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Insulin Signaling in Arthritis

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Inflammatory arthritis is burdened by an increased risk of metabolic disorders. Cytokines and other mediators in inflammatory diseases lead to insulin resistance, diabetes and hyperlipidemia. Accumulating evidence in the field of immunometabolism suggests that the cause-effect relationship between arthritis and metabolic abnormalities might be bidirectional. Indeed, the immune response can be modulated by various factors such as environmental agents, bacterial products and hormones. Insulin is produced by pancreatic cells and regulates glucose, fat metabolism and cell growth. The action of insulin is mediated through the insulin receptor (IR), localized on the cellular membrane of hepatocytes, myocytes and adipocytes but also on the surface of T cells, macrophages, and dendritic cells. In murine models, the absence of IR in T-cells coincided with reduced cytokine production, proliferation, and migration. In macrophages, defective insulin signaling resulted in enhanced glycolysis affecting the responses to pathogens. In this review, we focalize on the bidirectional cause-effect relationship between impaired insulin signaling and arthritis analyzing how insulin signaling may be involved in the aberrant immune response implicated in arthritis and how inflammatory mediators affect insulin signaling. Finally, the effect of glucose-lowering agents on arthritis was summarized.

Keywords: rheumatoid arthritis, insulin, insulin receptor, metabolism, T cell, macrophage, synoviocyte

INTRODUCTION

Insulin, the main actor of glucose homeostasis, exerts its action through the transmembrane insulin receptor (IR), expressed on target cells such as hepatocytes, adipocytes, synoviocytes, or muscle cells (1). However, IR can also be found on the membrane of T cells, macrophages or dendritic cells, and an immunoregulatory function of insulin has been suggested. Indeed, glucose is necessary for immune cells to produce energy and to maintain normal activity (2). For this reason, insulin plays a pivotal role in maintaining physiological immune response. In diabetic patients, administration of insulin may decrease levels of C-reactive protein (CRP), reduce the ability of neutrophils to generate reactive oxygen species (ROS) and suppress transcription of different Toll-like receptors (TLRs) on circulating mononuclear cells (3, 4). The interplay between inflammation, immunity and

metabolism has been outlined (5) and, in this context, insulin signaling, similarly to what is observed in type 2 diabetes (T2D) or in metabolic syndrome, may be involved in the dysregulation of immune response in inflammatory diseases. Epidemiological and laboratory studies reported a possible correlation between insulin resistance and osteoarthritis (OA), rheumatoid arthritis (RA), spondyloarthritis or systemic lupus erythematosus (6–13).

In this review, we summarize the available literature about the bidirectional cause-effect relationship between impaired insulin signaling in inflammatory and degenerative arthritis, analyzing how insulin signaling may contribute to the aberrant immune response found in arthritis and how inflammatory mediators impair insulin signaling. Finally, the effect of glucose-lowering agents on arthritis was reviewed.

PHYSIOLOGY OF INSULIN RECEPTOR AND INSULIN SIGNALING CASCADE

The IR is a dimer located on cellular membrane and composed of four domains linked by disulfide bonds: two extracellular (α) and two intracellular (β). The α domains host the binding site of insulin, while the β domains have tyrosine kinase activity (14–17). Once circulating insulin binds the α subunits, IR undergoes autophosphorylation, with consequent phosphorylation of intracellular substrates. In the first step, IR substrates 1 and 2 (IRS-1 and IRS-2) and the docking protein Src-homology collagen (Shc) are phosphorylated, leading to the activation of two main pathways, metabolic and mitogenic (Figure 1). The former involves phosphoinositide-3-kinase (PI3K), while the latter is mediated by mitogen activated protein kinase (MAPK) (17).

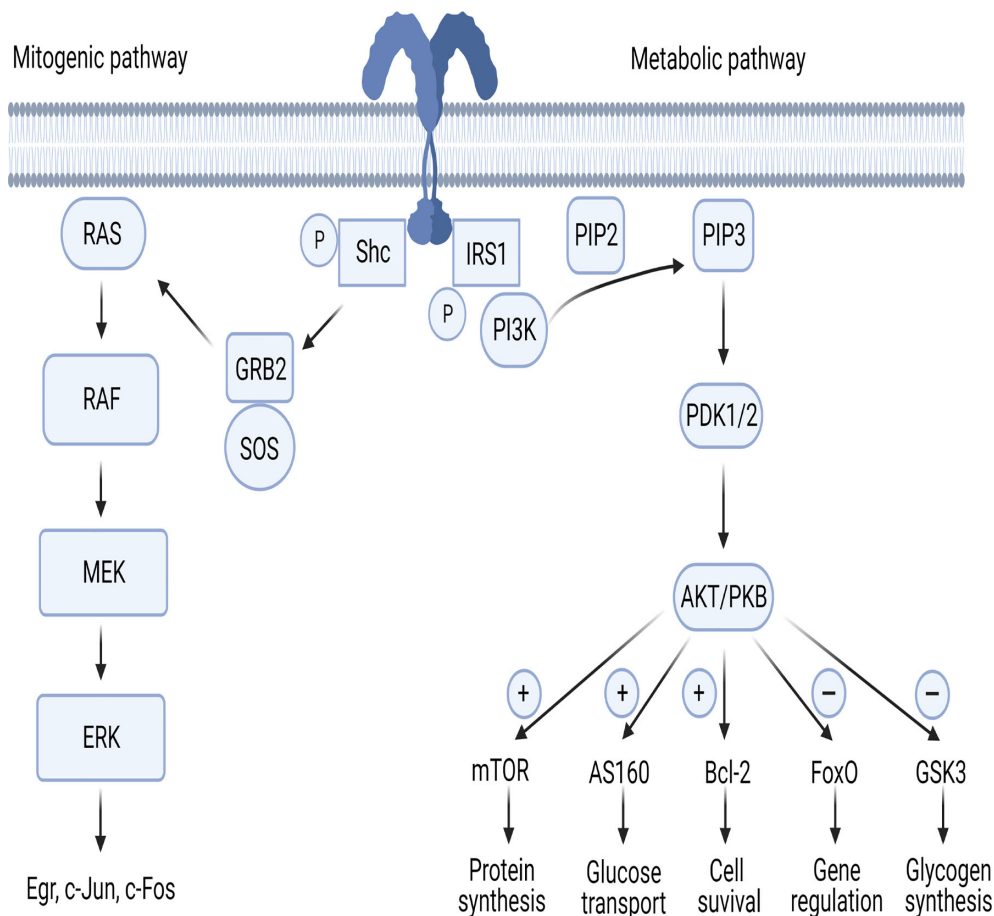


FIGURE 1 | The mitogenic and metabolic pathways of insulin signaling. AKT/PKB, protein-kinase B; AS160, AKT substrate of 160kDa; Bcl-2, B-cell lymphoma 2; ERK, extracellular signal-regulated kinases; FoxO, forkhead box-containing protein O subfamily; GRB2, growth factor receptor-bound protein 2; GSK3, glycogen synthase kinase 3; IRS, insulin receptor substrate; MEK, MAPK/ERK Kinase; mTOR, mammalian target of rapamycin; PDK1/PDK2, phosphoinositide-dependent protein kinase; PI3K, phosphoinositide-3 kinase; PIP₂, phosphatidylinositol (4,5)-bisphosphate; PIP₃, phosphatidylinositol (3,4,5)-trisphosphate; RAF, rapidly accelerated fibrosarcoma; RAS, Rous sarcoma; Shc, Src-homology collagen; SOS, son of sevenless. **Figure 1** has been created using BioRender (www.biorender.com).

The Metabolic Pathway

In the first step of the metabolic pathway, the PI3K regulatory subunit p85 or p55 binds to IRS-1 and IRS-2 activating the PI3K cascade. Next, the p110 catalytic subunit activation results in phosphatidylinositol-3,4,5-triphosphate (PIP3) generation leading phosphoinositide-dependent protein kinase (PDK) 1 and 2 to activate the three isoforms of AKT/PKB (**Figure 1**). PDKs become then activated after binding to PIP3 in the cell membrane (18, 19). AKT/PKB regulates five main substrates: 1- activates mammalian target of rapamycin (mTOR), responsible of protein synthesis; 2- inhibits glycogen synthase kinase 3 (GSK3), responsible of glycogen synthesis; 3- inhibits forkhead box-containing protein O subfamily (FoxO), involved in the regulation of gluconeogenic and adipogenic genes; 4- increases the AKT substrate of 160kDa (AS160), responsible of glucose transport (20, 21); 5- upregulates Bcl-2 expression, involved in cell survival (22).

The Mitogenic Pathway

In the first step of the mitogenic pathway, growth factor receptor-bound protein 2 (GRB2) is activated by phosphorylated Shc protein (**Figure 1**). GRB2 acts as a bond that links IRS-1 to son-of-sevenless (SOS), which is a guanine nucleotide exchange factor. GRB2/SOS promotes exchange of GDP with GTP on Rous sarcoma virus (Ras), thus activating it (23). Activated Ras recruits Raf serine/threonine protein kinase and then the MAPK pathway transcription factors MEK, ERK and p90 inducing the activation of the Egr genes c-Jun and c-Fos (24, 25).

INSULIN, IMMUNE CELLS AND ARTHRITIS

Immune cells need glucose to produce energy (14) and, similar to adipose, muscle and liver cells, also immune cells express IR on their surface (26, 27). Through IR, insulin acts as a glucose-regulating hormone and behaves as a growth-like factor and cytokine regulator (28–30), exerting its immunomodulatory effects (2, 31).

Insulin modulates the immune response either indirectly through the glucose-lowering effect or directly by acting on immune cells and influencing their proliferative responses and signal transduction (32) (**Figure 2**). Regarding the first point, hyperglycemia has negative effects on the immune system since it induces cell stress and leads to the generation of advanced glycation end products (AGEs) and ROS, which stimulate release of various pro-inflammatory mediators. It can therefore be hypothesized that insulin, through its glucose-lowering role, reduces “glucose toxicity” and cell stress, exerting an anti-inflammatory effect (33).

In addition to these actions on glucose metabolism, insulin exerts anti-inflammatory effects *via* the stimulation of various intercellular pathways. Activation of PI3K/Akt pathway reduces the transcriptional activity of FoxO proteins that in turn suppress TLR4 signaling in response to lipopolysaccharides (LPS) in

leukocytes (34) leading to a downregulation of the immune system. Furthermore, insulin antagonizes the pro-inflammatory transcriptional activity of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) and activates the mTOR complex (mTORC), enhancing p62 phosphorylation and then p62-mediated degradation of the Kelch-like ECH-associated protein 1 (Keap1), thus allowing antagonism of pro-inflammatory processes mediated by nuclear factor erythroid 2-related factor 2 (Nrf2). Lastly, insulin inhibits the transcription of various TLRs on circulating mononuclear cells, including TLR1, 2, 4, 7 and 9 (35), causing a decreased immune response.

On the other hand, several investigations suggested a role of insulin as pro-inflammatory hormone. Studies in healthy, nondiabetic subjects explored the effects of insulin on polymorphonuclear (PMN) leukocytes functions. In vivo experiments with hyperinsulinemic clamp demonstrated that insulin stimulated PMN chemotaxis ability and phagocytosis but it didn't affect ROS production or density of surface receptors such as IR, CD11b, CD15, CD62L and CD89 (36). Similar experiments in monocytes demonstrated a suppressive action of insulin on formyl-methionyl-leucyl-phenylalanine-induced ROS production. Furthermore, again in monocytes, insulin inhibits in a dose-dependent manner the upregulation of tissue factor procoagulant activity. The inhibition is caused by a mechanism that interferes with the regulation of cyclic AMP and intracellular calcium, independently of the PI3K-PKB pathway (37).

RA is an autoimmune inflammatory joint disease often characterized by the presence of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs). Epidemiological studies suggested a direct relationship between diabetes and rheumatoid arthritis especially in female patient (38).

Treg cells mediate tolerance to self-antigens, whereas Th17 cells are involved in the pro-inflammatory reaction to pathogens. In RA and in other autoimmune diseases, the Treg-Th17 equilibrium is altered. Glycolytic pathways and increased glucose consumption lead to a metabolic switch from low-energy to highly active state in RA (39). Insulin and insulin-like growth factors (IGFs) are similar polypeptide hormones. Insulin regulates the use of carbohydrates, while IGF-1 is involved in cell growth, differentiation, and survival. Insulin and IGFs use signaling pathways involving PI3K and Akt or Ras and MAPK, which are also involved in other cellular stimuli (40). RA is characterized by an alteration of IGF-1 axis and its receptor (IGF-1R), which is expressed on chondrocytes, synovial fibroblasts and leukocytes (41–43). In RA patients there is upregulation of the IGF-1R expression on CD4+ T cells compared to healthy controls and in RA patients the IGF-1 levels are lower (44).

Moreover, the proinflammatory adipokine resistin, involved in obesity and diabetes, has a relevant role in the pathogenesis of RA and in the induction of the inflammatory response (45). When resistin is suppressed, the result is reduced expression of IGF-1R and decreased phosphorylation of Akt (42). Resistin modulates Akt-dependent processes and IGF-1R expression in human synovial tissue interfering with IR/IGF-1R signaling.

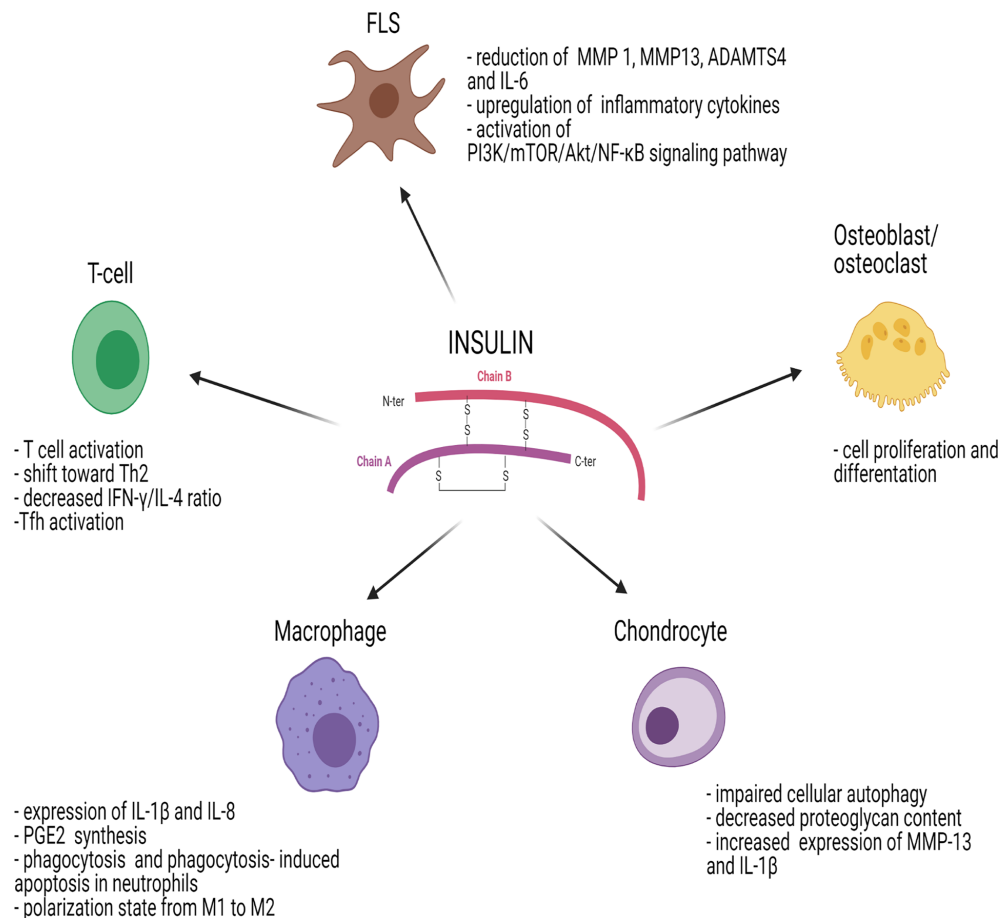


FIGURE 2 | Effects of insulin on immune cells and joint cells. ADAMTS4, metalloproteinase with Thrombospondin Type 1 Motif 4; AKT/PKB, protein-kinase B; FLS, fibroblast-like synoviocyte; IL, interleukin; IFN- γ , interferon gamma; MMP, matrix metalloproteinase; mTOR, mammalian target of rapamycin; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; PGE2, prostaglandin E2; PI3K, phosphoinositide-3-kinase; Tfh, follicular helper T cells; Th2, T helper 2. **Figure 2** has been created using BioRender (www.biorender.com).

Similar to insulin, IGF-1R signaling plays a role in inflammation mediated by T cells in arthritis. IGF-1R has an inhibitory effect on the level of IR substrates, reducing IL6-dependent formation of Th17 cells. The effects of insulin on different immune cells and joint cells are summarized in **Figure 2**.

Insulin Signaling in T Cells

While IR can be detected on the surface of B cells, monocytes and resting neutrophils, it is not expressed on resting T cells (36, 46). However, IR is significantly upregulated on activated T cells (47, 48) and it is essential to meet the large glucose demand that T cells need to acquire full effector functions. Insulin signaling in T cells promotes T cell activation by increasing protein synthesis, glucose uptake and amino acid transport (49). Viardot et al. demonstrated *in vitro* that insulin induced a shift toward T helper type 2 (Th2) response, reducing the T helper type 1 (Th1) to Th2 ratio (**Figure 2**). This resulted in a change of cytokine secretion with decreased interferon-gamma to IL-4 ratio with enhanced phosphorylation of extracellular signal-regulated kinase (ERK) (48), one of the four MAPK signaling pathways.

Experiments on IR knockout mice demonstrated that there was an impairment of polyclonal activation of CD4⁺ T cells and of cytokine production, migration and proliferation (50). Similar results were observed also in CD8⁺ T cells showing impaired cytotoxicity in response to alloantigens. Studies on obese patients have outlined that insulin resistance and related disorders are characterized by a cytokine imbalance, with high levels of TNF α , IL-6, IL-1 β , CRP, and NF- κ B (51). In this regard, Tao et al. found an imbalance between Th17 and regulatory T cells (Treg) in insulin resistance state (52). Th17 and Treg represent two CD4⁺ T cell subsets that share some developmental elements but express different phenotypes with opposite actions. The former have pro-inflammatory activity and the latter show anti-inflammatory activity (53). An altered balance between Treg and Th17 cells is involved in RA and other immune-mediated conditions (54).

Stimulation of the T cell receptor (TCR) complex and ligation of the co-receptor CD28 by co-stimulatory molecules activate quiescent T cells (55). Engagement of the TCR stimulates intracellular signaling through the ERK/MAPK pathways, while the PI3K-Akt-mTOR axis is activated by CD28 signaling (56, 57).

PI3K-Akt signaling activates glycolysis and increases glucose transporter 1 (Glut1) expression and thus glucose uptake. Overexpression of Glut1 enhances T follicular helper cells (Tfh) differentiation, a T cell subset involved in B cell regulation (58), potentially favoring autoimmunity in both type 1 diabetes and RA (59). Downstream, PI3K-Akt activates mTOR, which promotes the differentiation of Th1, Th17 and Tfh cells (60). Furthermore, mTOR can inhibit the formation of long-lived Tregs favoring effector Tregs (61). Treg knockout for mTOR reduced their frequency, leading to spontaneous effector T cell activation and inflammation (62).

AMP-activated protein kinase (AMPK) can inhibit cellular growth *via* suppression of the mTORC1 pathway (63). AMPK activation and interruption of mTOR signaling mitigated the inflammation in experimental arthritis. AMPK-dependent control of fatty acid metabolism may also impact cell fate decisions in CD4+ T cells, particularly the balance between Th17 and Treg lineages (64).

In addition, growth factors such as insulin, IGF-1 or IL-2 can stimulate PI3K-Akt-mTOR signaling. The roles played by insulin and IGFs are different, but they share the PI3K-AKTmTOR and RAS-RAF-MEK-ERK signaling pathways. Signaling through IGF-1 receptor (IGF1R) activates the Akt-mTOR pathway, increases aerobic glycolysis and ultimately favors Th17 cell differentiation over Treg cells. In experimental models, the inhibition of IGF-1R signaling may improve arthritis by decreasing IL6 production and modifying the balance between Th17 and Treg generation dependent on IL6 (44).

Insulin Signaling in Synoviocytes

Insulin signaling plays an important role in synoviocytes, which express a large number of IRs. In synoviocytes, insulin promotes the inflammatory phenotype of fibroblast-like synoviocytes (FLSs), increases cell viability, promotes production of inflammatory cytokines and chemokines and facilitates chemotaxis of macrophages, leading to synovial membrane inflammation (Figure 2). In synovial tissue isolated from patients with OA, a condition with persistent low-grade inflammation, and T2D, there was phosphorylation of Akt and reduced autophosphorylation of the IR induced by insulin. In OA patients with T2D, insulin resistance may develop not only in insulin-sensitive tissues such as muscle, liver or fat, but also in the synovial membrane. Furthermore, Hamada et al. demonstrated that insulin markedly reduced TNF α -stimulated production of matrix metalloproteinase (MMP) 1, MMP13, ADAMTS4, BMP2 and IL-6 in nondiabetic human FLSs without reducing TNF α itself, implicating a pivotal role of insulin in the inhibition of synovial inflammation (6, 65).

Qiao et al. showed that, in FLSs, insulin activates the PI3K/mTOR/Akt/NF- κ B signaling pathway and inhibits autophagy. Insulin can also upregulate inflammatory cytokine receptors whereas PI3K/mTOR/Akt/NF- κ B signaling inhibitors can reverse this process in FLSs (66).

Insulin Signaling in Osteoblasts and Osteoclasts

Previous studies supported the role of insulin signaling in the biology and pathology of the joint (67), mainly through its

capability to control bone architecture acting on osteoblasts and osteoclasts (68–73) (Figure 2). In vitro experiments demonstrated that insulin upregulated IR expression. Moreover, through MAPK and PI3K pathway, insulin stimulated cell proliferation and differentiation by increasing alkaline phosphatase activity, secretion of type I collagen and expression of osteocalcin in MG-63 cells (69). In IR knockout mice, increased expression of osteoprotegerin in osteoblasts and inhibited osteoclastogenesis and osteoclastic activity were observed (74, 75). The activation of mTORC1 by IGF-1, which is released in the bone resorption phase, stimulates osteoblast differentiation of mouse bone marrow stromal cells (BMSC) (76). mTORC1 is in fact required for the transition of pre-osteoblasts to mature osteoblasts (77).

However, insulin acts also on osteoclasts. Through the ERK1/2 pathway, insulin induces the upregulation of receptor activator of nuclear factor- κ B (RANK) contributing to the enhancement of osteoclast differentiation by RANKL (78). The effects of mTORC1 on osteoclasts have not been completely elucidated. In osteoclast precursors, the deletion of *raptor* leading to inactivation of mTORC1, or the activation of mTORC1 by deletion of tuberous sclerosis complex 1 (Tsc1), could respectively increase or reduce osteoclastogenesis. Mechanistically, this was due to mTORC1 inhibition of NF- κ B and nuclear factor of activated T Cells 1 (NFATc1), both critical transcription factors of osteoclastogenesis (79). Another study shows how RANK ligand (RANKL)-dependent osteoclastogenesis is impaired in Tsc1-deficient bone marrow macrophages, where TSC1 is a negative regulator of mTORC1 (80).

Dai et al. suggested that in bone marrow macrophages, inhibition of mTORC1 by treatment with rapamycin or by genetic deletion, suppressed *in vitro* osteoclast differentiation rescued by upregulation of mTOR downstream target S6K159 (81). Collectively, these studies outline how the insulin/mTOR pathway plays a role in bone biology, however further investigation is needed to properly dissect its anabolic and catabolic role.

Insulin Signaling in Chondrocytes

Insulin resistance and hyperinsulinemia were shown to be involved in the pathogenesis of OA and metabolic syndrome (82, 83) (Figure 2). In human chondrocytes, insulin increases the mTOR signaling pathway and Akt phosphorylation in a dose-dependent manner, leading to impaired cellular autophagy, an important mechanism regulating the removal and degradation of damaged intracellular products (84). Treatment with rapamycin, an mTOR inhibitor, reversed the effects of insulin on autophagy activity and beneficial effects on cartilage integrity were observed (85). Furthermore, insulin reduced the content of proteoglycans and upregulated MMP-13 and IL-1 β , which have a significant role in chondrocytes and in cartilage degradation (84, 86).

Insulin Signaling in Macrophages

During insulin resistance state, Akt signaling is impaired leading to hyperactivation of mTORC1 and increased glycolysis. In macrophages, increased glycolysis affects responses to pathogens and danger signals (87). Insulin significantly

enhances the LPS-dependent expression of IL-1 β and IL-8 and the induction of enzymes involved in the prostaglandin E2 (PGE2) synthesis by macrophages (88) (**Figure 2**). In vivo and *in vitro* studies suggested that insulin re-established phagocytosis and fostered phagocytosis-induced apoptosis in neutrophils. Furthermore, insulin treatment induced macrophages to change their polarization state from M1 to M2 (87).

Insulin Resistance and Arthritis

Prevalence of insulin resistance is increased in RA patients (89–92) and it is correlated with disease activity and disease-specific factors such as chronic systemic inflammation and use of glucocorticoids which may cause dysfunction of pancreatic β cells (90, 93, 94). Indeed, it has been hypothesized that the glucose intolerance observed in RA is contributed by the inefficacy of β cells to compensate for insulin resistance (93) and that, in β cells of non-diabetic RA patients not receiving glucocorticoids, there is an impairment of proinsulin to insulin processing possibly explained by the sustained pro-inflammatory state (95).

Furthermore, in OA, it has been suggested that pathophysiological mechanisms similar to those observed in T2D are present and insulin resistance-related traits might have a role in the development of the disease (96).

GLUCOSE-LOWERING AGENTS AND ARTHRITIS

Increasing evidence suggests that glucose-lowering agents exert a number of anti-inflammatory activities (97). The anti-arthritis effects of metformin, thiazolidinediones (TZDs), dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists were investigated in several studies and are summarized in **Table 1**. Currently, no data exist about the sodium-glucose cotransporter type 2 (SGLT2) inhibitors.

Metformin

Metformin represents the first line treatment of T2D and insulin resistance states. Besides its anti-hyperglycemic effects, metformin has antiproliferative, antifibrotic, and antioxidant potential (98, 99) (**Table 1**). The main mediator of the anti-inflammatory properties of metformin is AMPK activation, which controls inflammation and immunity through a variety of mechanisms (100). The anti-inflammatory effects of metformin are also independent from AMPK. Indeed, metformin is a potent inhibitor of mitochondrial respiratory chain complex I (NADH: ubiquinone oxidoreductase) (101, 102) which is implicated in the production of ROS (103).

TABLE 1 | Effects of glucose-lowering agents on arthritis.

Metformin

- antiproliferative, antifibrotic, and antioxidant potential
- $\downarrow$ Th17 cells and $\downarrow$ proinflammatory cytokines
- inhibition of mitochondrial respiratory chain complex I and $\downarrow$ ROS
- $\downarrow$ STAT3 phosphorylation via AMPK/mTOR pathway and $\downarrow$ Th17 differentiation
- phosphorylation of AMPK
- in synovial fibroblasts $\uparrow$ glycolytic activity and $\downarrow$ IL 6, IL 8 and monocyte chemotactic protein 1
- in osteoclasts $\downarrow$ osteoclastogenesis by the AMPK-mediated inhibition of mTOR
- in macrophages $\downarrow$ of TNF α , IL-6, and MCP-1; $\uparrow$ release of IL-10
- $\downarrow$ inflammatory cytokines by suppressing NF- κ B pathway

Thiazolidinediones

- anti-inflammatory activity, immuno-modulation, antioxidant effect
- in macrophages $\downarrow$ proliferation
- in T-cells $\uparrow$ immunosuppressive effects
- $\downarrow$ production of IL-17; $\downarrow$ mRNA expression levels of inflammatory mediators; $\downarrow$ levels of MMPs
- in synoviocytes/synovial fibroblast $\downarrow$ growth and $\downarrow$ IL 1 β induced PGE2 synthesis
- maintained expression of aggrecan and type II collagen
- $\downarrow$ inflammatory cell infiltration, $\downarrow$ pannus formation, $\downarrow$ cartilage/bone damage
- $\downarrow$ TNF α , IL-1 β , MCP-1 and RANKL mRNA, $\downarrow$ osteoclasts differentiation
- in chondrocytes $\downarrow$ NO synthase expression, $\downarrow$ IL-1 β and MMP-13
- in chondrocytes/synovial fibroblasts $\downarrow$ COX-2 expression and PGE2 production
- $\downarrow$ NF- κ B pathway

Dipeptidyl peptidase-4 inhibitors

- $\downarrow$ proliferation of T cells
- $\downarrow$ anti-CCP, RANKL, TNF α and IL-6 by $\downarrow$ TLR/NF- κ B pathway
- action on cytokine secretion, T cell-dependent antibody production and immunoglobulin isotype switching of B cells
- in chondrocytes $\downarrow$ degradation of type II collagen by MMP-1, MMP-3, and MMP-13
- $\downarrow$ oxidative stress
- $\downarrow$ ADAMTS-4 and ADAMTS-5 leading to $\downarrow$ degradation of aggrecan
- $\downarrow$ p38 MAPK signaling pathway and $\downarrow$ NF- κ B

Glucagon-like peptide 1 analogues

- in FLSs $\downarrow$ TNF α , IL-6, IL-8, IL-1 β , MMP-3, MMP-13, HMGB-1, MCP-1, p38/MAPK and NF- κ B pathways
- in FLSs improved oxidative stress and prevented cell death
- in chondrocytes $\uparrow$ anti-apoptotic marker Bcl-2 and $\downarrow$ apoptotic proteins active caspase 3 and Bax
- in chondrocytes $\uparrow$ deterioration of type II collagen and aggrecan

Metformin was found to decrease IL-1 β and to boost IL-10 as well as to inhibit ROS production in LPS-activated murine macrophages in an AMPK independent manner (103).

In a mouse model of autoimmune arthritis, metformin downregulated Th17 cells decreasing proinflammatory cytokines and inhibiting the differentiation of Th17 differentiation through inhibition of STAT3 phosphorylation (104).

The phosphorylation of AMPK induced by metformin may partially improve synovial inflammation in RA. Under physiologic conditions, phosphorylation of AMPK reconstitutes cell stores of ATP, generating new ATP and inhibiting the inflammatory pathways, which are energy-expensive (105, 106). In RA synovial fibroblasts, metformin increases glycolytic activity and decreases oxidative phosphorylation and generation of IL-6, IL-8 and monocyte chemoattractant protein 1. Metformin can also suppress the differentiation of osteoclasts and the AMPK-mediated inhibition of mTOR negatively regulates osteoclastogenesis (107). In vitro, metformin can act on macrophages to inhibit the release of TNF α , IL-6, and MCP-1 while enhancing IL-10. In vivo, metformin can reduce inflammatory cytokine production leading to clinical improvement of arthritis. These effects were exerted by correcting the impaired autophagic flux and selectively degrading I κ B kinase causing suppression of NF- κ B-mediated signaling (108).

Thiazolidinediones

TZDs act as insulin sensitizing agents in liver, fat and skeletal muscle cells, through the activation of the nuclear peroxisome proliferator-activated receptor γ (PPAR γ). When PPAR- γ is activated, insulin-responsive genes controlling glucose and lipid metabolism are transcribed. Similar to metformin, also TZDs have pleiotropic properties including anti-inflammatory activity, immuno-modulation and antioxidant effects (109–114) (**Table 1**). From a molecular point of view, the anti-inflammatory action is exerted through the inhibition of NF- κ B signal pathway (115). PPAR γ acts as an E3 ubiquitin ligase, physically interacting with NF- κ B p65 subunit to induce its ubiquitination and degradation thus limiting pro-inflammatory cytokine production (116).

Interestingly, PPAR- γ ligands seem to have an immunomodulatory role on monocytes and macrophages. Pioglitazone suppressed macrophage proliferation without inducing apoptosis (117, 118). Furthermore, PPAR γ ligation induces T-cell immunosuppressive effects (118, 119).

The role of pioglitazone has been investigated in models of IL-17-induced human intervertebral disc degeneration. Its administration reduced the levels of inflammatory cytokines such as IL-17, and downregulated mRNA expression of inflammatory mediators. Furthermore, pioglitazone suppressed MMPs and preserved the expression of the extracellular matrix molecules aggrecan and type II collagen (120).

Anti-inflammatory effects of TZDs were demonstrated also in models of RA. In vitro, the growth of RA synoviocytes is inhibited by PPAR- γ ligands which also downregulate, in RA synovial fibroblasts, the synthesis of PGE2 mediated by IL-1 β (121).

Indeed, available evidence suggests that synthetic PPAR γ agonists such as rosiglitazone and troglitazone, but also the natural PPAR γ ligand 15-deoxy-Delta (12,14)-prostaglandin J2, can improve arthritis in murine models (122, 123).

In another set of experiments, it has been suggested that using methotrexate in combination with pioglitazone may have a synergistic effect in RA combining inhibition of inflammatory cytokines TNF α , IL-1 β and prevention of the activation of ROS (124, 125).

Tomita et al. explored the effects of THR0921, a PPAR- γ ligand, in mice models of collagen-induced arthritis. Compared with normal mice, those treated with THR0921 had milder synovial hyperplasia, with no pannus formation, lower degree of inflammatory cell infiltration and modest damage to cartilage and bone (126). Furthermore, where joint damage was observed, the expression levels of TNF α , IL-1 β , MCP-1 and RANKL mRNA were reduced. Koufany et al. explored the role of oral treatment with pioglitazone and rosiglitazone in murine models with adjuvant-induced arthritis, observing decreased expression of IL-1 β and TNF α in inflamed synovial tissue (127). Treatment with PPAR- γ ligands inhibits nitric oxide synthase expression induced by IL-1 β in OA patients' chondrocytes. PPAR- γ ligands reduced IL-1 β and MMP-13 production in a dose-dependent manner. The inhibitory effect of PPAR- γ activation was also demonstrated on the generation of nitric oxide and MMP-13 induced by TNF α and IL-17 (128). Finally, in human chondrocytes and synovial fibroblasts, the activation of PPAR- γ decreases IL-1 β induced COX-2 expression and production of PGE2 (129). Since high levels of COX-2-induced prostaglandins are associated with the generation of free radicals and lipid peroxide (130), pioglitazone exerts antioxidative and anti-inflammatory effects also through modulation of COX-2. Moreover, PPAR- γ agonists can inhibit the NF- κ B pathway, having an anti-arthritic role (109).

Dipeptidyl Peptidase-4 Inhibitors

DPP-4 inhibitors have been widely used in T2D. They act by reducing the degradation of the incretin hormones inhibiting the DPP-4 enzymes (**Table 1**). Incretins lead to improved glycemic control by delaying satiety, favoring the release of insulin, inhibiting the production of glucagon and preserving β -cell mass. DPP-4 can modify the functioning of immune system and also disease pathogenesis interfering with mechanisms of T cells development and migration but also with cytokine secretion, T cell-dependent antibody production and immunoglobulin isotype switching (131, 132). In large, prospective, population-based cohort studies, the risk of developing an autoimmune disease was lower in patients receiving antidiabetic therapy with DPP-4 inhibitors compared to T2D patients not treated with DPP-4 inhibitors (133, 134). In a series of pioneering studies conducted *in vivo*, Tanaka et al. demonstrated that DPP-4 inhibitors suppressed inflammation in two murine models of collagen-induced and alkyldiamine-induced arthritis, with pathological characteristics similar to RA. In particular, the inhibition of DPP-4 reduced mitogen-induced and antigen-induced proliferation of T cells (135, 136).

Ibrahim et al. (137) evaluated the effects of a combination therapy with sitagliptin and tofacitinib on JAK/STAT and TLR-4/NF- κ B pathways in murine models of adjuvant-induced arthritis. The separate administration of both tofacitinib and sitagliptin resulted in a reduction of anti-CCP, RANKL, TNF α and IL-6 compared to untreated mice, but the combination of both drugs produced a more significant decrease of the serological markers compared to each therapy alone (137).

Hu et al. demonstrated the anti-inflammatory effects of saxagliptin on articular chondrocytes exposed to AGEs. Saxagliptin reduced the expression of mRNA of enzymes such as MMP-1, MMP-3 and MMP-13, which are involved in type II collagen degradation. Furthermore, it significantly inhibited expression of ADAMTS-4 and 5, resulting in less aggrecan degradation. Oxidative stress was reduced by the inhibition of DPP-4 by inhibiting ROS generation and increasing levels of glutathione. Exposure to AGEs activated the p38 MAPK signaling pathway and increased the degradation of I κ B α , upregulating NF- κ B. In OA, saxagliptin was able to affect this pro-inflammatory process (138).

Glucagon-Like Peptide 1 Analogues

GLP-1 is an incretin mimetic hormone exerting different effects on glucose metabolism (Table 1). It can increase the secretion of insulin induced by glucose, delay gastric emptying and stimulate satiety. Moreover, GLP-1 plays a diuretic role and modulates the proliferation of β -cells (139). Growing evidence suggests that gut hormones act as key signals in regulating the interplay between the metabolic axis and the immune system and may also be involved in the response to immunomodulatory therapy for RA (140). In RA patients, the incretin-insulin axis and the incretin effect are impaired (64). The first study exploring the effects of GLP-1 analogues on the pathological characteristics of RA in human FLSs was conducted using lixisenatide. Lixisenatide downregulated TNF α , IL-6, IL-8 and MMPs, inhibiting the inflammatory response through blockage of cellular signaling pathways such as c-Jun N-terminal kinase (JNK), activator protein 1 (AP-1) and NF- κ B. Moreover, treatment with lixisenatide caused a reduction in oxidative stress and prevented cell death in FLSs (141).

Chen et al. explored the role of GLP-1 receptor (GLP-1R) in OA demonstrating that liraglutide could protect chondrocyte apoptosis and extracellular membrane degradation by regulating endoplasmic reticulum stress. Liraglutide upregulated the anti-apoptotic marker Bcl-2 and diminished the expression of apoptotic proteins active caspase 3 and Bax (142). The activation of GLP-1R/PI3K/Akt signaling by GLP-1 analogues is involved in various metabolic processes. The inhibition of PI3K/Akt signaling impaired the protective effects of GLP-1R increasing apoptotic activity and endoplasmic reticulum stress. The activation of GLP-1R inhibited the NF- κ B pathway thus decreasing the release of inflammatory mediators. The same results were obtained also in a model of knee OA (142).

Tao et al. studied the role in RA pathogenesis of GLP-1R on human FLSs using the selective GLP-1 agonist exenatide. FLSs were exposed to TNF α in the presence or absence of exenatide. Exenatide treatment significantly reduced expression of IL-1 β ,

IL-6, MMP-3, MMP-13 and MCP-1. Moreover, by preventing I κ B α degradation, the treatment inhibited activation of the p38/MAPK and NF- κ B pathways (143).

Similar results were observed in RA human FLSs incubated with TNF in presence of dulaglutide. Dulaglutide treatment significantly downregulated proinflammatory mediators such as IL-1 β , IL-6, MCP-1, HMGB-1, MMP-3 and MMP-13. The effects of dulaglutide were mediated by the inactivation of JNK and increased phosphorylation of I κ B α , causing a reduction of NF- κ B (144).

The inhibitory effect of dulaglutide on OA-related cytokines and chemokines was demonstrated also in chondrocytes treated with AGEs. In chondrocytes, the AGEs-mediated deterioration of articular extracellular matrix components, such as type II collagen and aggrecan, was reduced by treatment with dulaglutide through inhibition of MMP-3 and MMP-13 (145).

EFFECTS OF DISEASE-MODIFYING ANTIRHEUMATIC DRUGS ON GLUCOSE METABOLISM

Compared with the general population, insulin resistance is more prevalent in patients affected by RA (7, 90, 92, 146, 147). Insulin resistance is influenced by both inflammation-related and metabolic factors (95, 147–149) but, in RA patients, it can be modified by the use of anti-rheumatic drugs. The cytokines involved in the pathogenesis of RA, in particular TNF α , IL-1 and IL-6, also promote the development of insulin resistance. The topic has been extensively reviewed elsewhere (7, 9, 150) but, briefly, by acting through IRS-1, TNF- α reduces IR tyrosine kinase activity and induces serine phosphorylation leading to inhibition of IR in skeletal muscle cells and adipocytes (151, 152). Anti-TNF α agents improve insulin sensitivity and decrease insulin resistance in RA patients, also reducing the risk of developing T2D (153–157). Moreover, similar effects on the decrease of insulin resistance were shown in RA patients treated with IL-6 antagonists (158–160), anti-IL-1 agents (161, 162) or T-cell costimulation blockade (163). In summary, the introduction of disease-modifying anti-rheumatic drugs can control inflammation and exert beneficial effects on insulin resistance and insulin sensitivity in RA patients, potentially reducing the risk of developing T2D in non-diabetic individuals or aiding in the achievement of better glucose control in diabetics.

CONCLUSIONS

In summary, through its integrated signaling network, insulin regulates intracellular and intercellular pathways in immune cells, in cartilage and in synovial tissue, behaving as a crucial modulator of the inflammatory response observed in arthritis. Finally, robust *in vitro* and *in vivo* evidence outlines the

effects of glucose-lowering therapies in arthritis. Metformin, TZDs, DPP-4 inhibitors and GLP-1 analogues may exert an immunomodulatory action downregulating the expression of proinflammatory cytokines and chemokines, thus reducing synovial inflammation and potentially leading to improvement of arthritis.

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AUTHOR CONTRIBUTIONS

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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