Review Article

Post-Translational Modifications as Molecular Mediators in the Pathogenesis and Complications of Diabetes

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ABSTRACT

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| Diabetes mellitus is a multifactorial metabolic disorder marked by chronic hyperglycemia and associated complications that affect millions globally. Recent advances in molecular biology have highlighted the central role of post-translational modifications (PTMs) in the pathogenesis and progression of all major types of diabetes, including type 1, type 2 and gestational diabetes. This review focuses on three pivotal PTMs- glycation, phosphorylation, and acetylation, along with their interrelated roles in disrupting insulin signaling, promoting inflammation and driving diabetic complications. Glycation leads to the formation of advanced glycation end-products (AGEs) that impair protein function and trigger the RAGE-mediated inflammatory cascade. Phosphorylation, when dysregulated by nutrient excess and stress-activated kinases, disrupts insulin signal transduction and exacerbates insulin resistance. Acetylation, particularly of histones and metabolic regulators, modulates gene expression patterns linked to the metabolic memory of prior hyperglycemic insults. We explore how these PTMs influence molecular and cellular mechanisms contribute to long-term complications, and offer novel diagnostic and therapeutic opportunities. By understanding the intricate crosstalk between these PTMs, this review advocates for integrated strategies targeting glycation, kinase signaling and epigenetic modulation to improve diabetes management and outcomes. |

*Keywords: Post-translational modifications; diabetes mellitus; glycation; phosphorylation; acetylation; insulin resistance; diabetic complications*

1. INTRODUCTION

Diabetes mellitus encompasses a group of metabolic disorders characterized by chronic hyperglycemia due to defects in insulin production and/or action. The major forms include type 1 diabetes (T1D), an autoimmune destruction of pancreatic β-cells leading to insulin deficiency, type 2 diabetes (T2D), characterized by insulin resistance and eventual β-cell dysfunction, and gestational diabetes mellitus (GDM), glucose intolerance first recognized during pregnancy(Jadon et al., 2024; Zgutka et al., 2024). These conditions share the common consequence of elevated blood glucose, which triggers a cascade of biochemical derangements.

Post-Translational Modifications (PTMs), which involve covalent changes to proteins after synthesis, are increasingly acknowledged as key contributors to the pathophysiology of diabetes(Chatterjee & Thakur, 2018; Karve & Cheema, 2011; Vanuopadath et al., 2016). In particular, three PTMs stand out for their roles in diabetic disease mechanisms- glycation, phosphorylation and acetylation(Arumugam et al., 2022; Werner et al., 2004; Zhang et al., 2025). Each of these modifications can alter protein function and signaling pathways, thereby contributing to insulin signaling defects, inflammatory cascades and the development of complications.

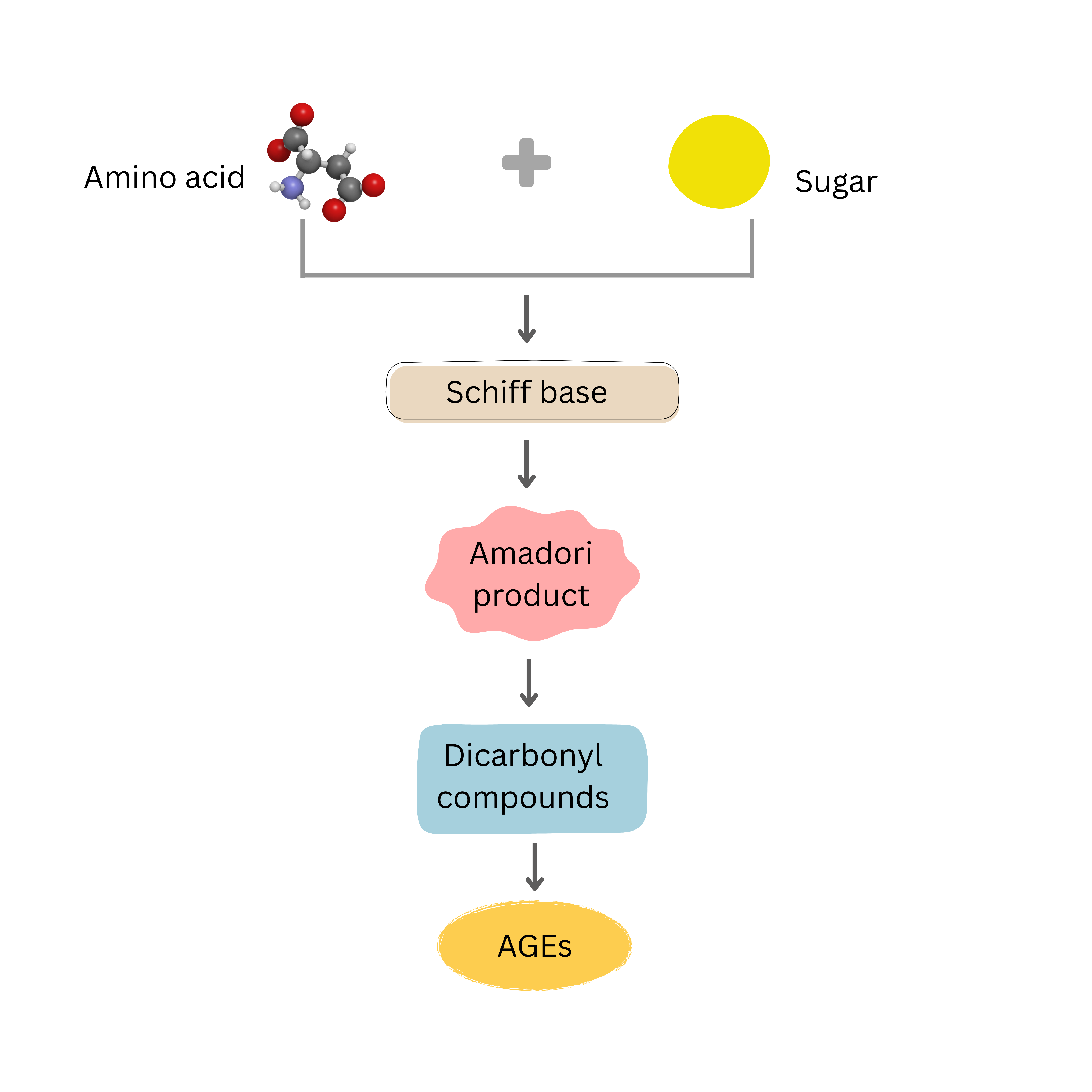
The prevalence of diabetes has reached epidemic proportions. T2D alone afflicts an estimated 400 million people worldwide(Carmichael et al., 2019a) and its hallmark insulin resistance is a key challenge in therapy. In all forms of diabetes, chronic hyperglycemia exerts toxic effects through multiple mechanisms, including excessive non-enzymatic glycation of proteins, dysregulation of kinase-mediated phosphorylation signaling and persistent epigenetic changes such as histone acetylation changes(Gao et al., 2004; Lehnen et al., 2013; N. Li et al., 2024; Pan et al., 2022; Shi et al., 2023; Zhang et al., 2025). These PTMs link the metabolic disturbance of diabetes to cellular dysfunction. For instances, glycation results in advanced glycation end-products that can damage tissues, aberrant phosphorylation underlies impaired insulin signal transduction and activates pro-inflammatory pathways, and altered acetylation of histones and other proteins can cause lasting changes in gene expression which is called the metabolic memory phenomenon.

This review provides a comprehensive overview of the roles of glycation, phosphorylation and acetylation in the biochemistry of diabetes. We have focused on how these PTMs influence insulin signaling, inflammatory pathways and diabetic complications across T1D, T2D and GDM. Besides, we have discussed the biomarkers and therapeutic strategies targeting these modifications.

2. Glycation and Advanced Glycation End-Products (AGEs) in Diabetes

**2.1 Mechanisms of Glycation:**

Glycation is a non-enzymatic PTM in which a reducing sugar, such as glucose, chemically reacts with amino groups on proteins, lipids or nucleic acids (Ulrich & Cerami, 2001). The process begins with the formation of a labile Schiff base between glucose and an amino group (e.g. the ε-amino group of lysine), which then rearranges into a more stable Amadori product(Rhee & Kim, 2018a; Zhang et al., 2025). Over time, Amadori intermediates undergo further dehydration, oxidation and cross-linking reactions, often involving dicarbonyl intermediates like glyoxal and methylglyoxal to form irreversible advanced glycation end-products (AGEs). This multistep Maillard reaction is favored by chronically elevated glucose levels and oxidative stress, conditions inherent in poorly controlled diabetes(Thorpe & Baynes, 1996; Zhou et al., 2024). Figure 1 illustrates the glycation pathway starting from initial Schiff base formation to Amadori products, reactive dicarbonyl compounds (such as glyoxal and methylglyoxal) generation, and ultimately the accumulation of AGEs. Common AGEs include Nε-carboxymethyl-lysine (CML) and Nε-carboxyethyl-lysine (CEL). AGEs accumulate in proportion to the degree and duration of hyperglycemia(Rhee & Kim, 2018b), and they can cross-link macromolecules or modify signaling proteins, contributing to diabetic complications.



**Fig. 1. Non-enzymatic glycation and AGE formation in diabetes.** *Simplified schematic of the Maillard reaction leading to advanced glycation end-products (AGEs), adopted from (Zhang et al., 2025). An amino group (e.g., on a protein lysine) reacts with a reducing sugar to form a reversible Schiff base. This rearranges into a stable Amadori product. Through autoxidation and peroxidation pathways, reactive dicarbonyl compounds are generated, which then rearrange and react further to form final AGEs.*

AGE formation is of great clinical relevance in diabetes. Hemoglobin A1c (HbA1c), an Amadori adduct of glucose with hemoglobin, serves as a key biomarker of chronic glycemia(Krhač & Lovrenčić, 2019; Lyons & Basu, 2012). Beyond HbA1c, a plethora of AGEs accumulate on long-lived proteins like collagen in vessel walls and the extracellular matrix. These modifications can alter protein structure and mechanical properties, for instance, AGE cross-links in collagens increase stiffness and trap lipoproteins in arteries(Rhee & Kim, 2018b). Importantly, AGEs are formed endogenously as a function of hyperglycemia and oxidative stress, but they can also be ingested from exogenous sources, such as dietary AGEs, compounding the total body AGE pool(Bansal et al., 2023).

**2.2 Pathophysiological Impact of AGEs:**

AGEs exert pathogenic effects through multiple avenues-

* **Direct Modification of Proteins:** AGEs can directly alter the structure and function of proteins. AGE cross-linking of serum and matrix proteins can render them dysfunctional, for example, glycated collagen in the basement membrane impairs its turnover and interaction with cells(Bansal et al., 2023). Key enzymes or receptors modified by glycation may lose activity or binding affinity.
* **Receptor-Mediated Inflammation:** AGEs trigger cellular signaling by binding to specific receptors. The best-characterized is the Receptor for AGEs (RAGE), a pattern-recognition receptor expressed on many cell types, including endothelial cells, macrophages, neurons, etc.(Teissier & Boulanger, 2019). Binding of AGEs to RAGE initiates a pro-inflammatory and pro-oxidative signaling cascade(Rani et al., 2025; Rhee & Kim, 2018b). Upon AGE-RAGE interaction, intracellular signaling pathways such as nuclear factor κB (NF-κB) are activated, leading to increased production of reactive oxygen species (ROS) and secretion of inflammatory cytokines (e.g., TNF-α, IL-6) and adhesion molecules. RAGE signaling thus propagates chronic inflammation in diabetic tissues. Notably, hyperglycemia itself upregulates RAGE expression, and diabetic patients show elevated RAGE in affected tissues. For instance, enhanced RAGE in atherosclerotic lesions correlates with poorer glycemic control(Barlovic et al., 2011; Rhee & Kim, 2018b). This creates a vicious cycle- more AGEs lead to more RAGE activation, which induces oxidative stress that in turn accelerates AGE formation and further RAGE expression.
* **Vascular Dysfunction and Thrombosis:** AGEs can perturb hemostatic balance and vascular function. AGE-RAGE signaling in the endothelium reduces nitric oxide (NO) bioavailability through oxidative inactivation of NO, promoting endothelial dysfunction(Pacinella et al., 2022; Rhee & Kim, 2018b). It also upregulates vasoactive mediators like endothelin and angiogenic factors like vascular endothelial growth factor (VEGF), contributing to abnormal angiogenesis seen in retinopathy(Rhee & Kim, 2018b). Moreover, AGEs enhance pro-thrombotic mechanisms. They stimulate tissue factor production and platelet aggregation, and inhibit anti-thrombotic prostacyclin, thereby increasing the thrombotic tendency in diabetes(Batten et al., 2023; Vaidya et al., 2021).

Through these mechanisms, glycation and AGEs are now understood to be key mediators of diabetic complications. Chronic vascular complications of both T1D and T2D, including retinopathy, nephropathy, neuropathy and accelerated atherosclerosis have been linked to the accumulation of AGEs in tissues(Mauricio et al., 2020; Pal & Bhadada, 2023). For example, in diabetic retinopathy, AGEs in the retinal capillary basement membrane correlate with microaneurysm formation and pericyte loss. In diabetic nephropathy, AGE-crosslinked proteins in the glomeruli contribute to basement membrane thickening and dysfunction. In large vessels, glycation of lipoproteins and matrix aggravates atherogenesis(Wang et al., 2024). The pathological significance of AGEs is further supported by experimental interventions. For example, inhibition of AGE formation or breaking AGE cross-links can ameliorate diabetic tissue damage in preclinical models(Rhee & Kim, 2018b).

**2.3 Metabolic Memory and Legacy Effect:**

A particularly compelling aspect of AGEs is their role in the “metabolic memory” of diabetes. This is a phenomenon wherein early periods of poor glycemic control have lasting effects on complication risk, even if glycemia is later well-controlled(Bain et al., 2019; Monnier et al., 2019). Long-term follow-ups of the Diabetes Control and Complications Trial (DCCT) and the U.K. Prospective Diabetes Study (UKPDS) showed that patients with intensive early glycemic control continued to experience reduced complications years after blood glucose levels equalized between groups(Rhee & Kim, 2018b). One hypothesis for this legacy effect is the slow turnover of AGEs(Rhee & Kim, 2018b). AGEs, once formed, can persist for months to years. For example, collagen cross-links have half-lives on the order of the collagen matrix, which can be several years(Nimni & Harkness, 2018). Strict glycemic control early in the disease minimizes AGE accumulation, whereas prolonged hyperglycemia irreversibly deposits AGEs that continue to wreak havoc even after normoglycemia is restored(Rhee & Kim, 2018b). Indeed, AGEs have been implicated as a key factor in metabolic memory as their lingering presence keeps RAGE pathways activated and sustains tissue damage. Consistent with this, higher tissue AGE levels have been correlated with progression of complications, and drugs targeting the AGE-RAGE axis are thought to potentially erase some of this “memory”(Rhee & Kim, 2018b; Taguchi & Fukami, 2023). Additionally, AGEs in the serum or their proxies like skin autofluorescence are being explored as biomarkers to predict long-term complication risk(Da Moura Semedo et al., 2017; Waqas et al., 2020, 2022).

**2.4 Glycation in Type 1, Type 2 and Gestational Diabetes:**

The glycation process is fundamentally driven by glucose concentration and exposure time, so it is common to all forms of diabetes(Antar et al., 2023; Khalid et al., 2022; Vlassara & Uribarri, 2014). However, there are some differences in glycation process among T1D, T2D and GDM-

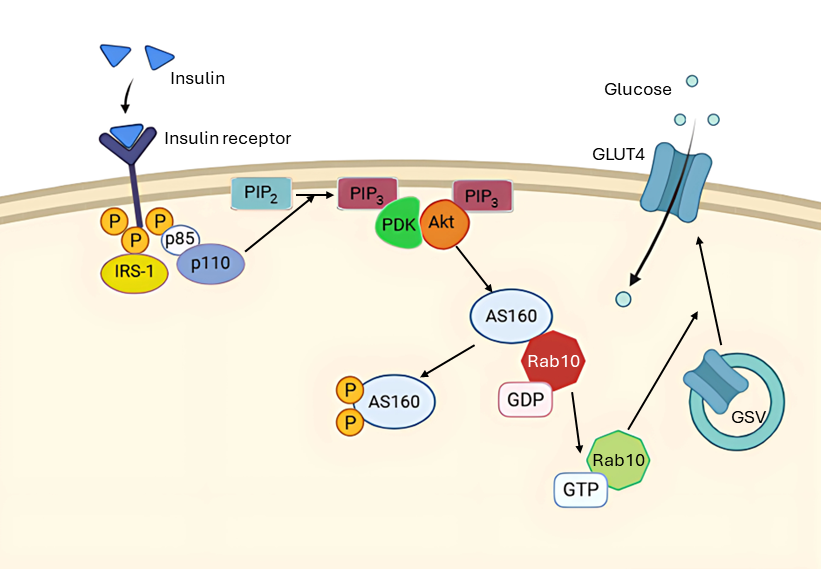
* **Type 1 and Type 2 Diabetes:** In uncontrolled T1D and T2D, sustained hyperglycemia leads to similar biochemical consequences of AGE accumulation. One distinction is that T1D often presents earlier in life, so the absolute duration of exposure to hyperglycemia prior to intervention might be shorter, whereas T2D can go undiagnosed for years(Skyler et al., 2017). Nevertheless, both types manifest microvascular complications mediated by AGEs, and both benefit from tight glucose control to reduce AGE formation.
* **Gestational Diabetes:** Gestational diabetes, being limited to pregnancy, represents a shorter window of hyperglycemia. however, it can still expose the developing fetus and placenta to high glucose and AGEs(Ma et al., 2015; Plows et al., 2018; Shi et al., 2023). Studies indicate that GDM placentas show increased AGE levels and altered function. For instance, AGEs can increase placental vascular permeability and inflammation(Shi et al., 2023). There is also concernthat maternal hyperglycemia and AGEs might induce epigenetic changes in the fetus that predispose the offspring to metabolic disease. Clinically, women with GDM are advised to control blood sugar to minimize glycation stress on the placenta and fetus. Additionally, GDM is a risk factor for future T2D in the mother, possibly due to lingering effects, including AGE-related tissue damage or pancreatic stress. Approximately, 16% of women with GDM develop T2D within 10–15 years(N. Li et al., 2024).

In summary, glycation represents a fundamental biochemical thread connecting hyperglycemia to tissue damage in diabetes. By generating AGEs that directly impair protein function and activate inflammatory signaling via RAGE, chronic hyperglycemia creates a self-perpetuating cycle of oxidative stress and inflammation. This underlies many complications and underscores the importance of early and sustained glycemic control. Therapeutically, strategies to reduce AGE accumulation through strict glucose control and dietary AGE restriction or to block AGE-RAGE signaling using soluble RAGE decoys or RAGE antagonists are being investigated as means to attenuate diabetic complications(Shi et al., 2023).

3. Phosphorylation and Insulin Signaling Dysregulation in Diabetes

**3.1 Insulin Signaling Under Physiological Conditions:**

Reversible protein phosphorylation is a cornerstone of insulin’s action and is acutely involved in glucose homeostasis. In healthy individuals, insulin binding to its receptor (IR) on cell membranes initiates a complex phosphorylation cascade that allows cells to uptake and store glucose(De Meyts, 2016). The insulin receptor is a tyrosine kinase that exists as a preformed dimer. Upon insulin binding, the receptor undergoes autophosphorylation on multiple tyrosine residues on its β-subunits (Goodsell et al., 2015; Tatulian, 2015). These phosphotyrosines serve as docking sites for insulin receptor substrates, IRS proteins, mainly IRS-1 and IRS-2 in metabolic tissues. IRS-1 is then phosphorylated on tyrosine residues by the receptor, creating binding sites for downstream signaling molecules such as the p85 regulatory subunit of phosphoinositide 3-kinase (PI3K)(Carmichael et al., 2019a; Myers Jr et al., 1994). PI3K activation leads to the production of the lipid second messenger PIP3 from PIP2 in the plasma membrane. PIP3 in turn recruits and activates PIP3-dependent kinase (PDK) and Akt (Protein Kinase B) via phosphorylation. Activated Akt dissociates from the membrane and phosphorylates a host of substrates, among which the most critical for acute glucose regulation is AS160 (also known as TBC1D4)(Fung Lee et al., 2019). Phosphorylation of AS160 releases its inhibition on the small GTPase Rab10, allowing GLUT4 glucose transporter vesicles to translocate to the cell surface. The end result is a rapid increase in glucose uptake by muscle and adipose tissues, which lowers blood glucose. In the liver, insulin signaling through Akt also phosphorylates and inactivates glycogen synthase kinase-3, thereby activating glycogen synthase and promoting glucose storage as glycogen. Insulin’s mitogenic arm of signaling involves the Ras/MAPK pathway- phosphorylated IRS-1/Shc recruit Grb2/SOS, activating Ras and the Raf–MEK–ERK cascade which affects gene expression and cell growth(Nelson et al., 2011). This pathway is less directly tied to glycemic control but is part of insulin’s overall effects. Figure 2 depicts the insulin signaling pathway leading to glucose uptake, highlighting key phosphorylation events.



**Figure 2: Insulin receptor signaling cascade (PI3K/Akt pathway) mediating glucose uptake.** *Insulin binds to the extracellular α-subunits of the insulin receptor (IR), triggering kinase activation in the β-subunits. The IR autophosphorylates on tyrosine residues, which then recruit and phosphorylate insulin receptor substrate-1 (IRS-1) on tyrosine residues. IRS-1 then recruits PI3K (p85/p110) and phosphorylates the p85 regulatory subunit. Activated PI3K converts PIP\_2 to PIP\_3 in the membrane, which brings PDK and Akt to the membrane via their PH domains. PDK phosphorylates Akt, activating it. Active Akt phosphorylates AS160, disabling AS160’s inhibition of Rab10. This allows Rab10-GTP to facilitate the fusion of GLUT4 vesicles (GSVs) with the plasma membrane, thereby increasing glucose uptake. In insulin resistance, excess fatty acids and inflammatory signals activate stress kinases (e.g. JNK, IKK, PKC) that phosphorylate IRS-1 on serine sites, reducing IRS-1’s ability to propagate the insulin signal. This impairs downstream PI3K/Akt signaling and GLUT4 translocation, contributing to hyperglycemia. Figure adopted from (Carmichael et al., 2019a).*

Under normal circumstances, this exquisitely coordinated phosphorylation network allows the body to maintain glucose homeostasis. About 80% of insulin-mediated glucose disposal occurs in skeletal muscle, making muscle a primary “glucose sink” tissue(Carmichael et al., 2019a). In the fasting state (low insulin), kinases such as glycogen synthase kinase and hormone-sensitive lipase are active, often via phosphorylation by AMP-activated kinase or PKA pathways, which promotes glucose production and fat utilization(Carmichael et al., 2019a; H. Yang & Yang, 2016). A surge of insulin after a meal rapidly flips these phosphorylation patterns, where insulin signaling dephosphorylates/inactivates catabolic enzymes and phosphorylates/activates anabolic enzymes, leading to glucose uptake and storage(De Meyts, 2016). This dynamic is fundamentally disrupted in diabetes.

**3.2 Insulin Resistance and Aberrant Phosphorylation:**

In T2D and often in GDM, target cells do not respond adequately to insulin, a condition known as insulin resistance. A central biochemical cause of insulin resistance is dysregulated phosphorylation of insulin signaling proteins, especially serine/threonine phosphorylation of IRS-1/2 that impairs their function(Gao et al., 2004). In insulin-responsive tissues, such as, muscle, fat and liver of obese or diabetic individuals, IRS-1 is often found to be hyperphosphorylated on specific serine residues. These modifications, mediated by stress-activated kinases, reduce IRS-1’s ability to be tyrosine-phosphorylated by the insulin receptor and to engage downstream effectors(Werner et al., 2004). Key kinases implicated in this process include c-Jun N-terminal kinase (JNK), IκB kinase (IKK), and certain isoforms of protein kinase C (PKC).

* **JNK:** JNK can phosphorylate IRS-1 at Ser307 in rodent IRS-1 (Ser312 in human), which interferes with the IRS-1/insulin receptor interaction(Carmichael et al., 2019a; Solinas & Becattini, 2017).
* **IKK-β:** IKK-β, a kinase downstream of inflammatory signals like TNF-α, has also been shown to phosphorylate IRS-1 and contribute to insulin resistance induced by free fatty acids(Gao et al., 2004).
* **PKC:** In obesity and GDM, elevated circulating fatty acids lead to accumulation of lipid metabolites (diacylglycerol, ceramides) in muscle and liver. This diacylglycerol can directly activate PKC isoforms (e.g. PKC-θ in muscle, PKC-ε in liver) which then phosphorylate IRS-1 on inhibitory sites(Carmichael et al., 2019a). Besides, ceramides can activate PP2A phosphatase or other pathways that blunt Akt activation.

Collectively, these mechanisms explain how overnutrition and inflammation create a biochemical block in the insulin signaling cascade downstream of the insulin receptor(Carmichael et al., 2019b). As a result, even though insulin is present, the normal tyrosine phosphorylation events are attenuated while counterproductive serine phosphorylation events are increased, leading to reduced GLUT4 translocation and hyperglycemia.

The “lipid overload” and inflammatory hypothesis of insulin resistance is supported by numerous studies(Ferroni et al., 2004; Gao et al., 2004; Johnson & Olefsky, 2013; Lark et al., 2012; Mthembu et al., 2022; Unger, 2003). For example, treating cells or animals with TNF-α or saturated fatty acids impairs insulin-stimulated tyrosine phosphorylation of IRS-1 and PI3K activation(Gao et al., 2004). Genetic knockouts of JNK1 or IKK-β in mice confer protection against diet-induced insulin resistance, underscoring the role of these kinases in mediating the antagonistic phosphorylation on insulin signaling proteins. Pharmacologically, salicylates (which inhibit IKK-β) and other anti-inflammatory agents have been shown to improve insulin sensitivity and glycemic control by relieving this inhibitory phosphorylation on IRS protein(Gao et al., 2004). In human T2D muscle biopsies, the level of IRS-1 serine phosphorylation is often elevated, and insulin receptor/IRS-1 tyrosine phosphorylation is blunted, correlating with the degree of insulin resistance(Copps & White, 2012). Thus, a network of serine/threonine kinases activated by nutrient-excess and inflammation essentially “hijacks” the insulin signaling pathway, imposing molecular brakes on the normal phosphorylation cascade.

It is worth noting that type 1 diabetes, in its classical etiopathology, is not caused by insulin resistance but by insulin deficiency due to autoimmune β-cell destruction(Roep et al., 2021). However, even in T1D, patients can develop insulin resistance, for instance, due to obesity or high doses of exogenous insulin leading to downregulation of receptors(Cleland et al., 2013; Kahn & Flier, 2000; Kaul et al., 2015). Moreover, from any cause once hyperglycemia is present, the same pathways of glucotoxicity and lipotoxicity can induce insulin resistance in peripheral tissues(Robertson & Harmon, 2006; Vilas-Boas et al., 2021; Weir, 2020). In contrast, gestational diabetes is often fundamentally a state of insulin resistance precipitated by placental hormones (such as human placental lactogen) superimposed on a genetic/metabolic predisposition(Rodriguez et al., 2024). The biochemical underpinnings mirror those of T2D, where pregnant women with GDM exhibit elevated levels of free fatty acids and inflammatory cytokines (e.g., IL-6, TNF-α) that activate serine kinases and impede insulin signaling(Omu, 2013). The placenta itself can be a source of inflammatory signals; GDM placentas show increased expression of inflammatory pathway components like toll-like receptors and IL-1, and evidence of insulin signaling defects in trophoblasts, indicating that phosphorylation pathways are disrupted in maternal and placental tissues alike(Zgutka et al., 2024) . Fortunately, in GDM the insulin resistance often resolves after delivery when placental hormones dissipate(Rodriguez et al., 2024). However, the affected women remain at higher risk for later T2D, suggesting that some molecular changes may linger(N. Li et al., 2024).

**3.3 Phosphorylation in Inflammatory Cascades:**

Beyond insulin signaling per se, phosphorylation events are integral to the inflammatory cascades that are both a cause and consequence of diabetes. Chronic, low-grade inflammation is a hallmark of T2D and obesity(Khanna et al., 2022; Pereira & Alvarez-Leite, 2014). Key pro-inflammatory pathways, such as the NF-κB pathway, are regulated by phosphorylation. In the resting state, the transcription factor NF-κB is sequestered in the cytoplasm by inhibitor IκB. Pro-inflammatory signals like TNF-α, lipopolysaccharide, or AGEs via RAGE activate the IKK complex, which phosphorylates IκB, targeting it for degradation. NF-κB is then translocated to the nucleus and induces genes encoding cytokines (TNF-α, IL-1β, IL-6, etc.), chemokines and adhesion molecules(N. Li et al., 2024; Pereira & Alvarez-Leite, 2014). In diabetes, the NF-κB pathway is chronically active in many tissues, such as, adipose tissue of obese individuals and vascular cells in diabetics. This pathway is driven by signals such as elevated fatty acids, AGEs and oxidative stress(Griffin, 2022; Oliver et al., 2010). Indeed, there is significant crosstalk between the AGE/RAGE axis and phosphorylation-dependent inflammatory pathways. RAGE activation leads to downstream phosphorylation of kinases like PKC, MAPKs and IKK, which converge on NF-κB activation(Rhee & Kim, 2018a). This results in a self-amplifying inflammatory state.

Mitogen-activated protein kinases (MAPKs) such as JNK and p38 are also activated by hyperglycemia and ROS, and they phosphorylate various transcription factors (c-Jun, ATF-2) to induce pro-inflammatory gene expression(Hou et al., 2008). Therefore, phosphorylation events act as molecular switches turning on inflammation in diabetes, which in turn can worsen insulin resistance, creating a vicious cycle. An illustrative example is that mice lacking IKK-β in myeloid cells have reduced inflammation and are protected from insulin resistance, highlighting how IKK-β/NF-κB signaling in immune cells contributes systemically(Arkan et al., 2005).

**3.4 Phosphorylation in Diabetic Complications:**

Protein phosphorylation changes are central to how hyperglycemia translates into organ damage. There are several pathways of protein phosphorylation in diabetic complications-

* **Protein Kinase C (PKC) pathway:** One prominent pathway of phosphorylation is the Protein Kinase C (PKC) pathway, which is markedly activated in hyperglycemic conditions. Hyperglycemia increases flux through glycolysis, raising diacylglycerol levels in cells. DAG is a direct activator of conventional and novel PKC isoforms. Activated PKC, particularly PKC-β and PKC-δ, has numerous downstream effects that align with the pathology of microvascular complications(Pan et al., 2022). PKC activation in endothelial cells reduces NO production by inhibiting eNOS and increasing NADPH oxidase-derived ROS, leading to vasoconstriction and endothelial dysfunction(Pan et al., 2022). It also increases expression of endothelin-1 (a vasoconstrictor) and vascular endothelial growth factor promoting abnormal angiogenesis as in retinopathy(Rhee & Kim, 2018a). PKC facilitates NADPH oxidase activation which greatly boosts oxidative stress in vascular cells(Pan et al., 2022). The result is damage to capillaries through increased permeability, impaired autoregulation of blood flow, basement membrane thickening (via overproduction of ECM components like fibronectin and collagen), and aberrant angiogenesis(Pan et al., 2022). These changes are exactly those observed in diabetic retinopathy, nephropathy, and neuropathy. In support of this mechanism, PKC-β inhibitors (such as ruboxistaurin) were tested in clinical trials for diabetic retinopathy. Although there was not a complete cure, the inhibitors showed some reduction in vision loss progression(Pan et al., 2022). This underscores that PKC-mediated phosphorylation events are indeed contributing to human diabetic tissue injury.
* **Hexosamine Pathway and p38 MAPK:** Another example of phosphorylation is the hexosamine pathway where hyperglycemia increases fructose-6-phosphate flux into hexosamine biosynthesis, ending in UDP-N-acetylglucosamine (UDP-GlcNAc) production(Paneque et al., 2023). This can lead to O-GlcNAcylation of proteins (a different PTM not the focus here), but also the byproducts can activate p38 MAPK and other stress kinases, again causing pathogenic phosphorylation of transcription factors that induce inflammation and fibrosis(Chen & Natarajan, 2022).
* **Other Phosphorylation Pathways:** In the kidneys, high glucose stimulates phosphorylation of signaling molecules like transforming growth factor-β (TGF-β) activators, driving glomerular sclerosis(López-Hernández & López-Novoa, 2012). In neurons, hyperglycemia can activate Ca2+-dependent kinases leading to phosphorylation of tau protein potentially linking diabetes to neurodegenerative changes(Qu et al., 2023; J. Wu et al., 2017).

Collectively, these data show that phosphorylation networks are at the heart of both metabolic signaling (insulin action) and stress signaling (inflammation, vascular dysfunction) in diabetes. The interplay is complex, for example, hyperglycemia and AGEs activate PKC, which causes both functional changes in blood vessels and further AGE accumulation by oxidative stress(Pan et al., 2022). Meanwhile, insulin resistance due to serine-phosphorylation of IRS-1 leaves more glucose in the bloodstream to feed into harmful pathways. Thus, dysregulated phosphorylation is a major point of convergence in diabetic pathology.

From a therapeutic standpoint, targeting these kinase pathways offers potential benefits. Aside from lifestyle interventions (weight loss, exercise) which are known to reduce inflammation and improve insulin sensitivity, several pharmacologic approaches have been explored- anti-inflammatory drugs (e.g. salsalate) to inhibit IKK/NF-κB, JNK inhibitors, and PKC inhibitors for complications(Group, 2005). While none are yet standard therapy for diabetes, they highlight the rationale of modulating phosphorylation cascades. Furthermore, for T1D and advanced T2D, insulin therapy itself can be viewed as an attempt to restore proper activation of the insulin phosphorylation cascade, where exogenous insulin will engage the insulin receptor and can partially override some of the resistance if given in high doses, although it does not directly fix the aberrant serine phosphorylation issue. In summary, maintaining a balance in phosphorylation signaling, that is promoting physiological insulin signaling while dampening stress kinase signaling is crucial in diabetes management, which is why multi-faceted approaches including glycemic control, anti-inflammatory treatments and possibly kinase modulators are being actively researched.

4. Acetylation, Epigenetics and Metabolic Memory in Diabetes

**4.1 Overview of Acetylation and Epigenetic Regulation:**

Acetylation is a PTM in which an acetyl group is covalently attached to a lysine residue of a protein(Drazic et al., 2016). In the context of chromatin, histone acetylation on lysine residues, particularly on histone tails such as H3 and H4, neutralizes their positive charge and reduces their affinity for DNA, resulting in a more open chromatin structure and typically increased gene transcription(Chen & Natarajan, 2022). Thus, histone acetylation is an epigenetic mark associated with active gene expression, whereas deacetylation condenses chromatin and represses transcription. The acetylation status of histones is governed by a balance between histone acetyltransferases (HATs), which add acetyl groups and histone deacetylases (HDACs), which remove them(Chen & Natarajan, 2022; Peserico & Simone, 2011). In mammalian cells, HDACs include a class of NAD+-dependent deacetylases known as sirtuins (SIRT1-7)(Jung et al., 2008; Schemies et al., 2010). These enzymes not only target histones but also many transcription factors and metabolic enzymes, making acetylation a widespread regulatory mechanism.

In diabetes, chronic metabolic perturbations induce changes in the cellular acetylation landscape, both on histones, affecting gene expression programs and on non-histone proteins that control metabolism and inflammation(Shvedunova & Akhtar, 2022; Y.-L. Wu et al., 2023). Such changes can be long-lasting, contributing to the metabolic memory of previous hyperglycemia even after glycemic control is improved(Chen & Natarajan, 2022). Epigenetic studies in diabetes have revealed distinct histone modification patterns in vascular cells, monocytes and even in pancreatic islets of diabetic versus non-diabetic conditions(D. Li et al., 2022). For instance, promoters of pro-inflammatory genes in diabetic vascular cells can exhibit a loss of repressive histone marks and gain of active marks, maintaining a state of “epigenetic activation” of inflammation(Chen & Natarajan, 2022).

**4.2 Histone Acetylation in Diabetic Complications:**

Prolonged hyperglycemia has been shown to alter the activity of both HATs and HDACs in target tissues. Notably, studies in models of diabetic complications like retinopathy found that hyperglycemia can paradoxically increase HDAC activity and decrease global histone acetylation in certain contexts(Chen & Natarajan, 2022). For example, in diabetic retinal cells, high glucose was reported to increase class I HDAC expression and reduce acetylation of histone H3. These changes persisted even after returning to normoglycemia, suggesting an epigenetic basis for continued gene dysregulation(Chen & Natarajan, 2022). Consistently, inhibiting HDACs in those models, which would increase histone acetylation, attenuated inflammation and cell death, indicating that an optimal level of histone acetylation is protective(Dong et al., 2024). On the other hand, specific gene promoters may become hyperacetylated in diabetes if they are driven by strong HAT activity. A prime example involves the NF-κB subunit p65 (RelA). Persistent hyperglycemia can lead to upregulation of the HAT p300/CBP which acetylates p65, enhancing NF-κB’s transcriptional activity and thus prolonging the expression of inflammatory genes even when glucose is normalized(Chen & Natarajan, 2022). This has been demonstrated in a “memory” setting where transient high glucose caused prolonged NF-κB activation in vascular cells via sustained p65 acetylation.

Another well-studied target is the promoter of the p66Shc gene which is involved in oxidative stress. Hyperglycemia induces persistent hypomethylation and hyperacetylation at the p66Shc promoter in endothelial cells, leading to its upregulation and increased ROS production, changes that were shown to last even after glucose normalization(Chen & Natarajan, 2022). These epigenetic alterations, including histone H3 acetylation changes, were linked to the phenomenon of metabolic memory in diabetic vascular complications(Chen & Natarajan, 2022).

In monocytes from patients with a history of poor glycemic control, pro-inflammatory genes, such as IL6 and TNFα have been found to be in a primed state, partly due to histone modifications. Indeed, intensive glucose control can gradually “reset” some of these epigenetic marks, but others remain, indicating that early hyperglycemia can leave a lasting imprint on the epigenome(Rhee & Kim, 2018a). This area is an active field of research, as it offers a molecular explanation for why early aggressive therapy is beneficial and why some complications progress despite later good control.

**4.3 Sirtuins Acetylation and Metabolic Regulation:**

Sirtuins, especially SIRT1, have emerged as important metabolic sensors linking acetylation to diabetes. SIRT1 is a NAD+-dependent deacetylase that targets numerous substrates including histones (e.g. H4K16), transcriptional regulators (p53, NF-κB, FOXO1, PGC-1α, PPARγ co-regulators) and others(Kitada & Koya, 2013; Y. Yang et al., 2022). It is highly relevant to diabetes for several reasons. Calorie restriction, which improves insulin sensitivity and extends lifespan in various organisms, upregulates SIRT1 activity. Conversely, overnutrition and aging, which are the risk factors for T2D, are associated with reduced SIRT1 activity.

In pancreatic β-cells, SIRT1 enhances insulin secretion in response to glucose and protects β-cells from oxidative and inflammatory stress by deacetylating and modulating factors like UCP2 and NF-κB(Kitada & Koya, 2013). In insulin target tissues, SIRT1 improves insulin sensitivity. For example, SIRT1 deacetylates PGC-1α and FOXO1 in the liver, which suppresses excessive gluconeogenesis and ameliorates hyperglycemia(Kitada et al., 2019). SIRT1 in skeletal muscle and adipose tissue influences adiponectin levels, mitochondrial function, and fatty acid oxidation, all contributing to better insulin action(Kitada & Koya, 2013). Mice overexpressing Sirt1 have a “calorie restriction-like” phenotype with improved glucose tolerance(Kitada & Koya, 2013), whereas mice with Sirt1 deficiency show metabolic derangements.

Importantly, SIRT1 directly antagonizes inflammation by deacetylating the p65 subunit of NF-κB at Lys310, a modification required for full transcriptional activity of NF-κB(Y. Yang et al., 2022). Thus, when SIRT1 levels are high, NF-κB is kept in check (less acetylated, more tightly bound to inhibitors), reducing inflammatory gene expression. In obesity and T2D, SIRT1 expression/function is often reduced, which correlates with heightened inflammation and insulin resistance. In fact, *sirt1* deletion in myeloid cells leads to exacerbated inflammatory responses due to hyperacetylation and activation of NF-κB, and can promote insulin resistance in mice(Kim et al., 2015). Conversely, SIRT1-activating compounds like resveratrol have been shown in animal models to improve insulin sensitivity and dampen inflammation(Kitada et al., 2019). Resveratrol-treated diabetic mice exhibit lower blood glucose and insulin levels, improved mitochondrial function, and reduced inflammatory cytokines, which are the effects largely attributed to SIRT1 activation. While resveratrol is not a cure-all and human data are mixed, it set the stage for development of more potent SIRT1 activators as potential T2D therapeutics(Kitada & Koya, 2013).

Another sirtuin, SIRT3, operates in mitochondria to deacetylate and activate metabolic enzymes like MnSOD (antioxidant enzyme) and components of the electron transport chain(Bause & Haigis, 2013). In diabetic complications, reduced SIRT3 activity has been linked to increased mitochondrial protein acetylation and oxidative stress. For example, in diabetic kidneys and nerves, low SIRT3 leads to accumulation of mitochondrial ROS, contributing to tissue damage(Locatelli et al., 2020). Enhancing SIRT3 activity or its downstream target superoxide dismutase ameliorates oxidative damage in these tissues. Thus, both nuclear and mitochondrial acetylation events play a role in diabetes pathogenesis.

**4.4 Gestational Diabetes and Epigenetic Changes:**

An emerging concern is that the hyperglycemic intrauterine environment in GDM can induce epigenetic modifications in the developing fetus, possibly affecting the child’s long-term health. Studies have found differences in DNA methylation and histone modification patterns in infants born to GDM mothers compared to those from normoglycemic pregnancies(Lehnen et al., 2013). For instance, endothelial cells from offspring of GDM pregnancies showed enduring epigenetic changes (like DNA hypermethylation) that could contribute to higher cardiometabolic risk(N. Li et al., 2024). One report noted that fetal exposure to GDM causes “enduring epigenetic changes” in the child’s cells, essentially a metabolic memory passed to the next generation(N. Li et al., 2024). While DNA methylation is a distinct modification, it often intersects with histone acetylation status. It has been hypothesized that GDM-related hyperglycemia and metabolic stress in utero might alter histone acetylation in key gene promoters in the fetus, predisposing them to obesity or glucose intolerance later(Lehnen et al., 2013). These findings highlight the importance of managing GDM not only for immediate pregnancy outcomes but also to prevent potential epigenetic “programming” of disease in offspring.

In the mothers, GDM can also leave residual effects. Although blood sugar usually returns to normal post-partum, women with GDM have about a tenfold higher risk of developing T2D in the following years(N. Li et al., 2024). It is possible that temporary hyperglycemia in pregnancy causes epigenetic modifications in the mother’s insulin-producing cells or other tissues that persist, for example, silencing of certain genes by DNA/histone methylation or altering SIRT1 activity, thereby accelerating the transition to T2D. Research in this area is ongoing(Lee et al., 2020).

**4.5 Therapeutic and Research Implications:**

The reversible nature of epigenetic modifications, including acetylation, presents a tantalizing therapeutic avenue. HDAC inhibitors (HDACi) are already used in oncology and could theoretically be repurposed to restore proper gene expression in diabetic complications. For example, small studies in models of diabetic nephropathy show that pan-HDAC inhibitors can reduce renal fibrosis and inflammation, presumably by increasing acetylation of histones at genes that produce anti-fibrotic factors or by de-repressing antioxidant genes(Dong et al., 2024). However, broad HDAC inhibition has side effects, so specificity is an issue. Targeting specific isoforms, like HDAC2 or HDAC3, which are linked to insulin resistance is one strategy under investigation(Suchitra et al., 2023).

Boosting sirtuin activity is another approach. The challenge is that early SIRT1 activators (e.g. resveratrol) have pleiotropic effects and poor potency. Newer SIRT1 activators and NAD+ precursors (such as nicotinamide mononucleotide, NMN, or nicotinamide riboside, NR) aim to enhance the cell’s deacetylation capacity and mimic calorie restriction benefits(Alegre & Pastore, 2023; Cantó et al., 2012). In rodent models, NAD+ supplementation has improved glucose metabolism and mitochondrial function, and clinical trials are exploring these in humans with metabolic syndrome(Covarrubias et al., 2021). The hope is that such therapies could reduce the chronic inflammation and metabolic dysregulation of diabetes by correcting the aberrant acetylation status of key regulators like NF-κB, PGC-1α, p53, etc.(Dewanjee et al., 2021).

Finally, understanding acetylation’s role in metabolic memory suggests that early intervention in diabetes is crucial not just to prevent early damage, but to avoid laying down a harmful epigenetic blueprint(Chen & Natarajan, 2022). If transient hyperglycemia can engrain a long-lasting “memory” via chromatin marks, then tight control from the onset of diabetes or even in pre-diabetes may prevent that epigenetic memory from forming. In this sense, the adage “legacy effect” has a molecular basis- every day of suboptimal control might cumulatively modify the epigenome in ways that are hard to reverse. Future therapies might include drugs that specifically erase or override those marks (for example, demethylating agents or inhibitors of bromodomain proteins that read acetylation), although such treatments would need to be targeted to avoid unwanted effects.

The table below summarizes the three major PTMs discussed glycation, phosphorylation, and acetylation, highlighting their mechanisms and roles in diabetes, as well as examples of therapeutic strategies targeting each.

**Table 1: Major Post-Translational Modifications in Diabetes – Mechanisms, Pathological Roles, and Potential Interventions**

| **PTM** | **Mechanism in Diabetes** | **Pathological Effects** | **Examples of Therapeutic Strategies** |
| --- | --- | --- | --- |
| **Glycation (AGE formation)** | Non-enzymatic reaction of glucose with proteins forming Schiff base → Amadori product → irreversible AGEs(Rhee & Kim, 2018a). Accelerated by high glucose and oxidative stress. Also contributed by dietary AGEs. | Alters protein structure/function via covalent modifications and cross-links(Zhang et al., 2025). Activates RAGE signaling, inducing ROS production and NF-κB-mediated inflammation(Rhee & Kim, 2018a). Leads to vascular stiffening, basement membrane thickening, and pro-thrombotic state. Responsible for “metabolic memory” since AGEs persist long-term. | *Strict glycemic control* – lowers AGE formation and slows complication progression(Rhee & Kim, 2018a). *AGE/RAGE inhibitors* – e.g., aminoguanidine (AGE formation inhibitor) and soluble RAGE (decoy receptor) tested in experimental models. *Dietary AGE reduction* – limiting foods high in preformed AGEs to reduce exogenous load. Antioxidants to mitigate oxidative amplification of glycation. |
| **Phosphorylation** (Insulin & stress kinase pathways) | Insulin receptor tyrosine phosphorylation initiates cascade (IRS→PI3K→Akt) for glucose uptake(Carmichael et al., 2019a; Goodsell et al., 2015). In diabetes, chronic nutrients/inflammation activate Ser/Thr kinases (JNK, IKK, PKC) that aberrantly phosphorylate IRS-1/IRS-2 on inhibitory sites(Carmichael et al., 2019a). Hyperglycemia also activates PKC via DAG, and MAPKs via oxidative stress. | **Insulin signaling:** Serine-phosphorylated IRS cannot properly transduce insulin signal, causing insulin resistance(Gao et al., 2004). Reduced Akt activation impairs GLUT4 translocation and glycogen synthesis, contributing to hyperglycemia(Carmichael et al., 2019a). **Inflammation:** Phosphorylation of IκB (by IKK) and other nodes activates NF-κB, elevating cytokines(Chen & Natarajan, 2022). JNK phosphorylation of c-Jun promotes inflammatory gene expression. **Complications:** PKC activation under hyperglycemia alters blood flow, permeability, and induces ECM overproduction(Pan et al., 2022); MAPKs increase angiogenic and fibrogenic factors. Net result: microvascular damage (retinopathy, nephropathy, neuropathy) and macrovascular acceleration. | *Insulin therapy/sensitizers* – e.g., metformin and TZDs indirectly reduce stress kinase activity and improve insulin signaling. *Anti-inflammatory agents* – e.g., salicylates (IKKβ inhibitor) to reduce NF-κB activation(Gao et al., 2004); experimental JNK inhibitors. *PKC β inhibitors* – e.g., ruboxistaurin, which showed partial benefit against retinopathy(Group, 2005) . *ACE inhibitors/ARBs* – not direct kinase inhibitors, but reduce AngII signaling that can exacerbate PKC and NADPH oxidase pathways(Rhee & Kim, 2018a), providing vasoprotection. Lifestyle interventions (diet, exercise) to lower FFA and inflammatory mediators, thereby modulating kinase activation. |
| **Acetylation** (Histone & protein acetylation) | Histone acetylation by HATs relaxes chromatin and increases gene transcription; HDACs/Sirtuins remove acetyl groups, repressing transcription(Chen & Natarajan, 2022). In diabetes, hyperglycemia and oxidative stress alter HAT/HDAC levels and NAD+ availability, disrupting acetylation balance. SIRT1 activity often reduced in obesity/diabetes(Kitada & Koya, 2013). Transient hyperglycemia can induce lasting changes in histone acetylation at promoters (epigenetic memory)(Chen & Natarajan, 2022). | **Epigenetic gene dysregulation:** Persistent histone acetylation changes at promoters of genes for inflammatory cytokines, growth factors, etc., leading to sustained up- or down-regulation even after glycemic normalization(Chen & Natarajan, 2022). **Inflammation:** Reduced SIRT1 ⇒ increased acetylation of NF-κB p65, enhancing NF-κB activity and inflammatory cytokine production(He et al., 2023). **Metabolic regulation:** Hyperacetylation of PGC-1α and FOXO1 impairs their function (affecting gluconeogenesis and antioxidant defenses); altered acetylation in pancreatic β-cells can influence insulin secretion and survival. **Aging and memory:** Epigenetic marks (including acetylation) laid down by early hyperglycemia contribute to complication progression (metabolic memory). In GDM, epigenetic acetylation changes may occur in the fetus, raising future metabolic disease risk(Rhee & Kim, 2018a). | *Sirtuin activators* – e.g., Resveratrol and synthetic SIRT1 activators to enhance deacetylation of harmful acetylation marks(Kitada & Koya, 2013). NAD+ precursors (NR, NMN) to boost sirtuin activity. *HDAC inhibitors* – being explored to reverse pathological histone deacetylation in complications (e.g., inhibit HDACs that repress anti-fibrotic genes). *Bromodomain inhibitors* – experimental drugs that block reading of acetylation marks, to suppress hyperacetylation-driven gene transcription (in inflammation or fibrosis). Strict glycemic control to prevent establishment of adverse epigenetic marks. Nutritional interventions (e.g., polyphenols, which may influence acetylation status) as complementary strategies. |

5. Conclusion

Post-translational modifications serve as pivotal biochemical links between the metabolic disturbances of diabetes and the resultant cellular dysfunction and tissue damage. Glycation converts the curse of chronic hyperglycemia into irreversible molecular damage through AGEs that mar proteins and ignite inflammatory signaling via RAGE. Phosphorylation events, when properly orchestrated, allow insulin to regulate metabolism, but when perturbed by nutrient excess and stress, they derail insulin signaling and activate deleterious pathways (kinases that drive inflammation, oxidative stress, and matrix deposition). Acetylation and related epigenetic modifications add a further layer, explaining how the “memory” of past hyperglycemia can persist in gene expression patterns long after glycemia is controlled, and highlighting the role of chromatin state in governing metabolic and inflammatory genes in diabetes.

These PTMs do not operate in isolation; rather, they interconnect in reinforcing loops. For instance, AGE-RAGE signaling can activate PKC and MAPKs(Pan et al., 2022), thereby influencing phosphorylation networks, and it can also affect nuclear transcription factors that alter acetylation patterns. In turn, inflammatory kinases (phosphorylation cascades) can facilitate more AGE formation by increasing oxidative stress, and can reduce sirtuin activity, leading to aberrant acetylation. This crosstalk means that effective therapeutic interventions in diabetes might need to address multiple PTMs simultaneously. Tight glycemic control remains the cornerstone, as it reduces substrate for glycation and eases glucotoxic stress on kinases and epigenetic regulators. Beyond that, new therapies targeting these molecular lesions are on the horizon. Breaking the AGE-RAGE axis, using anti-inflammatory or kinase-inhibiting drugs to improve insulin signaling, and modulating epigenetic enzymes to erase harmful chromatin marks are all strategies under exploration. The challenge is to do so specifically and safely, given how ubiquitous and finely tuned these PTM processes are in normal physiology.

From a clinical perspective, the insights into PTMs reinforce several key principles. First, early intervention in diabetes is critical, not only to prevent immediate metabolic decompensation but also to avoid long-term irreversible modifications such as AGE accumulation and epigenetic changes that drive complications(Rhee & Kim, 2018a). Second, treating diabetes is not just about glucose, addressing insulin resistance and inflammation through weight management, diet and possibly anti-inflammatory agents will favorably influence the phosphorylation and acetylation landscape, complementing glycemic control. Third, personalized medicine approaches may emerge, for example measuring circulating AGEs or epigenetic marks as risk predictors, or tailoring therapies (such as NAD+ boosters) to patients who show evidence of premature epigenetic aging due to diabetes.

In conclusion, glycation, phosphorylation, and acetylation are three major PTMs that play distinctive yet interrelated roles in the biochemistry of diabetes. They translate the metabolic hallmark of the disease, hyperglycemia and associated dyslipidemia, into the cellular malfunctions of impaired insulin action, chronic inflammation and tissue injury. By deepening our understanding of these modifications, we pave the way for novel biomarkers and therapeutic targets that could better prevent and treat the dire complications of diabetes. Ongoing research and clinical trials inspired by these molecular insights hold promise to alleviate the burden of diabetes by intervening at the level of its fundamental biochemistry.

**DISCLAIMER (ARTIFICIAL INTELLIGENCE)**

Author(s) hereby declares that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

**COMPETING INTERESTS DISCLAIMER:**

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

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