

Psoriasis Exacerbates the State of Insulin Resistance in Patients with Type 2 Diabetes

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Purpose: Although psoriasis (PsO) is highly associated with insulin resistance (IR), the role of PsO on activity of insulin secretion or its action in diabetic patients has not been explored.

Materials and Methods: In-patient data on type 2 diabetes (T2D) with or without PsO from 2016–2019 in our hospital were analyzed. Data for 42 diabetic patients with PsO were compared with that of the control group (T2D only). Blood examinations with reference to the levels of fasting blood glucose, C-peptide, insulin, HbA1c, plasma lipids, lipoproteins, and kidney function were explored. HOMA-IR and HOMA- β models were established to explore IR and pancreatic β -cell function.

Results: HOMA-IR level was significantly higher ($P=0.0003<0.05$) in patients with PsO compared with the controls. Although the durations of diabetes in patients with PsO were significantly shorter compared with that of patients with diabetes only ($P=0.012<0.05$), analysis of mean BMI, eGFR, plasma lipids, and lipoprotein showed no significant differences. Analysis of the level of fasting glucose and HOMA- β showed no statistical differences between the two groups. On the other hand, the levels of C-peptide of PsO group were significantly high in both fasting state ($P=0.0182<0.05$) and after glucose challenge ($P=0.0011<0.01$).

Conclusion: The findings of this study show that under the same fasting conditions, patients with PsO may have relatively preserved pancreatic β -cell function, and PsO significantly increases IR.

Keywords: psoriasis, type 2 diabetes mellitus, IR, β -cell function

Introduction

Psoriasis (PsO) is a common chronic inflammatory skin disease.¹ Individuals with PsO are at higher risk of developing other chronic and severe health diseases including psoriatic arthritis, metabolic syndrome, cardiovascular disorders, anxiety and depression, non-alcoholic fatty liver disease, Crohn's disease, and lymphoma.^{2,3} Diabetes is a group of metabolic diseases characterized by chronic hyperglycemia due to absolute or relative deficiency of insulin secretion and IR.⁴ Currently, there is increased interest in exploring the relationship between the PsO and T2D. Previous epidemiological studies report that the risk of diabetes in patients with PsO is significantly higher compared with that in individuals without PsO. Studies project additional 125,650 new diagnoses in T2D per year worldwide in patients with psoriasis compared with those without PsO.⁵ In addition, severity of PsO is correlated with the risk of T2D.⁶ Notably, PsO and T2D show genetic and pathological similarities and common targets, such as CDKAL1, PSORS2, PSORS3, PSORS4, which are susceptible genes for PsO and are also associated

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with T2D.^{7,8} Studies report that inflammatory cytokines (such as TNF- α and IL-17),⁹ adipocytokines (such as resistin and chemerin),¹⁰ and gastrointestinal peptide (Incretins)¹¹ are associated with pathology of both PsO and T2D. Furthermore, anti-inflammatory or immune-restricting therapy are effective in modulating glucose metabolism in T2D and inflammation in PsO.^{12,13} However, the effect of PsO on insulin activity in T2D has not been explored. Therefore, this study explored changes in IR by determining HOMA-IR level in diabetic patients with PsO, and provides a possible strategy for effective management of glucose homeostasis in diabetic patients with PsO.

Methods

Source of In-Patient Data

Patients' data were obtained from an in-patient information system of Shanghai Pudong Hospital. Forty-two patients with a T2D history hospitalized in the Department of Endocrinology diagnosed with PsO were included in this study. Exclusion criteria included patients who are prediabetes, have type 1 diabetes, have latent autoimmune diabetes for adults (LADA), other special types of diabetes, gestational diabetes, presence of chronic inflammatory diseases other than PsO, severe anemia, pregnancy, or breastfeeding. The control group comprised patients with a history of T2D and without PsO, and met the exclusion criteria used for the PsO group. Diagnoses for T2D were based on the guidelines reported by the World Health Organization (WHO) in 1999.

Baseline Information Evaluation

Baseline data obtained included gender, age, duration of T2D, history of drug use, BMI, and related contents (Table 1). Treatments approaches for PsO included ultraviolet radiation, urea ointment, budesonide ointment, methotrexate, and vitamin A.

Blood Glucose Level, and Evaluation of Lipid Metabolism and Kidney Function

Fasting plasma glucose (FPG), 120 minute post-meal plasma glucose (PPG), HbA1c, fasting C-peptide (FCP), 120 minute post-meal C-peptide (PCP), fasting insulin (FIN), and 120 minute post-meal insulin (PIN) were determined. Lipids test included determination of total triglyceride (TG), total cholesterol (TC), High density lipoprotein (HDL), and Low density lipoprotein (LDL).

Table 1 Baseline Information of Diabetic Patients with and without PsO

	PsO+T2D	Controls	P
Patients (n)	42	99	/
Gender (Male/Female)	31/11**	47/52	0.003
Age (years)	62.00 \pm 16.86	64.28 \pm 13.06	0.436
Duration (years)	7.73 \pm 7.32 *	11.38 \pm 7.94	0.012
T2D drugs (Insulin/OADs [§] /combination)	11/15/6***	55/37/0	<0.001
PsO drugs (n)	11 [#]	/	/
BMI (kg/m ²)	26.10 \pm 4.44	25.39 \pm 3.65	0.415
HbA1c (%)	8.678 \pm 2.383	9.052 \pm 2.099	0.360

Notes: *P<0.05; **P<0.01; ***P<0.001; [§]Oral antidiabetic drugs for PsO: eight patients used metformin, five used α -glucosidase inhibitors, nine used sulfonylureas, none used Glinide, two used Thiazolidinedione (TZDs), and none used dipeptidyl peptidase IV (DPP-IV) inhibitors, one patient was unknown; combinations of insulin and OADs: three patients used metformin and insulin, one used sulfonylureas and insulin, one used Glinide and insulin, one used TZDs and insulin, one patient was unknown. For controls using OADs: 29 patients used metformin, 12 used α -glucosidase inhibitors, 22 used sulfonylureas, one used Glinide, nine used Thiazolidinedione (TZDs), and none used dipeptidyl peptidase IV (DPP-IV) inhibitors, one patient was unknown. [#]The 11 patients with PsO+T2D received PsO drugs, including two patients with only oral retinoic acid therapy, one patient administered with only oral methotrexate, one patient using only urea ointment, one using budesonide cream combined with oral retinoic acid and ultraviolet therapy, and six using traditional Chinese medication therapy.

Abbreviations: PsO, psoriasis; T2D, type 2 diabetes; OADs, oral antidiabetic medications; BMI, body mass index; HbA1c, hemoglobin A1c.

In addition, kidney function tests including eGFR were performed.

Establishment of HOMA-IR and HOMA- β Models

Fasting glucose and fasting C-peptide were used to perform homeostasis model assessment to quantify and compare IR and β -cell function between the PsO group and control group. HOMA-IR and HOMA- β models were developed using a calculator obtained from the University of Oxford database (<http://www.dtu.ox.ac.uk/>).

Statistical Analyses

Statistics analyses were performed in SPSS (IBM, version 24.0) and Prism (GraphPad, version 8.0). Independent *t*-tests were used to compare differences between BMI, duration of diabetes and eGFR of HOMA-IR and HOMA- β groups.

Two-way ANOVA was used to compare the levels of plasma lipids and lipoprotein, glucose, insulin, C-peptide change between the two groups. Statistical significance was determined at $P \leq 0.05$ level for all analyses.

Results

IR Was Significantly Higher in the PsO Group Compared with the T2D Group without PsO

Analysis showed significantly higher levels of HOMA-IR, FPG, and C-peptide in the PsO group (PsO) compared with the levels in the control group (T2D) (Mean±SD: PsO vs T2D: 5.863±21.070 vs 1.042±0.763, $P=0.0003$, PsO: n=42; T2D: n=99; Figure 1).

BMI, Estimated Renal Glomerular Filtration Rate (eGFR), Plasma Lipids and Lipoproteins in the PsO Were Not Statistically Different from Those in the Control Group

Analyses of anthropometry of BMI, and biochemistry tests of renal eGFR, plasma lipids and lipoprotein, showed no statistical differences between the two groups (Mean±SD: PsO+T2D vs controls: BMI: 26.10±4.44 vs 25.39±3.65 kg/m², $P=0.415$; eGFR: 81.93±33.84 vs 89.06±25.59 mL/min*1.73 m², $P=0.2673$; TG: 2.19±1.15 vs 1.79±1.52 mmol/L, $P=0.1552$; TC: 4.09±0.98 vs 4.20±1.17 mmol/L,

$P=0.9696$; LDL: 2.38±0.91 vs 2.54±0.94 mmol/L, $P=0.8738$; HDL: 0.93±0.33 mmol/L vs 1.04±0.29 mmol/L, $P=0.9654$) (Figure 2).

Analyses of Pancreatic β -Cell Function Showed Significant Differences in Levels of C-Peptide, but Not in HOMA- β , Plasma Glucose, and Insulin between the PsO and Control Group

C-peptide level in both fasting state and after 120 minutes was significantly higher in the PsO group compared with the level for the control group (0 minutes: $P=0.0182 < 0.05$; 120 minutes: $P=0.0011 < 0.01$; PsO: n=42; controls: n=99), whereas the HOMA- β , plasma glucose level, and insulin level showed no significant disparity in the PsO group compared with the control (Mean±SD: HOMA- β : PsO vs controls: 47.844±33.839 vs 41.296±30.774; $P=0.3387 > 0.05$; glucose level: 0 minutes: $P=0.4805 > 0.05$; 120 minutes: $P=0.2187 > 0.05$; insulin level: 0 minutes: $P=0.9984 > 0.05$; 120 minutes: $P=0.3479 > 0.05$, PsO: n=42; controls: n=99; Table 2 and Figure 3).

Discussion

PsO and type 2 diabetes mellitus (T2D) are chronic diseases that share common mechanisms including chronic inflammation in multiple organs and tissue. Studies report that PsO is highly correlated with metabolic syndrome, obesity, IR, diabetes, atherosclerosis, and cardiovascular diseases.¹ However, the effect of PsO on glucose metabolism in T2D has not been explored. Therefore, the current study sought to retrospectively explore the effect of PsO on metabolic profiles including plasma glucose, C-peptide, insulin, and lipids levels. In addition, HOMA models were established to explore IR and β -cell function in the PsO and the control groups. Gender proportion, duration of diabetes, proportion of drug administration in T2D, HOMA-IR, and C-peptide level showed significant differences between the two groups. The findings of this study show the role of PsO in pathophysiology of T2D, and provide a possible strategy for treatment of diabetic patients with PsO.

Analysis showed that the prevalence of PsO was higher in male diabetic patients compared with female diabetic patients (Table 1), which is consistent with findings from a previous epidemiological study.¹⁴ Previous studies report that systemic therapy results in better outcome of PsO

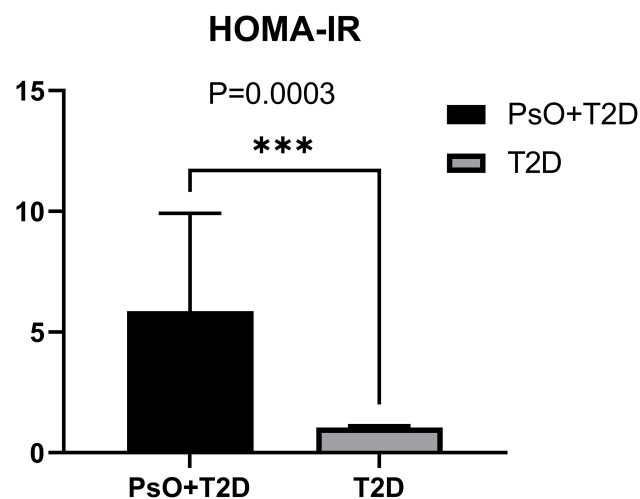


Figure 1 Comparison of IR represented by HOMA-IR in the PsO group and controls.

Note: *** $P=0.0003$.

Abbreviations: HOMA-IR, homeostasis model assessment of IR; T2D, type 2 diabetes mellitus control group; PsO+T2D, group of type 2 diabetes mellitus with psoriasis.

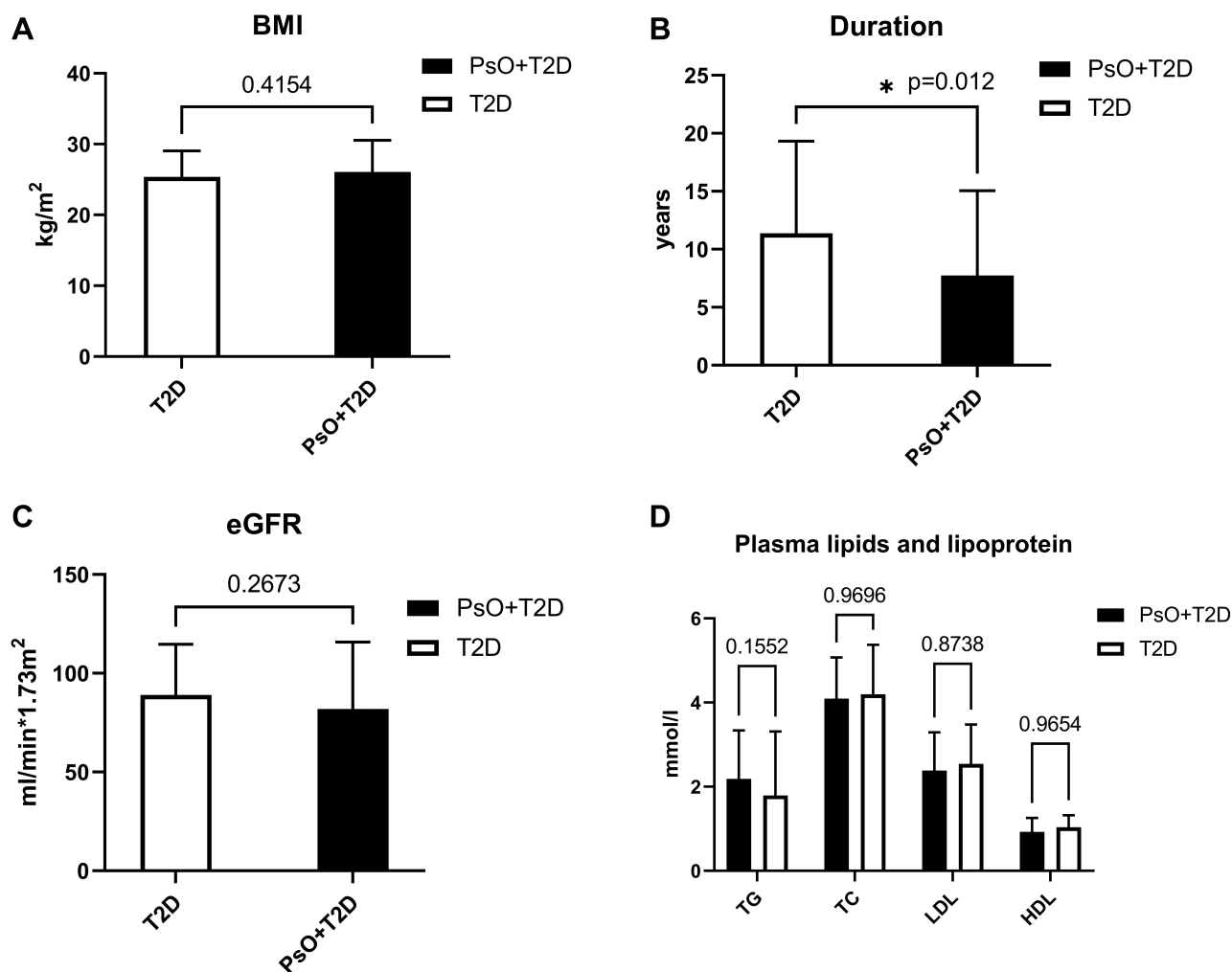


Figure 2 BMI (A), duration of diabetes (B), eGFR (C), plasma lipids and lipoproteins (D) in the PsO group and diabetic patients without psoriasis.

Note: * $P < 0.05$.

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; TG, total triglyceride; TC, total cholesterol; LDL, low density lipoprotein; HDL, high density lipoprotein; T2D, type 2 diabetes mellitus controls group; PsP+T2D, the group of type 2 diabetes mellitus with PsO.

female patients compared with male patients.¹⁵ However, these findings should be validated using a larger sample size and through other possible basic methodologies. Notably, the duration of diabetes for patients with PsO was significantly shorter compared with that for the T2D only group ($P=0.012 < 0.05$, Table 1, Figure 2). Analysis of age, BMIs, and HOMA- β level (Figure 3) showed no significant differences between the two groups. This finding indicates that similar levels of BMIs and pancreatic islet function occur within the same age group. PsO may induce significant IR compared with patients with T2D alone. Notably, increased IR may not be solely attributed to dissimilarities in progress of T2D. In addition, the PsO group showed a slightly higher mean BMI compared with the normal BMI. Studies report that higher BMI or obesity

is a critical risk factor of progression of PsO.^{16,17} These findings are consistent with findings from previous studies that patients with PsO are at higher risk of developing T2D,¹⁸ and have a risk of developing IR. Analysis showed no significant differences in HbA1c between the groups, implying that the levels of hyperglycemia management in the two groups in the past 3 months were similar. However, the mean blood glucose level determined by HbA1c in the past 3 months was analyzed, and oral drugs like retinoic acid and methotrexate were administered to the PsO group during this time, which may influence regulation of blood glucose. However, a previous study reports that the effect of retinoic acid therapy is through transiently decreasing HOMA- β and HDL level. Notably, this change was not associated with change in

Table 2 Levels of Plasma Glucose, C-Peptide, and Insulin at 0 and 120 minutes between PsO+T2D and Control Patients

		PsO+T2D	Controls	P-value
Plasma glucose (mmol/L)	0 min	9.6±5.061	8.6±3.495	0.481
	120 min	15.8±5.528	14.2±5.412	0.219
C-peptide (nmol/L)	0 min	0.6611 ±0.440	0.3633 ±0.252	0.018*
	120 min	1.2247 ±0.984	0.8162 ±0.613	0.001**
Insulin (pmol/L)	0 min	131.726 ±81.041	129.106 ±110.337	0.998
	120 min	459.670 ±356.122	381.525 ±270.788	0.348

Notes: * $P<0.05$; ** $P<0.01$.

Abbreviations: PsO, psoriasis; T2D, type 2 diabetes.

adipocytokines derived from adipose tissue such as adiponectin, resistin, and tumor necrosis factor alpha (TNF- α),¹⁹ implying that it does not modulate systemic inflammation which is associated with IR. A previous study reports that administration of methotrexate for 6 months had no effect on HOMA-IR level despite the level of HbA1c declining significantly. This implies that these oral PsO individual drugs do not induce a significant increase in IR. In addition, analysis of different treatment paradigms of diabetes between the two groups show that the proportions of insulin replacement are relatively low in PsO group compared with the group without PsO. This can be attributed to the preserved pancreatic β -cell function, indicating that the pathogenesis of PsO is a systemic inflammatory process mainly affected by insulin action rather than insulin production.²⁰

Further, analysis using HOMA-IR and HOMA- β models showed that PsO may exacerbate reduction in insulin sensitivity in T2D. The findings of this study show that there is no significant difference in BMI between the two groups, which partially reflects pancreatic islet β -cell function and nutritional status of patients.²¹ In addition, a decrease in mean eGFR was observed in the two groups, however, no significant difference was observed. This finding implies that PsO may induce chronic pathological changes in the vascular systems including implications on kidney function.²² A recent study reported an increase in 24-hour microalbuminuria (11.53±7.29 vs 9.79±3.72, $P<0.05$) and 24-hour proteinuria (0.24±0.21 vs 0.18±0.09, $P<0.005$) in patients with PsO compared with

controls without hypertension or diabetes.²³ An increase in IR in PsO patients may result in progression to renal insufficiency earlier compared with diabetic patients without psoriasis. Moreover, analysis of the profile of lipids and lipoprotein in this study showed no statistical differences between the two groups. This finding implies that there is the baseline matching of the two groups, and IR resulting from systemic inflammation in the two groups were similar. However, further studies should explore lipid malfunction and adipocytokine release in T2D patients with PsO. Notably, analysis showed that HDL level was significantly lower compared with the management level required in T2D (HDL<1 mmol/L). This finding is consistent with reports from a previous study that HDL level is lower in PsO patients compared with normal controls.²⁴ Changes in HDL-cholesterol levels have been reported in psoriasis patients. HDL and associated apolipoprotein (apo) potentially suppress immune cell effector responses, and PsO could in turn affect HDL composition, metabolism, and function, thus promoting disease progression and increasing risk of cardiovascular diseases and infections.²⁵ The mean level of TG in the PsO group was slightly higher compared with the recommended level, which was consistent with findings from a recent study that explored the risk biomarkers of cardiovascular diseases in PsO with T2D.²⁶

Moreover, glucose metabolism related indices between two groups were explored. Analysis showed that the mean HOMA- β , glucose level, insulin concentration, and C-peptide were higher in PsO compared with the levels in the control group. Previous studies report that patients with PsO have a relatively preserved pancreatic β -cell function, but with increased IR.²⁷ FPG levels were not significantly different between the two groups, implying that disequilibrium of blood glucose in PsO may not totally be attributed to impairment of pancreatic function, since FPG level is a marker for the basic function of the pancreas.²⁸ In addition, PIN, PCP, and PPG levels were significantly higher in the PsO group compared with the controls, indicating the compensating state of the pancreas in PsO. Similar findings were reported by a study that used a mice model of psoriasis-like skin inflammation, which showed that a pre-diabetic phenotype displayed by compensating function of pancreas, and signs of metabolic dysfunction in subcutaneous and other multiple organs.²⁹ This preliminary study only reports the general distributions of glucose metabolic diversity between normal T2D patients and T2D with PsO in our hospital, therefore, there

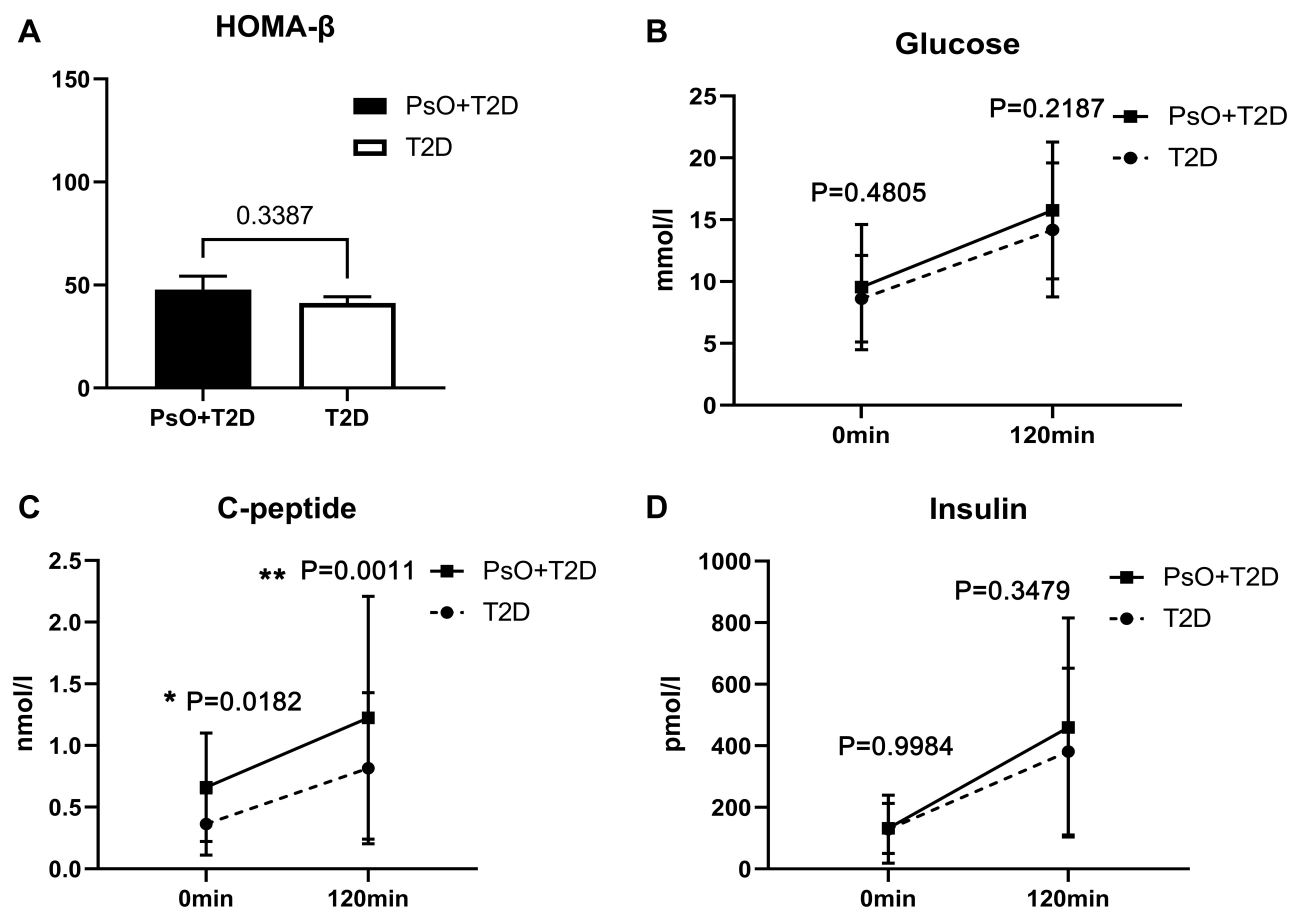


Figure 3 HOMA-β (A), plasma glucose (B), C-peptide (C), and insulin (D) in the PsO group and control group.

Notes: * $P < 0.05$; ** $P < 0.01$.

Abbreviations: HOMA-β, homeostasis model assessment of β-cell function state; T2D, type 2 diabetes mellitus controls group; PsO+T2D, the group of type 2 diabetes mellitus with PsO.

is need to explore the underlying molecular and genetic mechanism of PsO on the pathophysiology of T2D.

PsO is a chronic and recurrent inflammatory skin disease caused by dysregulated interactions of innate and adaptive components of the immune system with resident cutaneous cell types.¹ It is characterized by proliferation of keratinocytes in the basal layer of the epidermis and a significant increase in systemic proinflammatory factors in vivo.³⁰ Psoriatic patients show a significantly high TNF-α level, and anti-TNF-α is an effective strategy for alleviating the pathological change of PsO.³¹ Increase in TNF-α induces IR in adipocytes and peripheral tissues by impairing insulin signaling through serine phosphorylation resulting in development of T2D. Anti-TNF-α treatment strategies have been developed to reduce the incidence of IR and development of T2D.³² Furthermore, interleukin-23/Th17 axis is critical in PsO, and several novel targeted

therapies have been designed against this axis.³³ Anti-IL-17 neutralizing antibodies and/or antibodies targeting Th17 cells protect high risk individuals from T2D development.³⁴ The findings from the current study show that the skin is a vital IR target organ, and PsO may modulate glucose regulation, thus exacerbating systemic IR (Figure 4). Further molecular studies should explore the role of the skin in insulin activity and energy metabolism.

The skin is the largest organ in the human body, and is associated with insulin action and its abnormality can result in IR (IR).³⁵ PsO and T2D are chronic inflammatory diseases which are associated with metabolic syndrome. Studies report that the two diseases share common pathophysiological and genetic mechanisms. The findings of this study have potential implications in development of novel effective therapy for diabetic patients with PsO. For instance, chronic inflammation in the subcutaneous

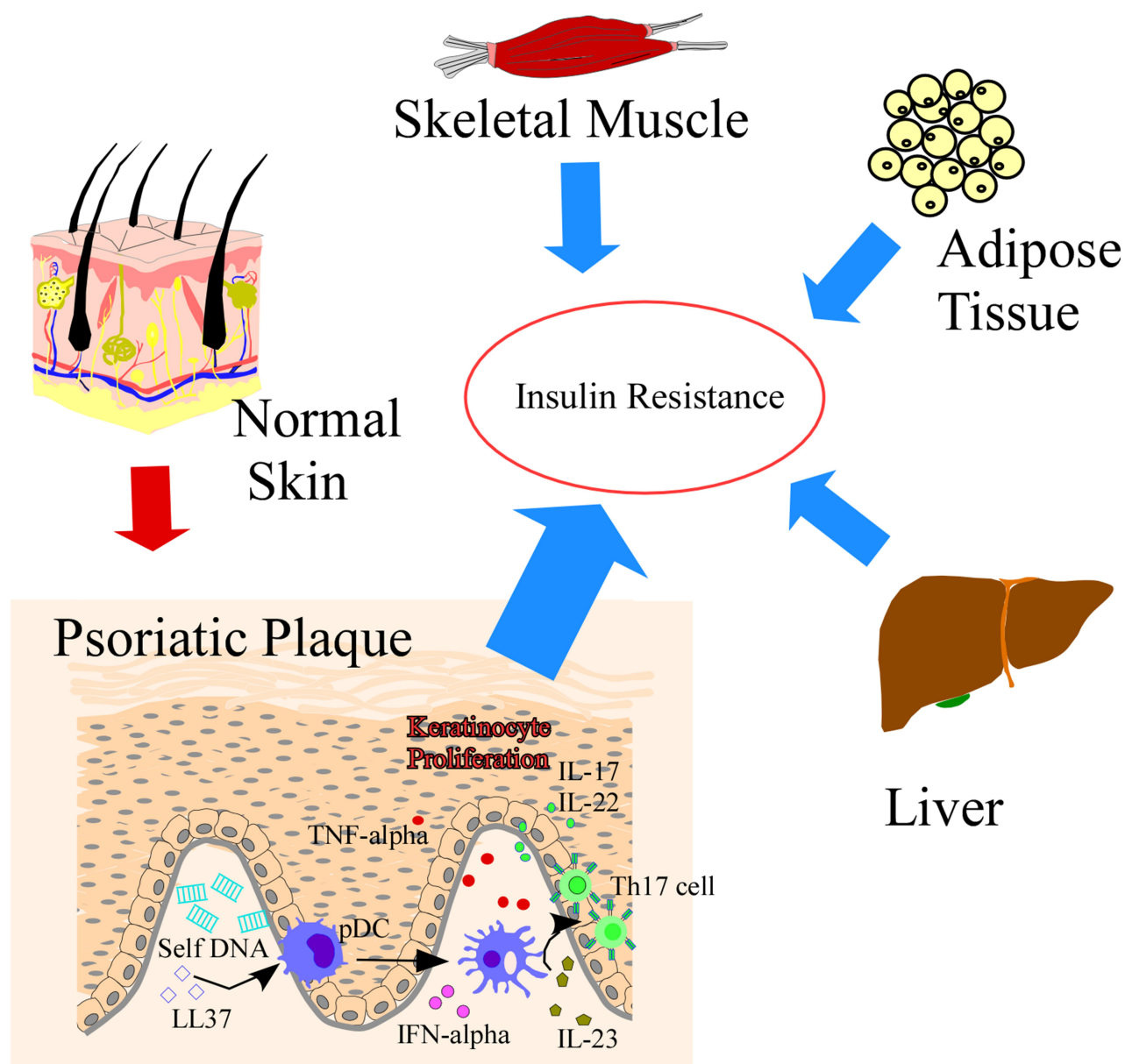


Figure 4 Possible mechanism of systemic IR and the role of skin PsO. Systemic IR can be contributed by multiple organs including skin, skeletal muscle, subcutaneous adipose tissue and liver. PsO of skin involves release of IFN- α by the dermal plasmacytoid dendritic cells, activation of dendritic cells which release IL-23 and TNF- α , and activity of Th17 cells which generate IL-17 and IL-22. These responses eventually increase proliferation of keratinocytes and other pathological alterations, resulting in inflammation of skin and an increase in IR.

Abbreviations: LL37, cathelicidin; pDC, dermal plasmacytoid dendritic cells; IFN- α , interferon alpha; TNF- α , tumor necrosis factor alpha; Th17, T helper cell 17; IL-23, interleukin 23; IL-17, interleukin 17; IL-22, interleukin 22.

adipose tissue, and pathologic change in the microvasculature may generate IR,³⁶ which is a component of systemic IR in addition to typical insulin targets such as liver and muscle. Higher IR associated with PsO has been reported in clinical background. One case study reported that PsO is causally associated with type B IR, an extremely rare condition of IR caused by circulating antibodies against insulin receptor.³⁷ Furthermore, a recent study

reported that HOMA-IR is positively correlated with digital ulcer in patients with systemic sclerosis.³⁸ Notably, low-grade inflammation in PsO is shown by elevated levels of high-sensitivity C-reactive protein (hCRP),³⁹ which is consistent with our unpublished data that hCRP is significantly associated with an increased insulin dosage in T2D patients with infection. Moreover, our previous clinical findings showed that anti-hyperglycemia agents

such as thiazolidinediones (TZD) can relieve PsO symptoms in diabetic patient and can change the chronic inflammatory status of the skin.⁴⁰

This study explored the epidemiological distributions and metabolic relationships of PsO and T2D. The findings of this study show that PsO plays a role in IR of skin which could exacerbate glucose metabolism and affect disease progression. However, further studies should explore the specific molecular targets, or the relationship of severity of PsO with extent of IR. The findings of the present study show that patients with T2D with co-morbidity of PsO may present higher IR, and amelioration of inflammation in local skin may be effective in improving overall insulin sensitivity.

Ethical Statement

Ethical approval for this study including surveys, sampling and examinations was obtained from the Ethics Committee of Shanghai Pudong Hospital (2020 No.WZ-01), Fudan University (Shanghai, China). Informed written consent was obtained from patients prior to the study. Guidelines outlined and procedures used in this study were in accordance with the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas. All authors have drafted or written, or substantially revised or critically reviewed the article. All authors have agreed on the journal to which the article will be submitted. All authors reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage. All authors agree to take responsibility and be accountable for the contents of the article.

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Disclosure

The authors declare no conflicts of interest.

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