




Diabetes and Psoriasis: Different Sides of the Same Prism

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Abstract: Diabetes and psoriasis are prevalent conditions with a spectrum of serious adverse outcomes. Both diseases are common comorbidities for each other, and diabetes is considered as a risk factor for psoriasis and vice versa. However, it is our contention that these diseases are not merely comorbidities of each other but rather share common underlying pathophysiologies (ie, genes and epigenetic changes, inflammation, abnormal environment, and insulin resistance) that drive disease. As such, they can be viewed as facets of the same prism. Genes can cause or permit susceptibility to damage from abnormal external and internal environmental factors, inflammation, and insulin resistance which can also drive epigenetic changes. These co-existing mechanisms act in a vicious cycle over time to potentiate cell and tissue damage to ultimately drive disease. Viewing diabetes and psoriasis through the same prism suggests potential for therapies that could be used to treat both conditions. Although additional controlled trials and research are warranted, we believe that our understanding of the overlapping pathophysiologies continues to grow, so too will our therapeutic options.

Keywords: genes, epigenetics, inflammation, abnormal environment, insulin resistance

Introduction

Affecting more than 30 million people in the US, diabetes mellitus (DM) is a disease characterized by a chronic hyperglycemic state with an associated spectrum of complications.¹ The complications and associated comorbidities of DM are well-established and range from retinopathy, nephropathy, neuropathy to cardiovascular disease, metabolic disease, cancers, dementia, nonalcoholic fatty liver disease, and beyond.¹⁻⁴ Our understanding of the known pathophysiologic mechanisms of DM continues to evolve, moving away from the notion of discrete disease subtypes (eg, Type 1, Type 2, Latent Autoimmune Diabetes of Adults) to a common underlying pathway of inflammatory, metabolic, environmental, and genetic insults that result in beta cell injury and a spectrum of phenotypes.^{2,5}

Psoriasis is a chronic, systemic inflammatory condition affecting approximately 8 million people in the US.^{6,7} The pathogenesis of psoriasis is thought to be a complex, immune-mediated process that results in damage that is more than skin deep.⁸ It is characterized by underlying inflammatory processes including regulatory immune cells, cytokines, and adipokines.⁷ Chronic inflammation with a dominant TNF- α -IL-23-Th17 axis leads to uncontrolled keratinocyte proliferation and dysfunctional differentiation, and neovascularization.⁸ Psoriasis has been associated with other chronic diseases including cardiometabolic disease (eg, DM, major adverse cardiovascular

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events, obesity, hypertension, dyslipidemia, metabolic syndrome), psoriatic arthritis, inflammatory bowel disease, non-alcoholic fatty liver disease, nonalcoholic steatohepatitis, chronic kidney disease, cancer, and mood disorders.⁶

Given its systemic nature and associated shared comorbidities with DM, it is not surprising that psoriasis has been associated with DM.^{6,8} Our own bias is not that psoriasis is a risk factor for DM but that the two diseases share overlapping pathophysiologies that link them. Here, we offer a coherent theory to explain the association between DM and psoriasis through our unified construct of DM, its pathophysiology, complications, and treatment. In this construct, we draw parallels between the genetic influences, inflammatory pathways, environmental influences, insulin resistance resulting in end-organ damage in DM and psoriasis, viewing the multifaceted aspects of the two diseases through the same prism (Figure 1). The specific phenotype of any individual will depend on which factors are involved and to what degree in each patient.

Epidemiology

There has been increasing evidence over the past several years describing the association between DM and psoriasis.^{6,9-11} Indeed it has been proposed that psoriasis is a risk factor for the development of DM and, conversely, that DM is an intrinsic risk factor for the exacerbation of psoriasis.⁹⁻¹¹ In 2013, Armstrong et al performed a systematic review and meta-analysis of 27 observational

studies, describing a 59% overall increased prevalence of DM in psoriasis patients, with up to 97% increased prevalence in those with severe psoriasis.⁹ In those studies that assessed incident cases of DM, patients with psoriasis were 27% more likely to develop DM compared to those without.⁹ Wan et al further evaluated the association between psoriasis severity and DM, describing significantly increased incidence of DM in psoriasis patients with more disease per body surface area.¹² More recently, a systematic review and meta-analysis of 38 studies by Mamizadeh et al found a similar significant association of DM in nearly 1 million psoriasis patients, reinforcing the notion that psoriasis is not limited to the skin.¹¹ It is our own bias that these 2 diseases are not merely comorbidities of each other but rather that they share the same pathophysiologies, and are facets of the same prism, which we aim to bring to light.

Pathophysiology of DM – 4 Basic Pathways

We believe the spectrum of DM is due to a common denominator, the defective beta cell.² This core defect results from four basic pathophysiologic processes comprising genes and epigenetic changes, inflammation, environment, and insulin resistance.² As a result, hyperglycemia arises through multiple pathways, the so-called Egregious Eleven.² The beta-cell dysfunction and related mechanisms of hyperglycemia and resultant endogenous fuel excess cause oxidative stress and epigenetic changes in tissues throughout the body, including worsening beta-cell dysfunction.² It is our view that some conditions associated with DM, such as psoriasis, are frequently concurrent due to overlapping pathophysiologies, especially shared genes and epigenetic changes (Figure 1).

Genes and Epigenetic Changes

The most important common pathophysiologic mechanism relating diabetes and psoriasis is the shared genetic mechanisms. Over the past 10 years, it has been increasingly evident that genes related to both Type 1 DM, Type 2 DM, and psoriasis share overlapping genes and susceptibility loci. In 2017, Wang et al examined 89 DM susceptibility loci in nearly 4500 psoriasis patients and 6000 controls in China, identifying the PTPN22, ST6GAL1, and JAZF1 genes as significant in both psoriasis and DM.¹³ The PTPN22 gene is known to encode an intracellular phosphatase that is thought to affect T-cell receptor signaling pathways in autoimmune diseases including Type 1 DM, Graves disease, rheumatoid arthritis, and systemic lupus erythematosus.¹⁴

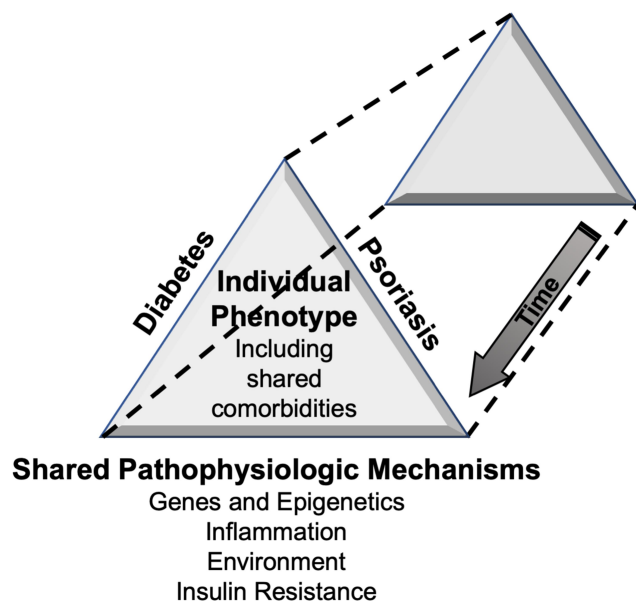


Figure 1 Diabetes and psoriasis: Different sides of the same prism.

The JAZF1 gene was found to contain an intron variant that was associated with psoriasis through an unknown mechanism, and has also been found to be a transcriptional repressor, negatively influencing glucose metabolism with associated beta-cell impairment.¹³ Finally, a noncoding variant was found within the first intron of the ST6GAL1 gene which is thought to encode a glycosyltransferase that participates in cell-surface carbohydrate determinants and antigen differentiation thought to be necessary in T cell activation, but the role in both DM and psoriasis is unclear.¹³ Furthermore, Quaranta et al noted different single nucleotide polymorphisms of the CDKAL1 gene were present in psoriasis and Type 2 DM cases.¹⁵ The function of the protein encoded by this gene is not definitively known but is thought to be associated with insulin production under glucotoxic conditions.¹⁵ Transcripts of this gene were found to be virtually absent from keratinocytes but clearly expressed in immune cells although downregulated in actively proliferating immune cells.¹⁵

With regard to epigenetics, dysregulation of miRNA expression or mutation in miRNA genes is associated with a wide variety of human diseases. Post-transcriptional changes by microRNAs (miRNAs) have also been implicated in DM and psoriasis.^{3,5} For example, Granata et al describes a link between DM and psoriasis through miR-21 which is up-regulated in T helper cells within psoriatic skin lesions, and activated as promoter of genes implicated in Type 1 DM.¹⁶ In addition, in pancreatic β cells, when the miR-21 gene promoter is activated, subsequent down-regulation of programmed cell death protein 4 (PDCD4) occurs, thus protecting pancreatic cells from apoptosis.¹⁷ As miR-21 is also upregulated in psoriasis, the miR-21-PDCD4 axis may play a crucial role in both DM and psoriasis, representing a potential therapeutic target for treating both diseases.¹⁷

Inflammation

The known underlying pathophysiologies of psoriasis are complex in nature with a strong focus on the immune response, both innate and adaptive.^{6,10} Inflammation is common, associated with both DM and psoriasis, and serves as a mechanistic link between the skin lesions and comorbidities in psoriasis and metabolic derangements in DM. Inflammation is necessary for the immune system to protect against various environmental and pathogenic insults, however when it becomes chronic it can do more harm than good, increasing the risk of developing other comorbidities, including metabolic syndrome, cardiovascular disease, inflammatory bowel

disease, cancer, and notably DM.¹⁸ The inflammatory cytokines implicated in psoriasis can increase the amount of insulin-like growth factor (IGF) in the skin and body.¹⁹ Binding of IGF to IGF receptors results in proliferation of keratinocytes and fibroblasts.¹⁹ Further, Davidovici et al demonstrated TNF- α secreted by macrophages in dermal and adipose tissue has been associated with altered adipokine gene transcription, increasing expression of pro-inflammatory leptin, and anti-inflammatory adiponectin.¹⁸

Environment

The pathogenesis of both DM and psoriasis is thought to be impacted by the environment, both externally and internally. Indeed an abnormal environment influences patients based on their unique genetic makeup and also triggers epigenetic modifications and impacts the immune system.²⁰ Lifestyle factors like diet and exercise are well-established modifiable risk factors in the development of DM and are largely related to the inflammatory state associated with obesity.²¹ Environmental risk factors that are thought to play a critical role in psoriasis include UV exposure, medications, smoking, diet and obesity, alcohol intake, infections, and stress.²⁰ Many of these are associated with downstream dysregulation of the immune system/immune responses, likely through epigenetic modifications.²⁰

The gastrointestinal (GI) environment has been shown to play a major role in glucose homeostasis, mediating up to 70% of postprandial insulin release via incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).²² These hormones have also been shown to promote proliferation and prevent apoptosis of beta cells, however their levels and function are noted to be reduced in Type 2 DM.²² Interestingly, Gyldenlove et al noted significantly reduced incretin effect (39%) in 12 non-diabetic psoriasis patients after oral glucose tolerance tests compared to matched controls (57%), suggesting GI-related mechanisms of glucose control (eg, incretin response) are impacted in psoriasis patients as well.²³

Insulin Resistance

Insulin resistance is an important pathophysiologic mechanism involved in DM and psoriasis. Importantly, insulin resistance and inflammation are closely intertwined. Indeed, inflammatory mediators (eg, cytokines and adipokines) involved in the development of insulin resistance are dysregulated in patients with psoriasis.^{18,24} It stands to reason that insulin resistance has been found in

patients with psoriasis and is significantly correlated with area and severity, even in patients without concomitant metabolic syndrome.^{18,24} Moreover, during times of hyperinsulinemia due to insulin resistance as often seen in Type 2 DM, insulin has the potential to bind to IGF receptors, resulting in keratinocyte and fibroblast proliferation.¹⁹ Further, levels of adiponectin, an enhancer of insulin sensitivity and inducer of anti-inflammatory cytokines, are found to be reduced in both DM and psoriasis.¹⁸

Associated Comorbidities

In addition to the link between DM and psoriasis through the four described overlapping pathophysiologies, both conditions have other similar associated comorbidities. When considering DM and psoriasis through the prism of these overlapping drivers, it is understandable that other comorbidities that are driven by similar influences are also shared. Below we focus on common comorbidities and their link with psoriasis, with the understanding that DM shares these links as well.^{1,2,4}

Psoriasis and Metabolic Syndrome and Obesity

Metabolic syndrome (MS), the co-existence of central obesity, hypertension, dyslipidemia, and hyperglycemia, are significant risk factors for DM and its associated complications.^{1,2} Although psoriasis patients are 2–3% of the population, over 30% of them have been found to meet criteria for MS, with up to 76% higher risk in certain populations, especially in women and those over age 40.^{19,25} Furthermore, when analyzing the prevalence of individual MS components, obesity, dyslipidemia, and hyperglycemia are each found more commonly in those with psoriasis compared to those without.²⁶

The relationship between psoriasis and obesity is largely based on a chronic inflammatory state.²⁷ White adipose tissue is metabolically active, consisting of adipocytes and immune cells like macrophages.²⁸ It is these cells that secrete adipokines, which are pro-inflammatory cytokines such as adiponectin, leptin, chemerin, resistin, visfatin, vaspin, free fatty acids, TNF- α , and several interleukins, most of which have also been implicated in the chronic diseases described above.²⁸ For example, levels of leptin and resistin levels are higher in patients with psoriasis and correlated with disease severity and higher concentrations of TNF- α and IL-6 are considered biomarkers for psoriasis.²⁹ Dysregulation of both pro- and anti-inflammatory adipokines that occurs with obesity leads to chronic inflammation.²⁹ This inflammation is

thought to lead to a wide array of metabolic disorders and chronic complications spanning not only psoriasis and DM, but also hypertension, lipid disorders, insulin resistance, infertility, and cancer.²⁹ In the case of psoriasis, inflammation in the fatty tissue related to metabolic dysfunction associated with obesity can directly affect inflammatory processes in psoriatic skin lesions.²⁹ Finally, certain epidemiological studies note that obesity might be an independent risk factor for psoriasis while others suggest that obesity is a consequence of psoriasis.²⁷ Therefore, the association between the two appears to be a bidirectional one.²⁷

Psoriasis and Cardiovascular Disease

With increased MS prevalence comes increased cardiovascular morbidity and mortality. Atherosclerosis associated with cardiovascular disease has been described as a process driven by inflammation.³⁰ Moreover, the underlying pathophysiology of psoriasis is deeply rooted in inflammatory cytokines that inhibit normal functioning of insulin receptors with eventual downstream endothelial dysfunction and hyperproliferation, bridging a link between atherosclerosis and the chronic skin condition.³¹ Additionally, psoriasis has been found to be a risk factor for myocardial infarction, with increased psoriasis severity being associated with greater risk of an event.³² In fact, severe psoriasis has been found to be an independent risk factor for death from cardiovascular disease.³³

Psoriasis and Cancer

A recent systematic review and meta-analysis of 58 observational studies by Trafford et al has found significant associations between psoriasis and both cancer incidence and mortality.³⁴ The cohorts that were analyzed demonstrated an 18% increased risk of developing cancer in psoriasis patients compared to those without, with 22% increased risk in those with severe psoriasis. Incidence of lymphoma, keratinocyte, esophageal, liver, and pancreatic cancers was noted to be higher in the psoriatic population.³⁴ Overall, psoriasis patients were found to have a 22% increased risk of dying from these cancers compared to the psoriasis-free populations.³⁴ This increased risk is thought to be in part due to the chronic inflammation associated with psoriasis.³⁴ Not surprisingly, however, the study authors deemed part of this increased risk due to lifestyle factors like obesity and smoking, as the studies that adjusted for these factors noted considerable attenuation of cancer risk.³⁴ Nonetheless, it is becoming clear to us that the cumulative effects of inflammation

and lifestyle factors are implicated in cancer, psoriasis, and DM.^{4,34}

Potential Treatment Implications

It has become evident that the current DM classification of discrete categories (eg, Type 1 versus Type 2) is outdated as we have learned so much more about the complexities of the disease spectrum.^{2,5} A co-author of this current paper has proposed a new model of classification around the abnormal beta cell and its pathophysiologic causes including genetic predisposition and epigenetic changes, inflammation, environmental influences, and insulin resistance – the aforementioned base of the DM-Psoriasis prism (Figure 1).^{2,5} The unique contributions of these factors that exist in any individual will define their diabetic phenotype which includes the presentation of their hyperglycemic state, the mechanisms behind their hyperglycemia, and the implications for more specialized therapeutic approaches. These common pathophysiologic mechanisms also contribute to cell and tissue damage within psoriasis.

Viewing these 2 conditions through the same prism suggests that some therapies may be potentially used to treat both psoriasis and DM. Indeed, non-pharmacologic approaches such as lifestyle modification (eg, diet, weight reduction, smoking cessation, increased physical activity) have beneficial effects in both patients with DM and psoriasis.^{21,35,36,37} This concept also applies to pharmacologic treatment. For example, several case studies have described significantly improved psoriasis severity in patients receiving GLP-1 agonists for DM.³⁸ Additionally, thiazolidinediones (TZDs), antidiabetic drugs that improve insulin sensitivity and decrease inflammation through peroxisome proliferator-activated receptors (PPAR)- γ , inhibit proliferation of keratinocytes (which express PPAR receptors).³⁹ A systematic review and meta-analysis found that the TZD pioglitazone significantly decreased psoriasis severity compared to placebo suggesting efficacy for the treatment of psoriasis.³⁹ Finally, metformin, a drug commonly used by patients with DM and metabolic syndrome based on its ability to decrease the rate of hepatic gluconeogenesis and potentially decrease insulin resistance, may also provide potential benefit with regard to psoriasis.^{40–42} In a large case-control cohort study, metformin use was associated with reduced risk of psoriasis, however this reduction in risk was only observed in males.⁴² It is hypothesized that this potential benefit may be conferred by the insulin-sensitizing effect as well as anti-inflammatory effects of metformin through activation of adenosine monophosphate-activated protein kinase (AMPK).^{40–42} Based on this, some have suggested metformin as a possible

add-on therapy in overweight male patients with metabolic syndrome, however further research in psoriasis patients with and without metabolic syndrome is clearly warranted.⁴¹

Conversely, current psoriasis therapies may potentially be used to treat DM. For example, TNF α -blockers that are approved for the treatment of psoriatic arthritis and psoriasis vulgaris are also being evaluated in DM due to the potential to improve insulin sensitivity.⁴³ A prospective study found that the anti-TNF- α therapy adalimumab showed significantly improved insulin sensitivity in psoriasis patients after 6 months of therapy.⁴⁴ In addition, first approved for the treatment of moderate-to-severe psoriasis in the US (but not available ex-US), alefacept is a biological drug tested in the TIDAL (inducing remission in new-onset Type 1 DM with alefacept) trial. This study has shown that alefacept is able to target pathogenic effector T cells, preventing β cell destruction in patients with new-onset Type 1 DM.⁴⁵ The beneficial effects reported for many drugs on both psoriasis and DM may underline the correlation between these diseases. More research is needed to evaluate the efficacy of shared treatments in both diseases.

We believe that as our understanding of the overlapping pathophysiologies between DM and psoriasis continues to grow, so too will our treatment armamentarium. We encourage further investigations of DM and psoriasis through the lens of our prism.

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