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REVIEW

Ouyang et al: Psoriasis–T2DM comorbidity mechanisms

Mechanistic insights into psoriasis and type 2 diabetes mellitus comorbidity – Implications for treatment: A review

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ABSTRACT

Psoriasis is a chronic systemic inflammatory disease primarily affecting the skin, yet it is increasingly recognized for its systemic implications, particularly its strong association with type 2 diabetes mellitus (T2DM). This review synthesizes recent mechanistic and clinical evidence to elucidate the shared pathways linking psoriasis and T2DM, as well as to explore therapeutic strategies for this comorbidity. We conducted a narrative review of studies published between January 2020 and October 2025, encompassing preclinical models, clinical trials, and high-quality reviews that address pathogenesis and treatment. Key findings indicate that shared genetic loci and molecular pathways, including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling, the IL-23/Th17 axis, and mitochondrial dysfunction associated with the activation of the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway, contribute to both cutaneous inflammation and systemic metabolic dysregulation. Additionally, adipokine imbalances and chronic low-grade inflammation exacerbate insulin resistance and psoriatic skin pathology. Therapeutically, IL-17/IL-23 inhibitors, metformin, glucagon-like peptide 1 (GLP-1) receptor agonists, and other immunomodulatory strategies demonstrate potential in addressing both dermatologic and metabolic features. These insights reinforce the notion of psoriasis as a systemic disorder with significant metabolic consequences, highlighting the need for integrated, multidisciplinary management. Future research should concentrate on precise gene-environment interactions, biomarker validation, and the development of treatments that simultaneously target both skin and metabolic pathology to advance precision medicine for patients with psoriasis-T2DM comorbidity.

Keywords: Psoriasis, type 2 diabetes mellitus, comorbidity, pathogenesis, treatment.

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INTRODUCTION

Psoriasis is a chronic systemic inflammatory disease that primarily affects the skin. It is characterized by inflamed, scaly plaques that cause considerable distress due to their visibility and symptoms such as pruritus and pain[1]. Global prevalence ranges from 0.1% to 3%, with the incidence similar between men and women[2]. Growing evidence indicates that psoriasis is not merely a cutaneous disorder but exerts systemic effects[3].

Among these, the association between psoriasis and type 2 diabetes mellitus (T2DM) has garnered significant attention. A retrospective cohort study reported that hyperglycemia is an independent predictor of severe psoriasis recurrence[4]. In mice, sustained glucose intake exacerbates psoriasiform dermatitis, an effect ameliorated by oral metformin[5]. Moreover, psoriasis itself may increase the risk of developing T2DM through systemic inflammatory mechanisms, reinforcing the concept of psoriasis as a systemic disease that disrupts metabolic homeostasis[6-8]. Several studies have noted overlapping distribution patterns and a positive genetic correlation between psoriasis and T2DM, further supporting their link[9]. In addition, the co-occurrence of psoriasis and diabetes has also been associated with an elevated risk of viral infections and retinal vein occlusion (RVO)[10].

Both psoriasis and T2DM are chronic disorders that significantly diminish patient quality of life. Understanding the mechanisms that drive both conditions and developing targeted management strategies are critical priorities. Emerging evidence reveals a bidirectional association, in which psoriasis and T2DM, along with obesity, exacerbate one another[11]. This relationship is rooted in common pathological processes, including obesity, insulin resistance, and persistent systemic inflammation[12, 13]. Here, we synthesize recent mechanistic findings from preclinical studies, clinical trials, and real-world datasets. We discuss the pathogenesis underlying the psoriasis-T2DM comorbidity and highlight therapeutic approaches that target these shared disease mechanisms.

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METHODS

We searched PubMed, Google Scholar and Web of Science for studies published between January 1, 2020 and October 1, 2025. The search terms were: psoriasis, psoriatic, type 2 diabetes mellitus and diabetes mellitus. Inclusion criteria were as follows: (1) studies that examined the relationship between psoriasis and T2DM; (2) clinical or experimental studies that reported complete data; (3) high-quality review articles that provided comprehensive background information and references; (4) articles published in peer-reviewed journals. Exclusion criteria were as follows: (1) studies that did not directly address the mechanisms or treatment of psoriasis and T2DM; (2) conference papers and studies with incomplete data; (3) studies with poor quality or inadequate experimental design. It should be noted that this review is narrative in nature, and no formal risk-of-bias assessment was conducted.

SHARED GENETIC SUSCEPTIBILITY AND MITOCHONDRIAL DYSFUNCTION

Trans-disease meta-analysis (TDMA) have identified psoriasis and T2DM shared susceptibility loci, including 2p14 ($p=9.6\times10^{-9}$), 10q24.31 ($p=1.0\times10^{-9}$), 11q13.1 ($p=1.0\times10^{-11}$) and 17q21.2 ($p=1.5\times10^{-9}$)[14]. Several proteins encoded by these loci, such as actin related protein 2 (ACTR2), ER lipid raft associated 1 (ERLIN1) and beclin 1 (BECN1), interact with TNF receptor associated factor 6 (TRAF6) in the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway[14]. This suggests that NF-κB may be an important molecular link between psoriasis and T2DM. Bioinformatics analysis of data from the GEO database has also identified 62 shared hub genes between psoriasis and T2DM[15]. These genes include inflammatory mediators such as interleukin (IL)-1β, IL-17A and several S100A family members. They also include metabolic regulators such as arginase 1 (ARG1) and aldo keto reductase family 1 member B10 (AKR1B10). In addition, the late cornified envelope (LCE) gene cluster is well known for its association with psoriasis[16]. It also shows important pharmacogenetic interactions. Dipeptidyl

peptidase-4 inhibitors (DPP-4i) are widely used to treat T2DM. In vitro cell experiments, these drugs increase LCE-1C and LCE-3C expression in keratinocytes. In three dimensional skin models, they also increase LCE-2 protein levels[16]. This increase in LCE expression may partly offset psoriasis related LCE-3B/C deletions. It may help restore the epidermal barrier and may provide a protective effect in psoriasis lesions.

In patients with psoriasis treated with methotrexate, those with the rs12025144 single nucleotide polymorphism (SNP) GG genotype have a higher rate of diabetes and a weaker response to treatment[17]. This suggests that this genotype may define a metabolic subtype of psoriasis. This subtype is marked by underlying metabolic dysfunction. In addition, The ST6GAL1 gene encodes a sialyltransferase that helps regulate both immune and metabolic processes[18]. Bioinformatic analyses show that the rs6783836-T allele of ST6GAL1 is linked to lower hemoglobin A1c (HbA1c) levels, reduced lymphocyte counts, and a lower risk of psoriasis[18].

Mitochondrial dysfunction is another important link between psoriasis and T2DM. Whole mitochondrial genome sequencing in 98 individuals showed that the M haplogroup, defined by an mitochondrially encoded cytochrome b (MT-CYB) variant, is associated with a fourfold increase in psoriasis risk (odds ratio, OR = 4.0, p = 0.003). This may be related to reduced activity of oxidative phosphorylation (OXPHOS) complex[19]. Haplogroup R0 and J had decreased the risk of T2DM (OR = 0.28, p = 0.007). The T16189C variant within this haplogroup correlates with higher fasting insulin levels and increased insulin resistance[19]. Functional studies in Arab cohorts have identified eight novel mitochondrial mutations[13]. These non-synonymous mutations affect key subunits of the respiratory complexes required for energy production, specifically in Complex I (ND2, ND4, ND5), III (CYB), and V (ATP6). These mutations may impair adenosine triphosphate (ATP) synthesis and elevate reactive oxygen species (ROS) production. Excessive ROS may damage insulin-sensitive β-cells, therefore exacerbating both cutaneous inflammation and metabolic dysregulation[13].

Mendelian randomization (MR) studies in Europeans have shown that psoriasis

and T2DM are positively correlated at the genetic level (genetic correlation, RG = 0.19, P = 3 × 10^{-3}), but there is no clear evidence of a direct causal relationship between the two[20, 21]. Part of their association is likely mediated by obesity, systemic inflammation, or other shared factors. As a result, the overall relationship cannot be reduced to a single, simple causal path in MR analyses. These findings suggest that the link between psoriasis and diabetes more likely reflects complex interactions between genetic background, environmental exposures, and clinical risk factors. Further mechanistic studies are needed to clarify these pathways.

IL-17: CENTRAL IMMUNOMETABOLIC MEDIATOR

Clinical studies have shown that patients with psoriasis and concomitant T2DM display significantly elevated levels of IL-17, IL-23 and tumor necrosis factor alpha (TNF-α) within affected skin[22]. Under stress, skin dendritic cells and keratinocytes can release IL-23. IL-23 then activates T helper 17 (Th17) cells and γδ T cells, secreting IL-17A, IL-17F, and IL-22[23]. In a basic research study, γδ T cells in normal mouse skin did not express C-C chemokine receptor 6 (CCR6)[24]. In imiquimod (IMQ) induced psoriasis mouse models, a functional subset of γδ T cells appeared. These cells expressed both CCR6 and IL-17A. The ligand C-C motif chemokine ligand 20 (CCL20) acted together with T cell receptor (TCR) signalling. This combination greatly increased IL-17A production, but had little effect on TNF-α levels[24]. Single cell transcriptomic analyses showed that epidermal $CCR6^{+}$ γδ T cells in psoriatic lesions expressed high levels of IL-17F, IL-22, and RAR related orphan receptor alpha (RORα)[24].

Recent findings have emphasised the importance of IL-17 in metabolic disorders such as type 1 diabetes mellitus (T1DM) and T2DM[25-27]. IL-17 is a key proinflammatory cytokine and a main effector of Th17 cells[28, 29]. Th17 cells drive autoimmune responses and play a central role in psoriasis. IL-23 promotes the differentiation of Th17 cells and stimulates the release of IL-17. IL-17 then may drive systemic inflammation, which can impair the function of distant organs, including

pancreatic β-cells[30]. Interestingly, IL-17 expression is markedly reduced in insulin-deficient pancreatic islets, suggesting a close relationship between IL-17 levels and the functional integrity of β-cells[27]. Studies using formalin-fixed paraffin-embedded (FFPE) pancreatic tissue from 21 human cadaveric donors show that pancreatic endocrine cells, including both β- and α-cells, may act as active sources of IL-17, rather than as passive immune targets[27]. Immunofluorescence analysis confirms IL-17 expression within islets from patients with T1DM and T2DM, mainly in β- and α-cells, rather than in $CD45^+$ immune cells[27]. Together, these findings suggest that IL-17 production may persist even as its overall level declines with progressive β-cell loss. Under metabolic or immune stress, islet cells can actively amplify local inflammation by secreting IL-17. High levels of circulating TNF-α and IL-17, together with locally elevated IL-23 may sustain cutaneous inflammation and promote systemic insulin resistance[31].

At the systemic level, patients with psoriasis-associated metabolic syndrome (PSO-MS) have much higher serum IL-17A concentrations (2108 pg/mL) than patients without metabolic abnormalities (162 pg/mL, $p = 0.009$)[32]. In contrast, IL-23 levels do not differ between these groups. This finding highlights the importance of IL-17, although the absolute values and fold changes may vary depending on the assay platform and detection method. The study did not provide a clear method of detection for reference. Mechanistic studies further show that IL-17A promotes insulin resistance. It may activate NF-κB and other signaling pathways, stimulate hepatic gluconeogenesis and adipose tissue lipolysis, and induce serine phosphorylation of insulin receptor substrate-1 (IRS-1) in skeletal muscle[32]. Together, these findings highlight IL-17 as a pivotal immunometabolic mediator that connects psoriasis-related inflammation with metabolic disturbances seen in diabetes **(Figure 1)**. Targeting IL-17 may thus offer new therapeutic opportunities for both psoriasis and diabetes.

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CHRONIC LOW-GRADE INFLAMMATION AS A SHARED PATHOLOGICAL BASIS

Chronic low-grade inflammation underlies the connection between psoriasis and T2DM. Persistent hyperglycemia drives the accumulation of advanced glycation end-products (AGEs), which interact with their receptor RAGE on cell surfaces[4]. This engagement can activate NF-κB signaling, leading to increased expression of TNF-α, IL-6, and IL-1β[35]. The resulting cascade amplifies oxidative stress and inflammation, impairs skin barrier function, and reduces antimicrobial peptide production. These changes heighten the risk of infection. Of note, the psoriasis-associated protein psoriasin can also serve as a RAGE ligand, further implicating the AGE-RAGE axis as a molecular bridge between psoriasis and diabetes[34].

In addition, pathway-level bioinformatic analyses reveal several shared signaling routes in psoriasis and T2DM, including the NF-κB, necroptosis, NOD-like receptor, TNF, and Toll-like receptor pathways[36]. These interactions may enhance psoriatic inflammation in the context of diabetes[36]. Dysregulation of necroptosis and NF-κB not only drives β-cell injury in diabetes but may also exacerbate keratinocyte hyperproliferation and cutaneous inflammation in psoriasis[36].

Among cytokines, IL-1β occupies a central position in sustaining inflammatory circuits. It induces the production of downstream mediators such as IL-6 and TNF-α, thereby promoting Th1 and Th17 immune responses[37]. In psoriasis, IL-1β directly drives epidermal inflammation and is closely linked to the IL-23/Th17 cells axis[37]. IL-6 serves important physiological functions in glucose metabolism and glucagon-like peptide 1 (GLP-1) secretion[38]. However, its levels rise pathologically in chronic inflammation. Excess IL-6 promotes Th17 cells polarization, enhances keratinocyte proliferation, and disrupts skin barrier integrity[38]. It also impairs insulin sensitivity and β-cell function[38]. These effects position IL-6 as a key molecular bridge connecting the pathogenesis of psoriasis and T2DM. IL-21 is a key cytokine produced by follicular helper T (Tfh) cells, peripheral helper T (Tph) cells, and some

Th17 cells[39]. Both IL-21 and its receptor, IL-21R, are markedly increased in psoriatic lesions and in serum. IL-21R is widely expressed on T cells, B cells, NK cells, and keratinocytes. Blocking IL-21 signaling suppresses keratinocyte proliferation and lowers the expression of interferon-γ (IFN-γ) and IL-17A[39]. These findings suggest that IL-21 enhances inflammation predominantly by modulating T cell activity. IL-21 is also crucial for the development and maintenance of tissue-resident memory T (TRM) cells. These cells are key drivers of psoriasis recurrence[39]. In diabetes, insulin resistance and high blood glucose promote the differentiation of Tfh cells and activate the mTOR-STAT3 pathway. As a result, $CD8^+$ T cells become more sensitive to IL-21 and TRM cells persist in the skin[39]. This mechanism helps to explain why T2DM may increase the risk of psoriasis or worsen its severity.

In addition to classical cytokines, emerging biomarkers support the involvement of systemic inflammation in the overlap between psoriasis and T2DM. Glycoprotein acetylation (GlycA) is a composite marker of chronic inflammation and is often elevated in these patients. Higher GlycA levels reflect persistent immune activation[30]. Intestinal fatty acid binding protein (I-FABP) serves as an indicator of gut barrier dysfunction and increased permeability. Elevated I-FABP is associated with insulin resistance and the progression of diabetes[30]. These findings highlight a role for impaired barrier integrity and a broader array of inflammatory mediators in linking psoriasis and T2DM.

THE CYCLIC GMP-AMP SYNTHASE (CGAS)-STIMULATOR OF INTERFERON GENES (STING) PATHWAY: A MITOCHONDRIAL STRESS-DRIVEN LINK

Animal studies show that diabetic mice induced by a high-fat diet and streptozotocin develop more severe IMQ-induced psoriasiform skin changes than non-diabetic controls[5, 40]. These mice have higher psoriasis area and severity index (PASI) scores, marked epidermal hyperplasia and increased dermal immune cell infiltration. The lesions also show higher malondialdehyde levels and lower

expression of mitochondrial transcription factor A (TFAM) and OXPHOS complex proteins[33]. These findings indicate marked mitochondrial dysfunction and oxidative stress. It is important to note that these models mimic psoriasiform dermatitis rather than true psoriasis, and that streptozotocin has direct toxic effects on β-cells. Further experiments showed that the selective STING inhibitor C-176 reversed these pathological changes in mice. The treatment group showed reduced levels of NF-κB, TNF-α, IL-17A and IL-23 in the skin[33]. The authors also examined skin samples from 22 patients. Psoriasis patients with T2DM (n = 6) had higher intensity of STING and phosphorylated interferon regulatory factor 3 (p-IRF3) staining than patients with psoriasis alone, patients with T2DM alone, or healthy controls[33].

Clinical data show that expression of STING in psoriatic lesions from patients with T2DM is higher than in patients with T2DM alone and in healthy controls[41]. This suggests a strong association between the STING pathway and disease severity. At the molecular level, co-stimulation of human keratinocytes with palmitic acid (PA) and IMQ causes mitochondrial membrane depolarization. This leads to the release of mitochondrial DNA (mtDNA) into the cytoplasm[33]. The cytosolic DNA is then sensed by cGAS, which produces the second messenger 2',3'-cGAMP. Cell-based western blot experiments further show that this molecule activates STING and promotes its oligomerization, followed by recruitment of TANK-binding kinase 1 (TBK1). TBK1 phosphorylates IRF3, leading to increased expression of IFN-β and chemokines such as C-X-C motif chemokine ligand 10 (CXCL10). These chemokines recruit Th1 cells and cytotoxic $CD8^+$ T cells to the epidermis and amplify local inflammation[33]. IFN-β can disrupt insulin receptor signaling, while CXCL10 may promote the infiltration of autoreactive $CXCR3^+$ $CD8^+$ T cells into pancreatic islets, contributing to β-cell damage. High glucose levels further enhance this signaling cascade[33, 41]. At the same time, NF-κB activation promotes TNF-α and IL-23 expression, driving Th17 cells signaling. Together, these pathways form a positive feedback loop that sustains psoriatic inflammation.

Moreover, commonly used metabolic drugs, including metformin and GLP-1 receptor agonists, may indirectly suppress this pathway by improving mitochondrial

function, reducing ROS generation, and limiting mtDNA release. These findings highlight the cGAS-STING axis as a pivotal inflammatory and metabolic hub, offering new opportunities for integrated treatment of psoriasis in diabetic patients.

ADIPOKINE IMBALANCE IN OBESITY

Obesity is recognized as a state of chronic, low-grade systemic inflammation[42]. In high-fat diet-induced obesity models, epidermal γδ T cells show increased co-expression of CCR6 and IL-17A during the early phase of wound repair[24]. In contrast, in IMQ-induced psoriasis models, obesity does not increase the overall IL-17 response. This indicates that the polarisation of epidermal γδ T cells towards the IL-17-producing γδ T17 phenotype is context dependent. Local factors related to obesity, such as higher levels of CCL20 in the skin, persistent low-grade inflammation and keratinocyte stress, may act together to lower the activation threshold of γδ T cells[24].

Beyond immune cell modulation, obesity fundamentally alters the endocrine function of adipose tissue. Clinical studies show that psoriatic patients with metabolic syndrome (MS) exhibit significantly higher serum leptin levels and reduced adiponectin levels, shifting the adipokine profile toward a proinflammatory and insulin-resistant state[32]. Among these adipokines, resistin plays a particularly crucial role. The serum resistin levels of psoriatic patients are approximately twice those of individuals without metabolic comorbidities[43]. These levels correlate positively with the PASI score, fasting glucose levels, the homeostasis model assessment of insulin resistance (HOMA-IR) index and inflammatory markers such as C-reactive protein (CRP), IL-6 and TNF-α[43]. Resistin acts synergistically with leptin and high mobility group box 1 (HMGB1) to establish a positive feedback loop that perpetuates systemic inflammation and insulin resistance[43]. Mechanistically, resistin signals through the TLR4/CAP1 axis, activating multiple downstream pathways including NF-κB, JAK/STAT, and PI3K/AKT[43]. In the skin, this activation drives keratinocyte hyperproliferation, inhibits apoptosis, and promotes the expression of Th 17

cells-associated cytokines such as IL-17, IL-23, and TNF-α, thereby exacerbating psoriatic inflammation. Circulating inflammatory mediators subsequently interfere with insulin signaling in peripheral tissues. Moreover, resistin enhances hepatic gluconeogenesis, stimulates lipolysis in adipose tissue, and induces serine phosphorylation of IRS-1 in skeletal muscle, collectively contributing to systemic insulin resistance[43]. Animal experiments provide further support for this mechanism. In IMQ-induced psoriasiform dermatitis combined with a high-sugar diet, mice display parallel elevations in blood glucose and serum resistin levels[43]. Anti-IL-17 therapy not only alleviates skin lesions but also restores glucose tolerance, suggesting that resistin is both a potential early biomarker and a therapeutic target for psoriasis complicated by T2DM.

In addition to adipokines, lipid metabolic disturbances driven by caloric excess play a key pathogenic role. When subcutaneous adipose storage becomes saturated, excess free fatty acids (FFAs) accumulate ectopically in the liver, skeletal muscle, pancreatic β-cells, and even epidermal keratinocytes[44]. Elevated FFAs activate protein kinase C (PKC) and NF-κB signaling, inducing TNF-α and IL-6 production and sustaining activation of the IL-23/Th17 cells inflammatory axis[44]. This dual effect exacerbates insulin signaling defects in metabolic tissues while maintaining abnormal keratinocyte proliferation and pathological angiogenesis in the skin, thereby establishing a vicious cycle between metabolic dysfunction and chronic cutaneous inflammation.

Elevated plasma triglycerides are associated with an increased risk of psoriasis in both observational and MR analyses. In the observational analysis, the multivariable-adjusted hazard ratio for psoriasis (ICD-10) was 1.26 (95% confidence interval (CI) 1.15-1.39) per doubling of plasma triglycerides, with a corresponding causal odds ratio for incident psoriasis of 2.10 (95% CI 1.30-3.38)[45]. Hypertriglyceridemia may worsen psoriasis through the mechanisms described above, and many studies support a strong link between psoriasis and metabolic syndrome components such as obesity and dyslipidemia. These findings underline the importance of lipid control. In the future, patients with psoriasis should be routinely

screened for lipid abnormalities to enable early detection and timely intervention.

SHARED METABOLIC DYSREGULATION

Studies using the K14-VEGF-A transgenic psoriasis mouse model have shown that with aging, spontaneous worsening of skin inflammation coincides with systemic metabolic disturbances, including elevated fasting glucose, impaired glucose tolerance, and dyslipidemia[46]. This model provides direct evidence that chronic skin inflammation alone can drive systemic metabolic dysfunction. Integrative analyses of gene expression in psoriatic skin and diabetic pancreatic islets have identified three shared signaling pathways, including phosphoinositide 3-kinase (PI3K)-protein kinase B (Akt), ras-related protein 1 (Rap1), and cGMP-PKG signaling pathway[15]. Further network analyses revealed three core hub genes: small nuclear ribonucleoprotein polypeptide N (SNRPN), GNAS, and insulin-like growth factor 2 (IGF2)[15]. SNRPN regulates systemic energy sensing, while GNAS encodes the Gαs protein that couples pancreatic β-cell and keratinocyte GPCR signalling. Meanwhile, IGF2 promotes both β-cell proliferation and epidermal hyperproliferation. These genes were consistently downregulated in independent validation cohorts and in peripheral blood samples from patients. This demonstrates their good diagnostic performance for comorbidity and offers new molecular insights into disease co-occurrence.

In experimental models of psoriasis with T2DM, phosphorylated AMP-activated protein kinase (p-AMPK) expression is markedly reduced, while keratinocyte growth factor (KGF) and signal transducer and activator of transcription 3 (STAT3) are upregulated[5]. As a key regulator of cellular energy metabolism, AMPK activation suppresses keratinocyte hyperproliferation and inflammatory responses[47, 48]. Both systemic and topical administration of metformin can reactivate AMPK signaling, downregulate KGF and STAT3 expression, reduce IL-17 receptor levels, and ultimately attenuate skin inflammation and hyperkeratosis[5]. These findings suggest that AMPK inhibition serves as a critical metabolic node connecting the two diseases and represents a potential therapeutic target.

Moreover, serum γ-glutamyl transferase (GGT) has been identified as an independent predictive marker for psoriasis, with stronger associations in patients with comorbid diabetes[49]. Under physiological conditions, GGT maintains intracellular antioxidant defense by breaking down extracellular glutathione (GSH). When GGT activity is abnormally elevated, it accelerates GSH depletion and promotes excessive ROS generation, causing oxidative damage[50]. In IMQ-induced psoriasis models, increased ROS and reduced antioxidant enzyme activity are observed in skin lesions, while GSH levels in the serum and skin of psoriasis patients are significantly decreased[51]. Clinical evidence shows that antioxidant therapies can effectively improve skin lesions[49]. This indicates that elevated GGT may drive skin inflammation and systemic insulin resistance by depleting GSH, accumulating ROS, and activating key inflammatory pathways such as NF-κB and IL-23/Th-17 cells.

THERAPEUTIC MANAGEMENT

Management of comorbid psoriasis and T2DM requires an integrated strategy. Treatment should address both skin lesions and systemic metabolic risk. Clinical observations show that poor glycemic control can reduce the effectiveness of psoriasis therapy. In a retrospective study, psoriasis patients with diabetes who received half-dose risankizumab had lower PASI 75 response rates than patients without diabetes[52]. This finding highlights the importance of good glycemic control for optimizing dermatologic treatment.

These two diseases may share a common inflammatory background. As a result, clinical guidelines increasingly recommend multidisciplinary care. Dermatology and endocrinology specialists should work together to control both inflammation and metabolic dysfunction[53]. This approach combines anti-inflammatory treatment with metabolic protection, as summarized in **Table 1**.

Biologics targeting the IL-23 or IL-17

IL-23 inhibitors such as risankizumab and IL-17 inhibitors such as ixekizumab not only clear psoriatic lesions and reduce PASI scores, but also improve markers of

subclinical atherosclerosis and vascular inflammation[52, 54, 65]. These agents provide both metabolic and immunological benefits. For patients with T2DM who need systemic treatment, these biologics are often the first choice. However, diabetes may slow the speed of clinical remission. In a post-hoc analysis of a randomized controlled trial (RCT), ixekizumab was given for 60 weeks. PASI 75 and PASI 90 response rates were similar in patients with normal blood glucose and in those with diabetes. The analysis included 406 normoglycemic patients, 118 patients with prediabetes and 40 patients with T2DM. However, patients with diabetes showed a clear delay in achieving complete clearance. PASI 100 was reached at 60 weeks in the diabetes group, compared with 12 weeks in the control group[54]. After adjustment for body mass index (BMI) and body weight, this delay remained significant, suggesting that diabetes itself is an independent risk factor for slower lesion clearance. Importantly, long-term IL-17A inhibition does not worsen fasting glucose, HbA1c, or lipid profiles, indicating a favorable metabolic safety profile. Case reports further demonstrate that bimekizumab and guselkumab are effective in refractory psoriasis with diabetes, including instances of Koebner phenomenon at insulin injection sites[55, 56]. These observations reinforce the central role of the IL-23/Th-17 cells axis in this comorbidity.

Beyond established biologics, novel immunomodulatory strategies are under development. One promising approach uses nano-based active immunization[37]. In a mouse model of psoriasis, supramolecular nanofibres that contain IL-1β B-cell epitopes and a universal T-cell epitope (PADRE) can induce strong and specific anti-IL-1β antibody responses. This vaccination reduces epidermal thickness and lowers skin levels of IL-1β, IL-6, IL-17, and TNF-α, with efficacy similar to direct IL-1β antibody therapy[37]. These findings point to new avenues for precision immunotherapy in chronic inflammatory disease.

Glucose-lowering medications with immunomodulatory effects

Several glucose-lowering drugs show promise for patients with both psoriasis and T2DM[66, 67]. These agents provide dual benefits by improving blood glucose and

reducing immune inflammation, which creates new options for combined therapy[68]. GLP-1 receptor agonists (GLP-1RAs) are among the most studied in this setting. In a meta-analysis of 32 patients, treatment with liraglutide led to a reduction in PASI (SMD -4.332, 95% CI -7.611 to -1.053, p = 0.01) and fasting plasma glucose (SMD -0.341, 95% CI -0.679 to -0.004, p = 0.048) compared with baseline[11]. In another RCT of 31 psoriatic patients with T2DM, 12 weeks of semaglutide plus metformin led to a PASI 90 response in almost half of the patients (6 of 13)[57]. The median baseline PASI score in the semaglutide group was 21 (IQR 19.8). After 12 weeks, the median PASI score decreased to 10 (IQR 6; p = 0.002)[57]. These patients also showed reductions in serum IL-6 and CRP. Case reports also describe near-complete skin clearance with liraglutide or semaglutide, together with improvements in dermatology life quality index (DLQI) and glycated hemoglobin (HbA1c)[6, 55, 69]. Current evidence is still limited to case reports and small RCTs. Larger trials are needed to confirm these findings. The immunomodulatory effects of GLP-1RAs are not yet fully understood. Several possible mechanisms have been suggested. First, weight loss reduces the release of pro-inflammatory cytokines such as IL-6 and TNF-α from adipose tissue. This may help to lower systemic inflammation[57]. Second, immune cells express GLP-1 receptors. Activation of these receptors can inhibit NF-κB signaling, reduce NLRP3 inflammasome formation, and downregulate mediators in the IL-23/Th17 pathway[6]. Third, GLP-1RAs can activate the AMPK pathway. This improves oxidative stress and increases insulin sensitivity, creating a less favorable environment for psoriasis development[6, 70]. Most studies report improvement, but a few cases of new-onset or worsened psoriasis during GLP-1RA treatment have been described[69]. This paradox suggests that the immunomodulatory effects of GLP-1RAs are complex and depend on the clinical context. Responses may differ with individual genetics, immune status, or specific drug characteristics. Careful monitoring of skin symptoms is therefore important during treatment.

Metformin, a first-line therapy for type 2 diabetes, has also shown benefits in psoriasis management[71]. Its mechanisms may involve activation of the AMPK pathway, which inhibits keratinocyte proliferation through the KGF/STAT3 axis and

suppresses NLRP3 inflammasome-driven IL-1β release[5, 72]. Recent evidence links its effects to modulation of the gut microbiota. Metformin increases the abundance of Akkermansia muciniphila, and its protein Amuc-1100 alleviates psoriasiform dermatitis in mice by regulating indole-3-acetic acid, a microbial tryptophan metabolite[71]. This results in the suppression of the epidermal antimicrobial peptide S100A8. Notably, combined use of metformin and alpha-glucosidase inhibitors (AGIs) such as acarbose increases psoriasis risk in a dose-dependent manner[58]. This risk may arise from changes in gut microbiota composition, with downstream effects on immune homeostasis.

SGLT2 inhibitors are widely used in diabetes for cardiovascular protection. They are also being studied for their potential effects on psoriasis. In IMQ-induced psoriasis mouse models, ointments with different concentrations of dapagliflozin and ointment with 0.05% clobetasol had similar effects on erythema and scaling, with no significant difference between groups. Treatment with dapagliflozin reduced inflammatory cytokines such as IL-17 and TNF-α, suggesting inhibition of the Th17 pathway[59]. However, in a large population-based, propensity score-matched cohort study, 550,195 patients with T2DM who received SGLT2 inhibitors were compared with 550,195 patients who received DPP-4 inhibitors. The outcome was new-onset inflammatory skin disease, including psoriasis, within 5 years after treatment initiation. The risk of psoriasis was higher in patients treated with SGLT2 inhibitors (3,767/1,313,282, No. of events/total person-years) than in those treated with DPP-4 inhibitors (4,495/1,732,071) (HR 1.08, 95% CI 1.03–1.13)[60]. These findings suggest that the immunomodulatory effects of SGLT2 inhibitors are complex and depend on the underlying disease state.

In a single-center RCT that included 118 patients with moderate psoriasis, the dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin enhanced the anti-inflammatory effect of narrowband ultraviolet B (NB-UVB) phototherapy when used in combination[61]. At 24 weeks, the mean change in PASI from baseline was greater in the sitagliptin combined with NB-UVB group than in the NB-UVB alone group (mean difference -1.0, 95% CI -2.0 to 0.0, p = 0.044). This benefit may result from

inhibition of excessive DPP-4 activity in the epidermis, which slows keratinocyte proliferation and modulates local T cell responses.

Thiazolidinediones (TZDs), represented by pioglitazone, act through activation of the PPAR-γ receptor[44]. This pathway directly suppresses NF-κB signaling and reduces key cytokines, including TNF-α, IL-6 and IL-17. A meta-analysis of six RCTs (n = 270) showed that pioglitazone was associated with a significant reduction in PASI score in patients with psoriasis vulgaris (weighted mean difference 2.68, 95% CI 1.41–3.94, P < .001)[62]. In subgroup analyses, pioglitazone monotherapy was effective in psoriasis vulgaris, and pioglitazone combination therapy was more effective than methotrexate, phototherapy or acitretin alone[44, 62].

These findings illustrate that glucose-lowering drugs exert diverse immunomodulatory actions on psoriasis through distinct molecular pathways. Careful consideration of both benefits and risks is essential. Such an approach will inform personalized strategies, maximizing outcomes for patients with T2DM and psoriasis.

Other immunomodulatory drugs and strategies

Apremilast, an oral phosphodiesterase-4 (PDE4) inhibitor, increases intracellular cAMP levels. This effectively inhibits pro-inflammatory cytokines like IL-17, TNF-α, and IL-23, while promoting the anti-inflammatory cytokine IL-10[12]. It is approved for moderate-to-severe plaque psoriasis and psoriatic arthritis. A 52-week prospective observational study confirmed that apremilast significantly improves skin symptoms (PASI score decreased by 75.2%), and reduces DLQI, nail psoriasis severity index (NAPSI), and joint-related scores[12]. Systemic inflammation markers (CRP and ESR) also decreased significantly. Notably, the study observed a potential glucose-lowering effect. Diabetic patients receiving insulin or oral hypoglycemic agents had their mean fasting blood glucose decrease from 132 mg/dL to 121 mg/dL, although HbA1c showed no significant change. These results indicate that apremilast is effective for skin lesions and may offer additional metabolic benefits for psoriatic patients with metabolic abnormalities. Its long-term efficacy and precise mechanisms warrant further study.

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Tacrolimus, a calcineurin inhibitor, primarily inhibits the NFAT signaling pathway, blocking T-cell activation and the production of key inflammatory cytokines like IL-2 and IFN-γ[73]. A case report demonstrated its successful use in a complex comorbid patient with T2DM and stage 4 chronic kidney disease (CKD) who developed acute generalized pustular psoriasis (GPP)[63]. After treatment with low-dose oral tacrolimus (3 mg/day), skin lesions nearly completely resolved within 2 weeks and remission was maintained during dose reduction at 3 months and follow-up at 6 months. Diabetes control remained stable without significant blood glucose fluctuations. This case suggests that tacrolimus may be an effective and manageable option for complex comorbid patients with relatively stable metabolism, although its immunologic mechanisms, long-term efficacy, and safety in this population require larger studies.

Systemic inflammation can also be addressed by non-pharmacological means. A case report described a psoriatic patient whose CRP levels dropped significantly, arthralgia resolved, and skin lesions cleared completely after 8 weeks of using an oral enzyme complex (OEC, containing bromelain, trypsin, and rutin)[64]. NSAID use was reduced. Symptoms recurred and CRP increased after discontinuation, but improved again upon retreatment, indicating the sustained role of this preparation in maintaining inflammatory remission. This provides a new approach to managing psoriasis and its comorbidities by modulating systemic inflammation. However, its long-term efficacy and specific immunomodulatory mechanisms in patients with diabetes and psoriasis need further validation in controlled studies.

CONCLUSIONS AND FUTURE DIRECTIONS

The comorbidity of psoriasis and T2DM is increasingly recognized as a consequence of intricate biological interconnections rather than mere coincidence. Shared genetic susceptibilities, persistent low-grade inflammation, and immunometabolic crosstalk converge to fuel both disease processes. Central to this nexus are the IL-23/Th17 cells axis, NF-κB signaling, and mitochondria-derived

stress responses, notably the cGAS-STING pathway, which collectively bridge cutaneous inflammation with systemic insulin resistance and metabolic dysfunction. This mechanistic convergence underscores psoriasis as a systemic disorder with profound metabolic repercussions and, conversely, implicates metabolic diseases such as T2DM in the potentiation of psoriatic inflammation.

This study has several limitations. First, psoriasis is a heterogeneous disease, including psoriasis vulgaris, pustular psoriasis, and psoriatic arthritis. Their mechanisms and treatments may differ. Second, population differences may limit the generalizability of our findings. Third, publication bias cannot be ruled out, especially in small observational studies that report positive results. Although we tried to include all available data, studies with null findings may be under-represented. In addition, our narrative (non-systematic) approach mean that some mechanistic and therapeutic conclusions remain provisional and depend on the specific context and type of evidence (preclinical, case-level, cohort, or randomized). These limitations should be considered when interpreting our results.

These insights support a shift toward integrated, multidisciplinary management. Given the strong comorbidity between psoriasis and diabetes, and the impact of diabetes on skin lesion recovery, clinicians should pay close attention to diabetes-related symptoms in patients with psoriasis, arrange timely screening, and ensure early diagnosis and intervention. Therapeutic interventions that target these shared molecular pathways, such as IL-17/IL-23 inhibitors and glucose-lowering agents with anti-inflammatory properties like GLP-1 receptor agonists and metformin, offer the dual benefit of improving both dermatological and metabolic symptoms. Comorbid conditions such as chronic kidney disease (CKD) and cardiovascular disease (CVD) may also influence treatment decisions in patients with psoriasis and T2DM. Some systemic agents, including traditional glucose-lowering drugs such as metformin, require caution or dose adjustment in patients with reduced renal function. In patients with CVD, glucose-lowering agents with cardiovascular benefits, such as SGLT2 inhibitors, are preferred. Therefore, clinicians should consider the presence and severity of CKD and CVD when selecting and monitoring treatments, and should

coordinate care with nephrologists and cardiologists when needed. Given the strong comorbidity between psoriasis and diabetes, and the impact of diabetes on skin lesion recovery, clinicians should also pay close attention to diabetes-related symptoms in patients with psoriasis, arrange timely testing, and ensure early diagnosis and intervention.

Future research must delineate the precise gene-environment interactions involved, identify robust biomarkers for patient stratification such as resistin and STING and develop novel therapeutics that can address skin and metabolic pathology simultaneously. For example, future work could include GLP-1RA randomized controlled trials in well-phenotyped psoriasis patients, with predefined skin and metabolic endpoints, as well as mechanistic human studies on cGAS-STING in both pancreatic islets and skin. Ultimately, a more complete understanding of the relationship between psoriasis and T2DM is crucial for developing precision medicine strategies that improve outcomes for people living with this challenging comorbidity.

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TABLES AND FIGURES WITH LEGENDS

Table 1. Therapeutic strategies for psoriasis and T2DM comorbidity

Agent	Specifics	Efficacy	Design	Notes
Biologics targeting the IL-23 or IL-17				
Risankizumab	75 mg at weeks 0 and 4, then every 12 weeks, for 52 weeks.	PASI 50/75/90/100 at week 40: 73.33/66.67/63.33/46.67%; at week 52: 67.86/64.29/60.71/42.86%. Disease duration in the DM+ group was significantly longer than in the DM– group ($p = 0.0498$; 0.0411)	Retrospective study; 30 patients[52]	Half-dose regimen (75 mg) still requires larger clinical studies to confirm efficacy.
Ixekizumab	Two injections (160 mg total) at Week 0; 80 mg every 2 weeks to	Similar PASI 75/90 response rates in patients with and without diabetes; delayed PASI 100 response in patients	RCT post hoc analysis; 564 patients[54]	No observed adverse effects on fasting glucose, HbA1c, or lipid profile.

	Week 12; then 80 mg every 4 weeks to Week 60.	with diabetes.		
Bimekizumab[55]	For 16 weeks.	Complete clearance of psoriatic lesions.	Case Report	-
Guselkumab[56]	Two injections.	Complete resolution of all plaques, including those at injection sites.	Case Report	Topical calcipotriol and betamethasone dipropionate are combined.
Traditional hypoglycemic drugs with potential to improve psoriatic skin lesions				
Liraglutide	-	Lower PASI (SMD -4.332, 95% CI -7.611 to -1.053, p = 0.01); lower fasting plasma glucose compared with baseline (SMD -0.341, 95% CI -0.679 to -0.004, p = 0.048).	Meta-analysis of 4 trials, 32 patients[11]	No significant change in HbA1c.
	Once daily before	Changes in PASI and DLQI from baseline	RCT,	Control treatment: Acitretin

	breakfast; titrated by 0.6 mg per week to a maximum of 1.8 mg; for 12 weeks.	were significantly greater in the treatment group ($p < 0.05$); HbA1c, HOMA-IR, and C-peptide decreased significantly from baseline ($p < 0.05$); Expression of IL-17, IL-23, and TNF-α in psoriatic skin was improved.	25 patients[22]	30-50 mg/day, calcipotriol ointment, and conventional antidiabetic drugs
Semaglutide	For 12 weeks.	Median PASI decreased from 21 (IQR 19.8) at baseline to 10 (IQR 6) at week 12 ($p = 0.002$); IL-6 and CRP decreased ($p < 0.05$).	RCT, 31 patients[57]	-
	0.25 mg/week for 4 weeks, then 0.5 mg/week; maintenance dose 1 mg/week reached at week 16 and then continued.	PASI 8.0 (-76.0%); HbA1c 6.4% (from 7.9%); fasting glucose 124 mg/dL (from 162 mg/dL) at week 16. PASI 2.6 (-92.2%); HbA1c 5.4%; fasting glucose 98 mg/dL at month 10.	Case Report[6]	Combined with metformin.

Metformin	Oral.	Psoriasiform dermatitis improved.	Animal study.	Some reports suggest that combined use with AGIs may increase psoriasis risk[58]
Dapagliflozin[59] (SGLT2i)	Topical.	Improved inflammatory markers and psoriatic lesions.	Animal study.	One study reported a higher risk of psoriasis in patients treated with SGLT2i compared with DPP4i (HR 1.08, 95% CI 1.03-1.13)[60]
Sitagliptin[61] (DPP-4i)	100 mg once daily (50 mg once daily in moderate kidney disease) for 24 weeks.	At week 24, the mean PASI change from baseline was -1.0 (95% CI -2.0 to 0.0), significantly greater in the sitagliptin + NB-UVB group than in the NB-UVB alone group (p = 0.044).	RCT, 118 patients.	With NB-UVB.
Pioglitazone[62](TZD)	15 or 30 mg once daily.	Marked reduction in PASI score in patients with psoriasis (WMD 2.68, 95%	Meta-analysis of 6 trials,	Some trials used combination therapy, not pioglitazone

		CI 1.41-3.94, p < 0.001).	270 patients.	monotherapy.
Other drugs				
Apremilast[12] (PDE-4i)	For 52 weeks.	75.2% reduction in mean PASI score; ESR and CRP decreased. Improved blood glucose in patients receiving insulin and/or oral hypoglycemic agents.	Prospective observational study, 137 patients.	Synergistic effect with insulin and/or hypoglycemic therapy.
Tacrolimus[63]	Initial dose 3 mg/day (0.05 mg/kg/day). For 2 weeks.	Skin lesions almost completely resolved.	Case Report	Low dose, short course; no increase in blood glucose; improved kidney function observed.
Oral enzyme combination (OEC)[64]	2 tablets twice daily for 8 weeks.	Complete remission of skin lesions; slight reduction in HbA1c; decreased CRP.	Case Report	Combined with exercise and dietary control.

Abbreviations: PASI: Psoriasis area and severity index; DM: Diabetes mellitus; RCT: Randomized controlled trial; SMD: Standardized mean

difference; CI: Confidence interval; DLQI: Dermatology life quality index; HOMA-IR: Homeostatic model assessment of insulin resistance; IQR: Interquartile range; AGIs: Alpha-glucosidase inhibitors; SGLT2i: Sodium-glucose cotransporter 2 inhibitors; DPP4i: Dipeptidyl peptidase-4 inhibitors; NB-UVB: Narrowband ultraviolet B; TZD: Thiazolidinedione.

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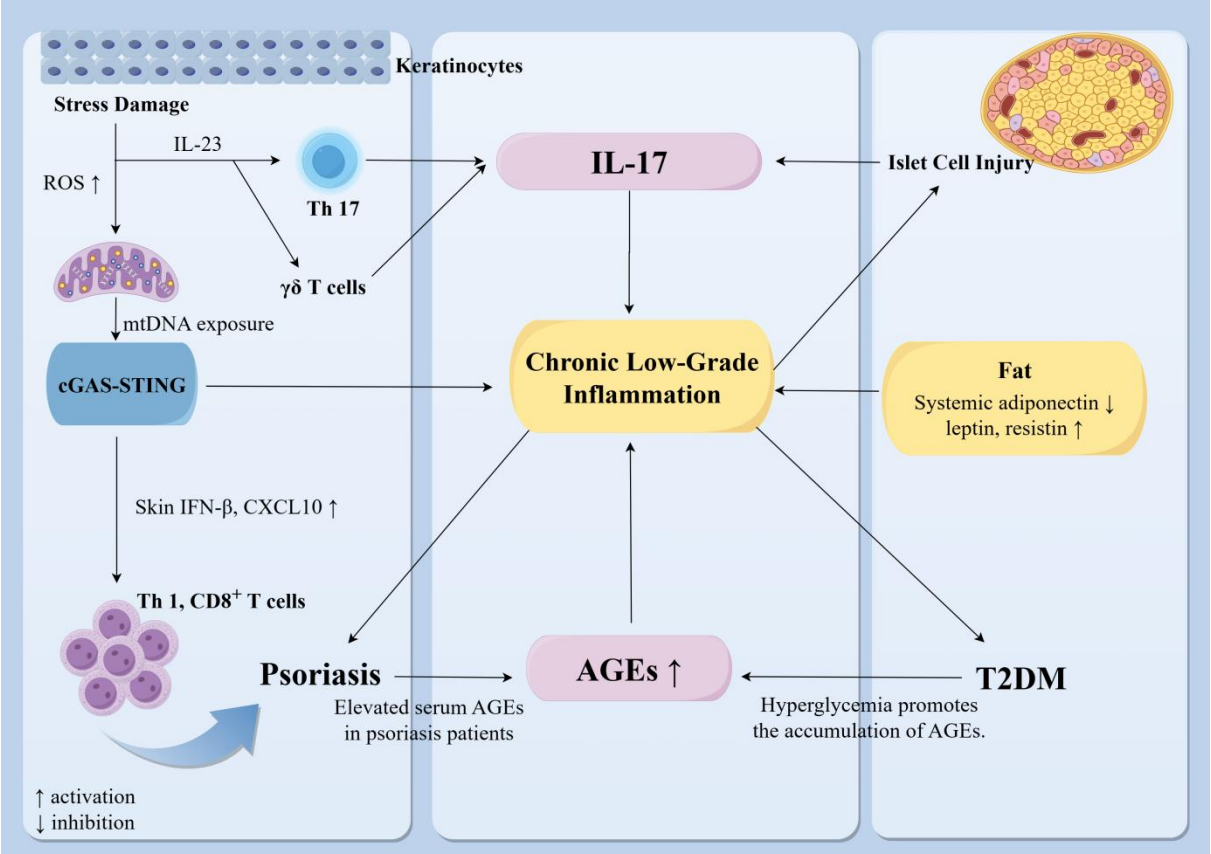

Figure 1. Partial mechanisms underlying the co-occurrence of psoriasis and T2DM. Under stress, skin dendritic cells and keratinocytes release IL-23, which activates Th17 cells and γδ T cells. These cells subsequently secrete IL-17A, IL-17F, and IL-22 [23]. Additionally, damaged pancreatic β-cells also produce IL-17, as demonstrated in animal studies [27]. Together with other cytokines, this process contributes to a systemic low-grade inflammatory state. Co-stimulation of human keratinocytes with palmitic acid and imiquimod induces the release of mtDNA into the cytoplasm. The cytosolic DNA is recognized by cGAS, which activates STING and promotes its oligomerization. This cascade results in increased expression of IFN-β and chemokines, such as CXCL10, which recruit Th1 cells and cytotoxic $CD8^+$ T cells to the epidermis, further amplifying local inflammation [33] (cell and animal studies). Elevated serum levels of AGEs are observed in psoriasis patients, with hyperglycemia in T2DM exacerbating circulating AGEs [34]. Furthermore, obesity exacerbates systemic low-grade inflammation [8]. Collectively, this chronic

low-grade inflammation serves as a common pathological basis for both psoriasis and T2DM. **Abbreviations:** T2DM: Type 2 diabetes mellitus; Th17: T helper 17; γδ T: Gamma delta T; β-cells: Beta cells; mtDNA: Mitochondrial DNA; cGAS: Cyclic GMP-AMP synthase; STING: Stimulator of interferon genes; IFN-β: Interferon-beta; CXCL10: C-X-C motif chemokine ligand 10; AGEs: Advanced glycation end-products. *This figure was created using Home for Researchers.*

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