of sulfonylureas is caused by mutation of phosphatidylinositol bisphosphate merely by increasing the probability of opening of potassium channels.

### Hydroxycarboxylic Acid Receptor 2 (HCA2)

The HCA2 receptors are called as receptors for niacin and are expressed in adipocytes and immune cells. Niacin activated HCA2 receptors in adipocytes causing inhibition of lipolysis. This inhibition was also mediated through epidermal cells of Langerhans causes flushing.<sup>[40]</sup> Activation of HCA2 stimulated the SGLT 1 and GLUT 2 for glucose uptake in jejunum. These activities are the reason behind the potential glycemic controls.<sup>[41]</sup>

### Melatonin Receptors (MT<sub>1</sub>R and MT<sub>2</sub>R)

The altered insulin response by the glucose stimulation causes increased cAMP and increased  $\beta$  cell mass. This response inhibits the glucose mediated insulin secretion in INS -1 cell and over expression of MTNR<sub>1</sub>B/MT<sub>2</sub>R, controlling the cAMP production in response to glucose. MTR are found to increase the risk of diabetes and associated complications by increased plasma glucose, insulin resistance and abolishing insulin response to

glucose.<sup>[42]</sup> The other association for diabetes is by genetic defect melatonin induced activation of  $G\alpha 1$  and  $G\alpha 2$  proteins recruitment of  $\beta$  arrestin 2.

### Heat Shock Proteins (HSPs)

HSPs are called as chaperones, the role of HSPs in correct the interactions between molecules of different proteins and protects the special structure of the denatured proteins. The HSPs level was found to be decreased in oxidative stress and diabetes by influencing the insulin signaling and promotes the inflammation in skeletal muscle and liver.<sup>[43]</sup> HSPs stimulate the active pathways such as AMPK, which limit the lipid levels by activating the fat catabolism. HSPs augmentation stimulates the mitochondrial biogenesis and function. Lower levels of HSPs initiate the CRP and cytokines tends to reduce the insulin signaling pathways and expression also.<sup>[44]</sup>

It is observed that the formation of glycosylated HSPs in diabetes also hinder their folding to active conformational status, thereby imparts function. Insulin resistance causes deactivation of HSP by inhibition of HSF-1 phosphorylation by the glycogen synthase kinase 3- $\beta$  and their transcriptions. This defect in the defense mechanism lowers the HSP levels and enhances the expression and activation of proinflammatory cytokines such as c-Jun-N-terminal kinases and I $\kappa$ B kinase. These events inhibit the insulin signaling and sensitivity by promoting the inhibitory phosphorylation of IRS -1 and prevails the diabetes.<sup>[44]</sup>

### Thioredoxin-interacting protein (TXNIP):

TXNIP acts as inhibitor of the thioredoxin by thiol – disulphide oxidoreductase, which are the potential agents to control the oxidative stress and maintain the balance of stress.<sup>[45]</sup> Thereby TXNIP promotes the stress induced diabetes in response to hyperglycemia in pancreatic  $\beta$  cell. The disulphide exchange of TRX forms TRX1 and TRX2. Both TRX1 and TXNIP contributed activation of NLRP3 inflammasome due to their redox dependent signaling pathway. The dissociated from of free TXNIP from the TRX activates the release of caspase -1 and IL 1 $\beta$  attributing to the death of pancreatic  $\beta$  cells, endothelial cells and intraocular vessels by stimulating NLRP3 inflammasome.<sup>[46]</sup> The redox signaling complex i.e TRX/TXNIP acts as link between the regulation of redox state and progression of diabetes.

### Autophagy

The cellular process of breakdown of protein into amino acids during the time of need or metabolism or starvation is called as Autophagy. Diabetes is a metabolic syndrome characterized by

Autophagy.<sup>[47]</sup> The formed amino acids are used for the energy production upon oxidative phosphorylation to ATP in mitochondria. It is observed that an inappropriate production of ATP is due to changes in autophagy at the sites of diabetic complications. Insulin is one of the controller switches to autophagy by limiting the productions of autophagosomes.<sup>[48]</sup> Autophagy was observed in diabetes complications due lack of insulin production and insulin resistance due to breakdown of cellular contents and damaged proteins. Autophagy was observed more in pancreatic  $\beta$  cells due to insulin resistance. The chronic over-reactivity and inactivity also may contribute to the diabetes and associated complications.<sup>[49]</sup>

### Epigenetic Changes

The hereditary also plays a notable role in diabetes. The alterations are due to specific and responsive to the environment. The epigenetic modification of respective genes such as absence of a sequence of DNA due to methylation and histone acetylation of DNA and RNA involved mechanisms. Some of the genes responsible for the development of diabetes and associated complications Adiponectin, ADIPOR1 (Adiponectin receptor), ApoE (Lipoprotein transport), CDKN2A/2B (cyclin dependent kinase inhibitors), CELSR2-PSRC1-SORT1 (CELSR2 cadherin super family), GLUL (Glutamate), HMG A1 (High mobility group A1), HNF1A (Hepatic nuclear factor 1A), HP (Hepatoglobin), Paraoxonase, PCSK9 (Proprotein convertase subtilism/Kexin type 9), PHACTR1 (Phosphatase and Actin regulator 1), SOD2 (Superoxide dismutase 2) and TCF7L2 (Transcription factor 7-like 2).

### CONCLUSION

Since research in the development of the new drugs with different mechanism of actions in diabetes is prompt, the existing drugs are not enough to control the incidence and mortality of diabetes and associated complications. The research is not only to establish new drugs as well as to develop new formulations and delivery systems to enhance the pharmacokinetic and pharmacodynamic properties to enhance the therapeutic efficacy and compliance of patients. The insulin, oral hypoglycemic agents, biguanides, thiazolidinediones,  $\alpha$  glucosidase inhibitors are most commonly used antidiabetic agents. Research need to extend for the improvement of existing mechanisms and development of unexplored class of drugs such as aldose reductase inhibitors, anti AGE agents, incretin mimetics, DPP4 inhibitors, SGLT2 inhibitors, AMPK activators, Glucokinase activators, GKRIP inhibitors,

PKC $\beta$  inhibitors and MNR1B inhibitors etc to the control and to prevent the progression of diabetes and associated complications.

## CONFLICT OF INTEREST

The authors declare no conflict of interest

## ABBREVIATIONS

**11 $\beta$  HSD1:** 11 $\beta$ -hydroxysteroid dehydrogenase type 1; **AGEs:** Advanced glycation end products; **AMPK:** AMP activated protein kinase; **DGAT:** Diacylglycerol Acyltransferase; **DPP4:** Dipeptidyl-peptidase 4; **GIP:** Glucose-dependent insulinotropic peptide; **GLP -1:** Glucagon-like peptide 1; **GPCRs:** G protein coupled receptors; **HCA2:** Hydroxycarboxylic Acid Receptor 2; **HSP:** Heat Shock Proteins; **MAPK:** Mitogen-Activated Protein Kinases; **MTR:** Melatonin Receptors; **PKC:** Protein Kinase C; **SCD:** Stearoyl-CoA desaturase; **SGLT2:** Sodium Glucose co-Transporter 2; **SUR:** Sulphonyl urea receptors; **TXNIP:** Thioredoxin-interacting protein; **GSH:** reduced glutathione; **GIP:** Glucose insulinotropic peptide; **PDX-1:** pancreatic duodenal homeobox -1 protein; **G6PDH:** glucose 6 phosphate dehydrogenase; **IRS -1:** insulin receptor substrate 1.

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