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Review Article:

Mechanisms and Linkage of Insulin Signaling, Resistance, and Inflammation

Khalil A. Hadid[1], Fawaz A. Alassaf [1], Mohammed N. Abed[2]

[1] Department of Pharmacology and Toxicology, College of Pharmacy, University of Mosul, Mosul, Iraq.
[2] Department of Pharmaceutical Chemistry, College of Pharmacy, University of Mosul, Mosul, Iraq.

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Abstract

Background: Chronic inflammation is responsible for low insulin sensitivity, making obesity a major risk factor for developing insulin resistance, type 2 diabetes mellitus, and metabolic syndrome. Increased expression of inflammatory cytokines activates several signaling pathways, consequently leading to the accumulation of fats in adipocytes and contributing to the pathogenesis of insulin resistance. **Aim:** The review aimed to provide an overview of the potential molecular correlation between the insulin signaling pathway and the inflammatory process in addition to their linkage to the development of insulin resistance and other metabolic diseases, with an exploration of the possibility of using drugs that target inflammation in the management of diabetes. **Results:** Based on the obtained data from the latest literature, the source of cytokines in insulin-resistant states is the insulin targets themselves including the adipose tissue and liver, but to a greater extent the activated macrophages. Prolonged inflammation in these tissues may result in systemic insulin resistance via endocrine signaling and localized insulin resistance by paracrine/autocrine cytokine signaling. **Conclusion:** Inflammation is involved in the pathogenesis of insulin resistance and diabetes type 2, consequently, in the management of insulin resistance, anti-inflammatory agents may benefit, and the risk assessment may benefit from the use of inflammatory biomarkers in such disorders.

1. Introduction

Chronic inflammation is responsible for low insulin sensitivity, making obesity a major risk factor for developing insulin resistance, type 2 diabetes mellitus, and metabolic syndrome. Increased expression of inflammatory cytokines activates several signaling pathways, consequently leading to the accumulation of fats in adipocytes and contributing to the pathogenesis of insulin resistance (1). The aim of the review is to provide an overview of the potential molecular correlation between the insulin signaling pathway and the inflammatory process in addition to their linkage to the development of insulin resistance and other metabolic diseases, with an exploration of the possibility of using drugs that target inflammation in the management of diabetes.

1.1. Insulin

Insulin, a key hormone in maintaining glucose homeostasis, is a peptide hormone of 51 amino acid sequences encoded by a gene (located on chromosome 19) (2). Insulin comprises two chains connected by a disulfide bridge, chain A of 21 amino acids and chain B of 30 amino acids. Insulin is secreted from the beta cells of islets of Langerhans of the pancreas in response to stimuli including glucose (3).

Insulin binds to its specific receptors which are dispersed throughout the body in numerous tissues including the liver, adipose tissues (ADT), and striated muscle which trigger a signaling pathway. Insulin plays an important role in regulating protein, lipid, and carbohydrate metabolism, and also regulates the uptake of potassium and amino acid by the cells in addition to glucose (4,5). Insulin or insulin-like growth factors (IGF1-2) bind to the insulin receptor,

*Corresponding author: *Khalil A. Hadid, Department of Pharmacology and Toxicology, College of Pharmacy, University of Mosul, Mosul, Iraq..*

Email: khalil.amjad@uomosul.edu.iq

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which is a member of a wide group called receptor tyrosine kinases (RTKS) and initiates the signaling cascade. The protein receptor is heterotetrameric, consisting of two transmembrane beta subunits and two extracellular alpha subunits (6).

1.2. Insulin signaling

Insulin attaches to the exterior domain of the insulin receptor tyrosine kinase (IRTK) receptor, causing a conformational change in the receptor protein's three-dimensional structure. Tyrosine residues in the receptor's beta subunits are autophosphorylated as a result, and phosphotyrosine binding molecules like insulin receptor substrate 1-4 (IRS 1-4), Src homology and Collagen transforming protein (SHC), growth factor receptor-bound protein-2 (GRB-2), GRB-10 and Src homology 2 domain-containing-transforming protein B (SH2B-2) are then activated (7). Either of these might mediate the insulin signaling pathway:

1.2.1. Insulin receptor substrate 1-4 (IRS 1-4)-mediated insulin signaling

The phosphorylation of IRS (1-4), with IRS1 being the most important, is a crucial factor in the action of insulin. IRS1 stimulates phosphatidyl-inositol-3-OH kinase (PI3K) and catalyzes the conversion of phosphatidyl-inositol-4,5-bisphosphate (PIP2) into phosphatidyl-inositol-3,4,5-trisphosphate (PIP3). PIP3 is involved in the activation of protein kinase C (PKC) in multiple isoforms including α, βII, δ, ε, and θ. Secondly, PIP3 may be forced to the plasma membrane to induce protein kinase B (Akt) activation by 3-phospho-inositide dependent kinase-1 (PDK1) and mechanistic target of rapamycin complex 2 (mtorc2). Finally, PIP3 phosphorylates various substrates in metabolic-related tissues, including the liver, striated muscle, and ADT (**Figure 1**) (8,9).

In the hepatic tissues, by preventing the expression of gluconeogenic genes regulated by forkhead box O1 (FOXO1), Akt reduces gluconeogenesis. Furthermore, via controlling glycogen synthase 2 (GYS2) and glycogen phosphorylase via glycogen synthase kinase 3 (GSK3) and protein phosphatase 1 (PP1), insulin promotes the production of glycogen. Lastly, insulin increases sterol regulatory element-binding protein 1C to stimulate hepatic de novo lipogenesis (10).

In striated muscle, the uptake of glucose by the translocation of glucose transporter type 4 (GLUT4) storage vesicles to the cell membrane is stimulated by Akt. Insulin promotes the production of glycogen by activating glycogen phosphorylase through GSK3 inhibition and dephosphorylating phosphorylase kinase to inactivate glycogen phosphorylase (11).

In white adipocytes, insulin suppresses lipolysis by reducing lipase activity. This, in turn, inhibits the synthesis of glucose in the liver by lowering gluconeogenic substrates. It is thought that phosphodiesterase 3B (PDE3B), PP1, and protein phosphatase-2A (PP2A) mediate this suppression. Moreover, insulin stimulates adipogenesis, lipogenesis, and glucose transport (9).

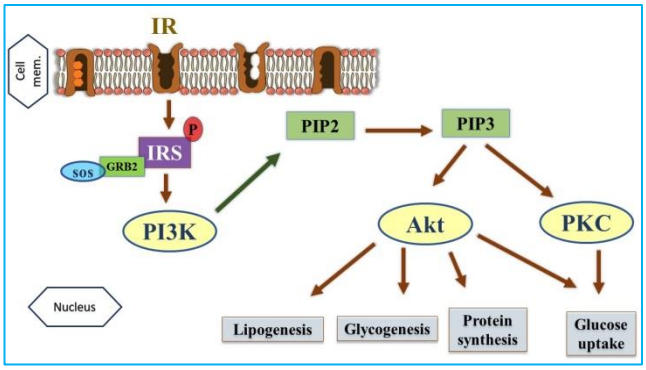

Figure 1. Insulin signaling pathway: the binding of insulin induces autophosphorylation of its receptor and subsequent phosphorylation of the tyrosine residue of IRS and SHC. Activated IRS stimulates PI3K and GRB2. Activated PI3K induces the activation of Akt and PKC. Such molecules mediate a variety of insulin actions (12).

IR, insulin receptor; **IRS,** insulin receptor substrate; **PI3K,** phosphatidylinositol-3-OH kinase; **Akt,** protein kinase B; **GRB2,** Growth Factor Receptor Bound Protein 2; **PIP2**, phosphatidyl-inositol-4,5-bisphosphate; **SOS,** Son of Sevenless; **PIP3,** phosphatidyl-inositol-3,4,5-trisphosphate; **PKC,** protein kinase C

1.2.2. Insulin signaling through non-IRS

Another pathway that mediates insulin signaling is the Ras/MAPK Pathway which is involved in many cellular processes, including cell proliferation and differentiation (13). Tyrosine residues on the Src homology 2 containing protein (SHC) can be phosphorylated by the phosphorylated insulin receptor. After that, SHC binds to the complex of growth factor receptor-bound protein 2 (Grb2), starting the Ras-MAPK signaling cascade. The heterotrimeric G protein is an additional insulin action mediator, Gαq/11 (14).

1.3. Insulin signaling and inflammation

Evidence from the 1950s suggests that there is a great correlation between inflammation and insulin resistance (InRs). It was noticed that the administration of high doses of aspirin (0.5-0.75 g per day) results in a hypoglycemic effect and reduces glucosuria in type 2 diabetes mellitus (DM2) (15). This creates the idea that aspirin affects insulin secretion but does not take into account the effect on InRs and the inflammatory process accompanying it. Later on, studies found that the target for aspirin was the IKappaB kinase-β (IKKβ)/Nuclear factor κB (NF-κB) axis, resulting in improved InRs in DM2 by reducing the inflammatory reaction (16–18).

More recently, it has become progressively evident that obesity and the emergence of chronic inflammatory processes are essential elements of InRs, this can be emphasized by increased levels of tumor necrosis factor (TNF-α), interleukin-8 (IL-8) and interleukin-6 (IL-6) in insulin-resistant patients (19). Moreover, C-reactive protein (CRP) is also elevated due to the direct effects of IL-6 and TNF-α on its level (20). Major roles in the recruitment of macrophages to ADT are performed by monocyte chemoattractant protein-1 (MCP1) and other chemokines (21).

1.4. InRs and the human body

InRs is also known as impaired insulin sensitivity, which is defined as a condition in which insulin is present in the circulation but with impaired ability of some tissues to respond normally to insulin. InRs cause a loss of insulin actions at baseline levels, necessities higher insulin levels to maintain normal functioning (22,23). Consequently, the pancreas develops a compensatory mechanism for more production of insulin. Over time, the cells stop responding to all insulin and the pancreas cannot create more insulin, which causes hyperglycemia (24).

Since striated muscles represent the largest site for glucose uptake, the liver, and adipose tissues are quantitively the pivotal regions for glucose metabolic pathways, and InRs in these sites have the most significant influence on the development of InRs within the body (22). InRs is the hallmark of many diseases affecting humans, in addition, the metabolic outcomes of InRs include elevated blood glucose, high blood pressure, disturbance in lipid profile, increased serum uric acid, increased mediators of inflammation, dysfunction of endothelial tissue, and a prothrombotic state. Development of InRs can lead to metabolic syndrome, nonalcoholic fatty liver disease (NAFLD), and DM2 (25).

1.4.1. Striated muscles and InRs

There are numerous explanations for how InRs occur in striated muscles, these include:

- Impaired GLUT4 translocation due to impaired signaling pathway
- Abnormalities of insulin signaling early in the pathway, such as, in the actions of IRTK, IRS1, PI3K, and AKT (26)
- Reduction in the activity of tyrosine kinase of IRTK in the striated muscle of obese diabetic patients
- Reduced the activity of IRS1 tyrosine phosphorylation and IRS1-associated PI3K (27).

1.4.2. InRs in liver and adipose tissue

Defects in ADT lipolysis and the de-suppression of the transcription factor FOXO1 in the hepatic tissues are closely related to defective suppression of hepatic gluconeogenesis. In addition, DM2 patients have lower levels of hepatic glycogen content due to defects in glycogen synthesis mediated by insulin and defective glycogen metabolism induced by fasting and feeding conditions (28). Additionally, lipolysis associated with InRs promotes hepatic triglyceride synthesis with the release of free fatty acids that can accumulate in ectopic sites and further complicate InRs (29).

1.4.3. Selective InRs

Not all insulin actions are less responsive in the case of InRs. Some insulin effects are still present, this is known as selective InRs. For example, in hepatic InRs, hyperglycemia, hyperlipidemia, and hepatic steatosis are present because insulin fails to impair glucose production but still stimulates lipogenesis (30).

In selective InRs, the exact mechanism is still not fully understood but many hypotheses are present, different substrates for Akt phosphorylation between gluconeogenesis and lipogenesis (31). Various intrinsic sensitivities of insulin-induced reduction of gluconeogenesis and activation of SERPINE 1 mRNA Binding Protein (SERBP-1c transcription factor) suggest that these processes need particular insulin concentrations. In contrast to glucogenesis, Insulin-regulated hepatic lipogenesis is mediated by stabilizing pleckstrin homology domain leucine-rich repeat protein phosphatase-2 (PHLPP-2). Nevertheless, PHLPP-2 inhibits Akt activity mediated by insulin (32). Lastly, Insulin-independent lipogenesis by fructose and monosaccharides leads to selective InRs (33).

1.5. The linkage between InRs and inflammation

According to the first concern of linkage, InRs might be induced by the proinflammatory cytokine TNF-α (34,35). This was a novel concept, a chemical produced by fat and overproduced by expanded fat had local and potentially systemic impacts on metabolism. The idea that ADT may generate cytokines and additional bioactive compounds besides TNF-α was rapidly established. These substances include resistin, retinol-binding protein-4, leptin, IL-6, monocyte chemoattractant protein-1 (MCP-1), angiotensinogen, visfatin, and others (36).

TNF-α, IL-6, resistin, and other pro- or anti-inflammatory cytokines appear to promote the initiation and maintenance of the subacute inflammatory state concomitant with obesity (37). The recruitment of macrophages to ADT is enhanced by MCP 1 and other chemokines (21). Generally, the elevated levels of the inflammatory mediators associated with adiposity can impair either of two major pathways of insulin action, the JNK or IKKβ/NF-κB pathways. The mechanisms by which adiposity interferes with c-jun N-terminal kinase (JNK) or IKKβ/NF-κB pathways occur in receptor or non-receptor pathways (38).

1.5.1. Receptor pathway

JNK and IKKβ/NF-κβ are stimulated by proinflammatory cytokines including TNF-α and IL-1β via conventional receptor-mediated activation (**Figure 2**). The surface proteins known as pattern recognition receptors, including as toll-like receptors (TLRs) and the receptor for advanced glycation end products (RAGE), which detect foreign compounds, also activate JNK and IKKβ/NF-κβ. Microbial compounds are the source of many TLR ligands, which are activated by saturated fatty acids found in adiposity. In addition to AGEs, a certain group of microbial compounds is also a RAGE ligand (39). Targeted proteins, particularly those with slow turnover rates, combine with glucose to generate nonenzymatic adducts known as AGEs. Prolonged elevation of blood glucose and the accompanying production of excess quantities of AGEs can stimulate NF-κB (40).

1.5.2. Non-receptor pathway

Reactive oxygen species (ROS) and endoplasmic reticulum stress (ER stress) have the potential to activate JNK and IKKβ/NF- κβ. One possible mechanism is that adipocyte lipid accumulation activates reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, increasing ROS generation (41–43). It has been demonstrated that this mechanism results in a reduction in adiponectin production and an increase in TNF-α, IL-6, and MCP-1 production. The unfolded protein response is triggered by lipid accumulation, increasing ER stress in the liver and fat cells. Moreover, ER stress is shown to activate JNK leading to

serine phosphorylation of insulin receptor substrate-1 (IRS-1), ER stress similarly activates NF-κB (44).

1.6. JNK versus IKKβ/NF- κβ in the pathogenesis of InRs

Both JNK and IKKβ/NF- κβ play an essential role in the development of InRs, nevertheless, each of them has a distinct mechanism to do this. JNK is a stress kinase that belongs to the mitogen-activated protein kinase (MAPK) family. It is mostly stimulated by ER stress and typically phosphorylates the serine residues in IRS-1, which in turn phosphorylates the c-Jun portion of the activating protein 1 (AP-1) transcription factor, promoting InRs.

Counterregulatory serine/threonine phosphorylation can reverse Insulin receptor signaling which usually happens via a tyrosine kinase pathway (45). IKKβ, on the other hand, has a strong preference for its physiological substrates, which are NF-κB protein inhibitors. IKKβ-mediated phosphorylation of IκBα directs its proteasomal breakdown, liberating NF-κB from the cytoplasm for translocation into the nucleus. Once in the nucleus, it stimulates the production of several target genes, the products of which trigger InRs (46). Instead of phosphorylating IRS-1 as JNK does, IKKβ activates NF-κB transcriptionally to produce InRs. To sum up, JNK influences phosphorylation and IKKβ influences transcription, which results in InRs (47).

The most important factors that interfere with the insulin signaling pathway and promote InRs through the JNK/NF-κB downstream pathway include ceramide, endoplasmic reticulum (ER) stress, and reactive oxygen species (ROS). Ceramide is an important bioactive lipid that is derived from sphingosine and an intracellular fatty acid. It is believed to have a role in mediating lipid-induced InRs (48). Ceramide's primary molecular mechanism for inducing InRs has not been proven. Nevertheless, the impairment of Akt translocation through the activation of atypical PKC (PKCζ), the activation of PP2A, and activated proinflammatory cytokines contribute to the ceramide role in InRs that activates JNK and NF-κB (49).

Additionally, ceramide induces beta cell apoptosis through activation of the extrinsic apoptotic pathway, increasing cytochrome C release, free radical generation, serine/threonine protein phosphatase (PP1), and cathepsin D activity and induction of endoplasmic reticulum stress. Ceramide reduces the synthesis of insulin by attenuation of insulin gene expression (50).

Because of the ER's extreme sensitivity to changes in homeostasis, proteins produced there may not develop in the proper conformation. Misfolded protein accumulation that aggregates in the endoplasmic reticulum (ER) induces endoplasmic stress and triggers the unfolded protein response (UPR) (51).

In ER stress, UPR promotes InRs by two main mechanisms.

- Interference with signaling pathway of insulin: Activation of JNKs and tribbles homolog (TRB3) by the UPR lead to inhibition of proximal insulin signaling (52).
- Interference with the total number of insulin receptors on the cell surface: Stress in the ER prevents newly generated insulin proreceptors from being transported from the ER to the plasma membrane, which prevents the proteolytic maturation of insulin proreceptors (53).

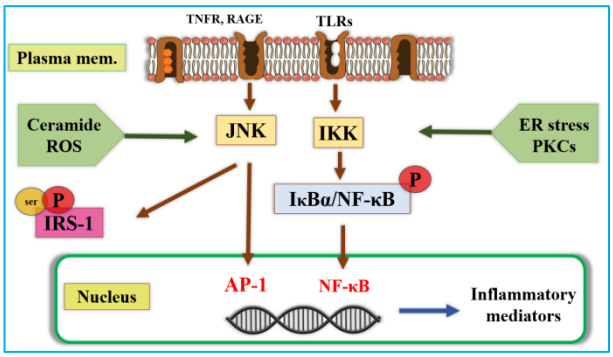

Figure 2. Inflammatory pathways linking inflammation to InRs. Serine kinase phosphorylation of IRS results from activation of the JNK and NF-κB pathways. This may block insulin signaling and ultimately induce IR. Furthermore, proinflammatory cytokines are produced by the JNK and NF-κB pathways, and these cytokines may then function as activation stimuli for the pathways.

Mem: membrane, **TLRs:** tool-like receptors, **TNFR:** tumor necrosis factor receptor, **RAGE:** receptor for advanced glycation end products, **JNK:** *c-jun N-terminal kinase*, **ROS:** reactive oxygen species, **ER:** endoplasmic reticulum, **PKCs:** protein kinase C, **IKKβ:** IKappaB kinase β, **NF-κB:** nuclear factor -κB, **IRS1:** insulin receptor substrate 1, **AP1:** activating.

1.7. The initiation of inflammation in insulin-resistant obese patients

Obesity is a key risk factor for InRs and associated disorders like DM2 and metabolic syndromes because it is a condition of low-grade inflammation brought on by excessive calorie consumption. This inflammation is also responsible for the loss of insulin sensitivity since it causes lipids to accumulate in adipocytes. Obesity might promote the production of certain inflammatory cytokines and initiate many pathways of signaling, both disrupt insulin action and signaling and contribute to the pathophysiology of InRs (54).

The precise physiological mechanism that initiates inflammation in obese patients is not fully understood. One theory is related to ADT as a pathogenic site of obesity-induced InRs, expansion of ADT occurs during obesity leading to hypertrophy and hyperplasia of adipocytes that impede local oxygen supply and initiate stress conditions (55). On the other hand, not all fats have the same potential for resistance, making them more likely to develop. Visceral fats have different sizes and metabolic activities, so it is more pathogenic than subcutaneous fat (56).

Local stressful circumstances promote the production of cytokines and other proinflammatory signals such as TNF-α, IL-6, MCP-1, PAI-1, and angiotensinogen. Adipocyte-secreted adipokines, including resistin, leptin, and adiponectin, can also impact insulin sensitivity and inflammation Locally released chemokines attract pro-inflammatory macrophages into the ADT as a component of the chronic inflammatory process, resulting in the formation of crown-like structures surrounding large dead or dying

adipocytes. ATMs are macrophages found in adipose tissue, and they are classified into two types: M1 and M2 (**Figure 3**) (57). The inflammatory program in nearby adipocytes is subsequently further activated by the cytokines released by these tissue macrophages, aggravating inflammation and InRs. Consequently, adipocytes initiate InRs and macrophages amplify the signal (58). Regarding the immune system, not only macrophages are involved, Blood monocytes are induced to migrate into the subendothelial area by MCP-1, and augments differentiation into macrophages (59). Moreover, IL-1 inhibits insulin secretion from the pancreas (60). Other cell types to be considered in adipose tissues other than adipocytes and macrophages are the vascular cells since ADT is highly vascularized and many capillaries present in contact with adipocytes. More nutrient storage is needed as a result of ADT enlargement in obesity, hypertrophy, and hyperplasia of adipocytes, which causes angiogenesis (61). Typically, leukocytes do not adhere to the endothelial layer of vascular tissue, nevertheless, as angiogenesis develops, ADT endothelial cells increase the expression of adhesion proteins as Intercellular Adhesion Molecule 1 (ICAM-1), Vascular cell adhesion molecule 1 (VCAM-1), E-selectin, or P-selectin (P-selectin expressed on platelets and leukocytes, E-selectin expressed on endothelial cells) (62). Additionally, the liver is also affected by adiposity and NAFLD is commonly accompanied by abdominal obesity. Inflammation plays a pivotal role in the development of this disease process. Defective suppression of hepatic gluconeogenesis, due at least in part to hepatic InRs, is an established contributor to hyperglycemia in DM2 (63). Steatosis leads to increased gene expression of inflammatory mediators and induces subacute inflammatory response in the liver. On the other hand, proinflammatory chemicals in the portal circulation that may be generated in abdominal fat might cause inflammation in the liver (18,64). Regardless, NF-κB is activated in the hepatocyte, and cytokines including IL-6, TNF-α, and IL-1β are overproduced in fatty liver (38). Inflammatory mediators in the liver promote InRs and activate Kupffer cells but not their number, this is in contrast to ADT, where macrophages increase numerically with adiposity (65). Hepatic stellate cells, liver sinusoidal endothelial cells, T and B lymphocytes, natural killer (NK) cells, and dendritic cells (DCs) are involved in inflammation-induced InRs in the liver (66). In striated muscle, the inflammatory process does not initiate with increasing adiposity, in contrast to the liver and ADT (67).

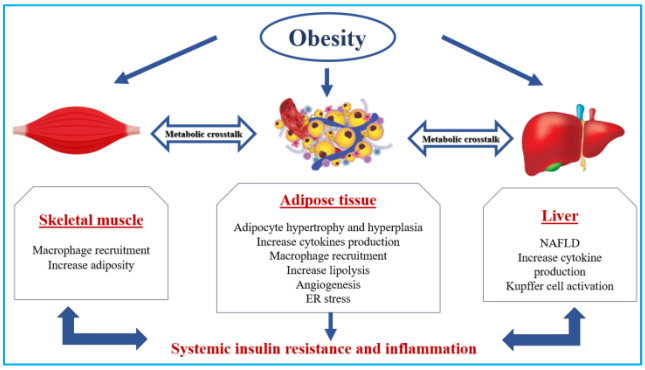

Figure 3. The development of inflammation and InRs in relation to obesity. Autocrine and paracrine signaling pathways in the liver, adipose tissue, and striated muscle are altered by obesity, which causes localized inflammation and InRs. The development of InRs in distant tissues is facilitated by endocrine-mediated cross-talk across insulin-target tissues. The final findings of these modifications include InRs and systemic inflammation. **ER,** endoplasmic reticulum; **NAFLD,** non-alcoholic fatty liver disease

1.8. Targeting inflammation in the management of DM 2

An increasing evidence links inflammation to DM 2. In addition, numerous anti-inflammatory drugs may prevent or postpone DM 2. It has been shown that statins lower inflammatory markers, but their effect in reducing the risk of DM 2 require further investigations (68). Some inflammatory markers are reduced by fibrates, and bezafibrate has been shown to lessen the probability of developing diabetes in a prospective study (69). Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers appear to lower various markers of inflammation, and a meta-analysis found that ACE inhibitors and angiotensin receptor blockers reduce risk of developing DM 2 (70). Metformin's mild weight-reducing effect is one of the reasons it is effective in lowering the risk of developing diabetes, and recent evidence suggests it also reduces C-reactive protein (71). The inflammatory markers are consistently reduced by thiazolidinediones, and this affect is shown even in the absence of an effect on body fat content (72). However, there has not yet been a large-scale trial to assess the effect of aspirin on the risk of developing diabetes, despite the fact that high-dose aspirin inhibits cyclooxygenase and IKKβ and decreases fasting plasma glucose concentration. Targeting the inflammation axis may be a promising method for treating and preventing DM 2, however, this will only be determined by research using more precise inhibitors of inflammatory pathways (such as interleukin- 6 blockers) and mendelian randomization (genetic studies) (73).

2. Conclusion

To sum up, the mechanisms underlying the association of insulin signaling, resistance, and inflammation have not fully yet been elucidated. A review of InRs and inflammation provides a better understanding of how these physiological processes interact with each other. The current research sheds light on the biomarkers linked to InRs and inflammation. To investigate the possibility of developing new strategies for treating InRs, this review focused on the correlation between insulin signaling, resistance, and inflammation at the molecular level.

In individuals with DM2 or obesity, abnormal glucose and lipid metabolism can lead to the activation of numerous pro-inflammatory cytokines, ER stress mediators, and adipokines. Therefore, in our opinion, the management of InRs may be achieved through the use of anti-inflammatory agents, and the risk assessment may benefit from the use of inflammatory biomarkers in such disorders.

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4. Conflict Of Interest

There is no conflict of interest.

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الية وارتباط اشارات الانسولين مع مقاومة الانسولين والالتهاب

الخلاصة

المقدمة: الالتهاب المزمن هو المسؤول عن انخفاض حساسية الانسولين، مما يجعل السمنة عامل خطر رئيسي لتطوير مقاومة الانسولين، ومرض السكري من النوع 2، ومتلازمة التمثيل الغذائي. يؤدي التكوين المتزايد من السيتوكينات الالتهابية إلى تنشيط العديد من مسارات الإشارات الخاصة بالأنسولين، مما يؤدي بالتالي إلى تراكم الدهون في الخلايا الشحمية والمساهمة في التسبب في مقاومة الأنسولين.

الهدف: تهدف الدراسة إلى تقديم لمحة عامة عن العلاقة الجزيئية المحتملة بين مسار إشارات الأنسولين والعملية الالتهابية بالإضافة إلى ارتباطها بتطور مقاومة الأنسولين والأمراض الأيضية الأخرى، مع التعرف على إمكانية استخدام الأدوية التي تستهدف الالتهابات في علاج مرض السكري. **النتائج:** استنادا إلى البيانات التي تم الحصول عليها من أحدث الدراسات، فأن مصدر السيتوكينات في الحالات المقاومة للأنسولين هو مناطق استهداف الانسولين نفسه بما في ذلك الأنسجة الدهنية والكبد، ولكن إلى حد كبير البلاعم المنشطة. قد يؤدي الالتهاب المطول في هذه الأنسجة إلى مقاومة الأنسولين الجهازية عن طريق إشارات الغدد الصماء ومقاومة الأنسولين الموضعية عن طريق إشارات السيتوكينات نظير الصماوي/الأوتوقراطية. **الاستنتاج:** الالتهاب هو من المسببات لمقاومة الأنسولين ومرض السكري من النوع 2، وبالتالي يمكن السيطرة على مقاومة الانسولين من خلال استخدام الادوية المضادة للالتهابات، وقد يستفيد تقييم المخاطر من استخدام المؤشرات الحيوية الالتهابية في مثل هذه الاضطرابات.

الكلمات المفتاحية: الانسولين، إشارة الانسولين، مقاومة الانسولين، الالتهاب