Diabetes: How should psoriasis patients with diabetes mellitus be managed?

A systematic review was conducted. The Method & Evidence Reports can be found below.

Results/Answer:

Moderate-to-severe psoriasis is commonly accompanied by metabolic disorders including type 2 diabetes mellitus, obesity, dyslipidaemia, nonalcoholic fatty liver disease and metabolic syndrome. [1]. In particular, several meta-analyses confirmed the association between psoriasis and diabetes as well as the new AAD guidelines [1-4]. Amstrong et al. [1] found that psoriasis had an odds ratio (OR) of 1.59 (95 % CI, 1.38-1.83) for diabetes. The pooled OR was 1.53 (95 % CI, 1.16-2.04) for mild psoriasis and 1.97 (95 % CI, 1.48-2.62) for severe psoriasis. A nationwide population-based cohort study involving 14,158 adults with psoriasis confirmed that the risk of diabetes in psoriatic patients correlated to the severity of psoriasis. [5] The association between psoriasis and diabetes could be explained considering a common genetic background, insulin resistance, and the unhealthy lifestyles such as over-eating and sedentary lifestyle, which are common in patients with psoriasis. [6] In addition, there is a strong association between psoriasis and obesity which induces itself insulin resistance. [7] Obesity itself is a significant risk factor to develop type 2 diabetes [4].

Systemic treatments for psoriasis could also impair glucose homeostasis and/or other metabolic parameters, especially in case of continuous and prolonged use. Short-term treatment with methotrexate does not appear to have a negative effect on carbohydrate metabolism parameters in patients with psoriasis or psoriatic arthritis [8-10]. However, MTX should be administered with caution in the case of diabetes and obesity, due to the increased risk of liver toxicity, liver enzyme increase and liver fibrosis [11-13]. Ciclosporin (CsA) can increase insulin resistance, interfere with fatty acid metabolism favouring the development of dyslipidaemia and the increase of serum uric acid [14]. In a prospective cohort study on the Psocare registry, it was found that CsA was associated with a significant risk of developing diabetes at week 52, which is not surprising because the calcineurin inhibitors either tacrolimus or CsA are associated with a higher risk of new-onset diabetes in transplant recipients [15]. The diabetogenic effect of CsA has been assumed to be related to inhibition of insulin secretion from pancreas islet cells [16], an effect that may be even more relevant in obese psoriatic patients.

Acitretin effects on insulin resistance are not clearly established. There is no evidence that fumarates and apremilast could affect insulin resistance. Additionally, diabetes is not a contraindication for the use of apremilast or fumarates.

The safety and efficacy of deucravacitinib in psoriatic patients with diabetes has not been investigated, yet. However, in POETYK PSO-1 clinical trial[17], there were no reports of metabolism disorders due to deucravacitinib leading to treatment discontinuation during weeks 0-52. The mechanism of action of deucravacitinib, i.e. blocking the tyrosine-kinase 2 protein and the cellular signals that run through, it is not expected to alter insulin sensitivity.

Clinically significant dyslipidaemia has been rarely reported in patients receiving TNFi, but this is not a common issue in clinical practice [18]. Body weight gain could occur in patients treated with TNFi [19, 20]. In contrast, ustekinumab[21], IL-17[22] and IL-23 inhibitors usually do not increase body weight in patients with chronic plaque psoriasis. Apremilast has been shown to cause weight loss in clinical trials [22]. Studies addressing the effects of TNF-α blockade on glucose homeostasis in patients with psoriasis and/or PsA were very limited and gave conflicting results. The Homeostasis Model Assessment (HOMA) and the Quantitative Insulin Sensitivity Check Index (QUICKI) are two widely used non-invasive surrogate markers of insulin resistance, used in the following studies. A study in 62 patients with chronic inflammatory rheumatic diseases, of whom 18 patients were affected by PsA, did not show any significant improvement in glucose homeostasis during the first six months of treatment with TNFi. [23] A recent prospective study in a cohort of 210 PsA patients treated with various TNFi (adalimumab n = 70, etanercept n = 70) or MTX (n = 70) found that those receiving TNFi had significant improvements in glucose levels and other features of the metabolic syndrome compared with those treated with MTX. [24] Similarly, the effects of TNFi on insulin sensitivity/resistance in patients with psoriasis gave discordant results. A small randomized, double-blind study in twelve psoriatic patients at high risk of developing type 2 diabetes failed to observe a significant effect of a two-week treatment with etanercept on insulin secretion and sensitivity. [25] No significant changes in either insulin sensitivity or levels of fasting blood glucose were observed in a study in psoriatic patients after twelve weeks of treatment with adalimumab. [26] In contrast, in two different studies respectively on nine and 89 patients with plaque psoriasis etanercept improved insulin sensitivity. [27, 28] Other TNFi also appear to improve insulin sensitivity in diabetic and non-diabetic patients with psoriasis [29, 30].

A pooled analysis of data from the phase III randomised controlled trials for secukinumab showed a neutral effect on fasting plasma glucose, lipid parameters and liver enzymes. In patients with fasting

plasma glucose >125 mg/dl at baseline (diagnostic criterion for diabetes) secukinumab treatment presented a trend towards lowering fasting glucose concentration compared to placebo treatment during the first 12 weeks [31]. Finally, patients with moderate-to-severe psoriasis are candidate for interventions aimed to reduce their cardiovascular risk profile. Screening for cardiovascular risks including diabetes, hypertension and dyslipidemia should be recommended for all psoriasis patients [4]. Non-pharmacological interventions, such as weight loss, should be recommended to obese patients. Indeed, it has been reported that a low-calorie diet inducing a moderate weight loss (i. e., 5 to 10 % of body weight) increases the responsiveness of obese patients with moderate-to-severe chronic plaque psoriasis to systemic treatments [32-35]. Moreover, body weight loss could also increase insulin sensitivity in obese patients with psoriasis.

Etanercept does not have an impact on the glycemic control in diabetes patients, which was shown in the PRISTINE trial [36].

Finally, it should be considered that diabetic nephropathy eventually occurring in patients with psoriasis could reduce the clearance of any systemic treatments for psoriasis including MTX and CsA. [37, 38] CsA should be considered cautiously in patients with diabetes mellitus as significantly increased serum creatinine concentration could be observed [39].

In addition to any medical treatment, appropriate supportive care should be offered, e.g. weight loss programs for obese patients with metabolic syndrome or dyslipidaemia.

Data from the CorEvitas Psoriasis Registry indicates a weaker treatment response[40] or shorter drug survival[41] to psoriasis treatments in diabetic patients with newly initiated tumour necrosis factor inhibitors (TNFi)[41], interleukin (IL)-17i[40], IL-12/23i[41], or IL-23i[41] than in non-diabetic patients. Van Muijen et al. found lower drug survival rates due to ineffectiveness in diabetic patients with psoriasis receiving with respect to guselkumab [42]. In contrast, Mendes-Bastos et al. indicated that patients with diabetes had a higher drug persistence than those without diabetes when treated with secukinumab [43].

In conclusion, diabetes is not a contraindication to the use of biological drugs or small molecules in patients with psoriasis for safety issues, but it could reduce their effectiveness.

We **suggest** considering alternatives to methotrexate in people with type 2 diabetes (if accompanied by metabolic syndrome and/or evidence of liver damage) when alternative treatments can be prescribed.	↑	STRONG CONSENSUS[1]  EXPERT CONSENSUS
We **suggest** considering alternatives to ciclosporine in people with type 2 diabetes (if accompanied by metabolic syndrome and/or evidence of liver damage) when alternative treatments can be prescribed.	↑	STRONG CONSENSUS[1]  EXPERT CONSENSUS
We **suggest against** using acitretin as a first line treatment in patients with dyslipidaemia.	↓	STRONG CONSENSUS[2]  EXPERT CONSENSUS

[1] due to personal-financial conflict of interest 3 abstentions

[2] due to personal-financial conflict of interest 2 abstentions

Living systematic review of the evidence on psoriasis treatment and diabetes mellitus

History

Table 1 History

Version	Search Date	Number of new studies	Additional information added	Implications for conclusions
Update 2	October 2022	4 (5 citations)	See below	See below
Update 1	June 2021	1	See below	See below
Original	September 2019	8	/	/

Summary of methods and results (2022/2023)

Authors: A. Pennitz and I. Vader (Update 2), M. Kinberger (Update 1), R. Jakubzyk (Original version)

Update 2 – 2022/2023 (blue = new data)

What was the aim of this systematic review?

The aim of this review update was to continuously inform the guideline development group of new evidence on patients with **psoriasis vulgaris and concomitant diabetes mellitus.**
Many patients suffering from psoriasis also have concomitant diabetes mellitus. In this systematic review, we investigated whether diabetes mellitus affects the efficacy and safety of psoriasis therapy. We also investigated whether psoriasis therapy had an impact on fasting blood glucose levels, long-term blood glucose and insulin resistance in diabetic patients.

What did we do?

We systematically searched in two medical databases. We only included studies with patients treated with systemic psoriasis vulgaris therapies who also had diabetes mellitus. We assigned Levels of Evidence for all studies included using the Center of Evidence Based Medicine Oxford recommendations [44] and used the risk of bias 2.0 for the randomized trials [45] and the IHE checklist for uncontrolled prospective cohort studies [46]. Effect measures were calculated where possible. For details, see Methods Report.

What are the main results of the review?

We found 6 prospective (1 study with 2 citations) [30, 36, 40, 41, 47-49] and 7 retrospective studies [10, 13, 39, 42, 43, 50, 51].

Change in psoriasis parameters (only prospective data available)

- Kimball et al. [47] conducted a subgroup analysis of an RCT comparing adalimumab against placebo in patients with diabetes mellitus. After 4 month, 46 of 73 (63%) participants in the adalimumab arm showed a PASI75 response compared to 2 of 52 in the placebo arm (PASI75 RR 16.4; 95% CI 4.16 to 64.5). The mean change in the DLQI score was -7.1±6.3 in the

adalimumab arm compared to -1.3±5.8 in the placebo group (DLQI MD -5.8; 95% CI -7.94; -3.66) (risk of bias low).

- Pinter et al. [52] pooled data from three RCTs and evaluated secukinumab, ustekinumab and etanercept. After four weeks, a PASI75 response was described for 16 of 27 (59.3%) patients in the etanercept group, for 56.6 of 69 (82.1%) in the secukinumab group and for 80.5 of 97.5 (82.6%) patients in the ustekinumab group (risk of bias unclear).
- Lin et al. [49] compared treatment with liraglutide alone (study arm not included here) with a treatment regime of acitretin, calcipotriol ointment and oral antidiabetics in patients with psoriasis and coexisting diabetes mellitus type 2. A PASI75 response after 12 weeks was seen in 1 of 13 (7.69%) participants in the acitretin and calcipotriol ointment group. The mean change in the DLQI score was -8.54±5.33 in this group (risk of bias unclear).
- By analysing data from the CorEvitas Psoriasis Registry, Enos et al. [40] investigated whether diabetes affected the response to newly initiated tumour necrosis factor inhibitors (TNFi), interleukin (IL)-17i, IL-12/23i, or IL-23i in patients with psoriasis. Patients with diabetes, receiving IL-17i, achieved PASI75 and PASI90 less often than those without diabetes 47.5% (104/219) vs. 60.6% (613/1011), aOR 0.61 (95% CI 0.45, 0.85) and 33.8% (74/219) vs. 44.4% (449/1011), aOR 0.69 (95% CI 0.49, 0.96), respectively. The odds ratio was adjusted for age, sex, race, smoking, education, duration of psoriasis, psoriatic arthritis, number of prior biologics, and obesity.

Change in diabetes mellitus parameters

Fasting plasma glucose (prospective study data, 76 patients)

- Al-Mutairi and Shabaan [30] compared TNFi (ADA, ETA, IFX) with conventional treatments (topical corticosteroids, calcipotriol, CsA, MTX) in patients with diabetes mellitus and psoriasis. In the TNFi group a mean change in the fasting plasma glucose of -2.74±0.34 vs -0.02±0.16 mmol/L in the conventional group after six month was described (MD -2.72; 95% CI -2.85; -2.59) (risk of bias high).
- Lin et al. [49] described a mean change of -0.20±1.49 in fasting plasma glucose in 13 patients treated with acitretin, calcipotriol ointment and oral antidiabetics after three month (risk of bias unclear).

Fasting plasma glucose (retrospective study data)

- In two retrospective analyses, Wu et al. [10, 51] investigated changes in diabetic parameters in patients with diabetes and psoriasis receiving MTX, MTX and TNFi or TNFi alone. One study reported a mean change of 3.7±18.6 in FPG with combined therapy (n=34) vs. 1.3±24.5 with MTX therapy alone (n=92). In the other study, no significant difference between TNFi (mean change 1.5±40.7) and MTX (mean change -15.6±54) was found (MD 17.1; 95% CI -3.93; 28.13). The Oxford level of evidence was 3 in both studies.

HbA1c (prospective study data)

- Koenig et al. [36] described a mean reduction in HbA1c of -0.3% in 35 patients treated with etanercept treatment after three months (risk of bias unclear).
- Al-Mutairi and Shabaan [30] found a mean change in the HbA1c of -1.3% vs. 0.2% in 34 patients treated with TNFi compared to 29 patients treated with conventional treatment, respectively after six month (risk of bias high).

- A mean reduction of -0.82%±0.73% in HbA1c was reported in the acitretin, calcipotriol ointment and oral antidiabetics group by Lin et al. [49] (risk of bias unclear).

HbA1c (retrospective study data)

- No relevant changes of HbA1c were reported by Wu et al. [51] comparing MTX with an additional TNFi (-0.1%±1.0%) and MTX alone (0.0%±0.8%).

HOMA-Index (only prospective data available)

- Al-Mutairi and Shabaan [30] described a mean change in HOMA-Index of 1.2±0.4 in 34 patients treated with TNFi vs -0.3±0.12 in the conventional treatment group (n=29) after 6 month.
- Lin et al. [49] reported a mean change of 0.37±2.09 in HOMA-Index after treatment with acitretin, calcipotriol ointment and oral antidiabetics combined for 3 months.

<u>Safety (prospective study data)</u>

- In the subgroup analysis by Kimball et al. [47] 3 of 73 (4.1%) patients treated with adalimumab and 2 of 52 (3.8%) patients in the placebo group reported severe adverse events.
- Enos et al. [41] conducted another analysis of the CorEvitas Psoriasis Registry. They explored, whether patients with psoriasis discontinued their newly implemented therapy with TNFi, IL-17i, IL-12/23i, or IL-23i more often if they had comorbidities. Discontinuations within 6 month occurred more frequently in patients with diabetes than in those without, if they received TNFi (33/96 (34.4%) vs. 111/455 (24.4%); $p < 0.05$) or IL-23i or IL-12/23i (25/192 (13%) vs 78/950 (8.2%); $p < 0.05$).

<u>Safety (retrospective study data)</u>

- In a retrospective registry study, Kalb et al. [50] described that the presence of diabetes mellitus is a significant predictor of serious infection in patients treated with adalimumab, etanercept or ustekinumab (HR, 1.7; 95% CI, 1.25-2.23; $p < 0.001$, n= 1459 with diabetes).
- In another retrospective analysis by Hong et al. [39], diabetic patients receiving ciclosporin seemed to have a higher risk for a greater than 10% increase in serum creatinine levels compared to non-diabetes patients (HR 2.34; 95% CI, 1.59–3.45; $p <0 .001$, n= 37).
- Rattanakaemakorn et al. [13] performed a retrospective cohort study in patients with psoriasis, treated with methotrexate or with a combination of methotrexate and acitretin. A multivariate regression indicated, that the risk of developing a hepatic fibroses was associated with a comorbid diabetes, no matter how high the cumulative MTX dose was (adjusted HR 2.40 (95% CI: 1.05–5.51)). There could be no information identified, what the regression model was adjusted for.
- Drug persistence at 104 weeks in patients (n= 302) treated with secukinumab was retrospectively analysed by Mendes-Bastos et al. [43]. In total, 84 patients with psoriasis discontinued therapy. Exploratory univariable analysis indicated that patients with diabetes had a higher drug persistence than those without diabetes. Results were only presented graphically and without details on effect size and confidence intervals.
- Van Muijen et al. [42] applied prospective and retrospective data to analyse drug survival rates in patients with psoriasis receiving guselkumab. A multivariate cox regression model suggested an association between a shorter drug survival due to ineffectiveness and comorbid diabetes mellitus type 2 (HR 3.69 (95% CI 1.14–11.98). The association between discontinuation due to side effects and diabetes mellitus type 2 was analysed in a univariate analysis HR 0.605 (95%CI 0.079–4.654).

Key message

Neither treatment with TNFi (n=484), MTX (n=635) nor acitretin (n=13) led to an increase in HbA1c or fasting glucose in patients with psoriasis vulgaris and concomitant diabetes mellitus. The methodological quality of the data varies. For MTX, only retrospective data was available. A total of 2 studies with 76 patients reported no or only small changes in HOMA-Index in patients with psoriasis vulgaris and diabetes mellitus treated with systemic psoriasis therapy.

Data from the CorEvitas Psoriasis Registry indicates a weaker treatment response[40] or shorter drug survival[41] to psoriasis treatments in diabetic patients with newly initiated tumour necrosis factor inhibitors (TNFi)[41], interleukin (IL)-17i[40], IL-12/23i[41], or IL-23i[41] than in non-diabetic patients. However, a comprehensive Cochrane network meta-analysis by Sbidian et al. [53] reports the efficacy of all systemic psoriasis treatments.

How up-to-date is this review?

We searched for studies that have been published up to 26 October 2022

Methods

Update 2

Inclusion criteria

Apart from the newly included drug, deucravacitinib we did not change the search strategy and the inclusion criteria of the previous version.

Table 2 Eligibility criteria for the review update on psoriasis and diabetes mellitus

Patients	Inclusion: adult patients with a clinical diagnosis of psoriasis and a concomitant diabetes mellitus of any type being treated for psoriasis Exclusion: patients with psoriatic arthritis only
Intervention	Conventional systemic treatment (acitretin, apremilast, ciclosporin, fumarates, methotrexate) and biologicals (TNFi: adalimumab, etanercept, certolizumab pegol, infliximab; anti-IL12/23: ustekinumab; anti-IL17: bimekizumab, brodalumab, ixekizumab, secukinumab; anti-IL23: guselkumab, risankizumab, tildrakizumab; tyrosine kinase 2 (TYK2) inhibitor: deucravacitinib (new))
Comparator	Comparisons with another included drug and/or placebo
Outcomes	Change in skin lesions based on PASI (Psoriasis Area Severity Index) or PGA (Physician Global Assessment) or another study specific assessment. Fasting plasma glucose, HbA1c or insulin sensitivity measured by HOMA (Homeostasis Modell Assessment) or other study specific outcomes Type and proportion of other adverse events Quality of life based on SF-36 (The Short Form (36) Health Survey), DLQI (Dermatology Life Quality Index) or another study specific assessment.
Study Design	Inclusion: randomized controlled trials, clinical trials (with and without comparison group), cohort studies, case control studies and cross sectional studies Exclusion: case series, case reports, retrospective studies with less than 100 patients

Information source

The search strategy was updated and the databases MEDLINE Ovid from 1946 and Embase Ovid from 1947 were searched for the period June 2021 to 27 October 2022. The full search strategy is shown below (see Table 6). We screened all identified abstracts/titles for eligibility. Included title/abstracts were then screened as full texts based on the above listed eligibility criteria.

Data collection, statistical analysis and evaluation

We performed the screening and did the data extraction using a standardized form. We recorded all full-texts excluded and the primary reason for exclusion (see Table 7).

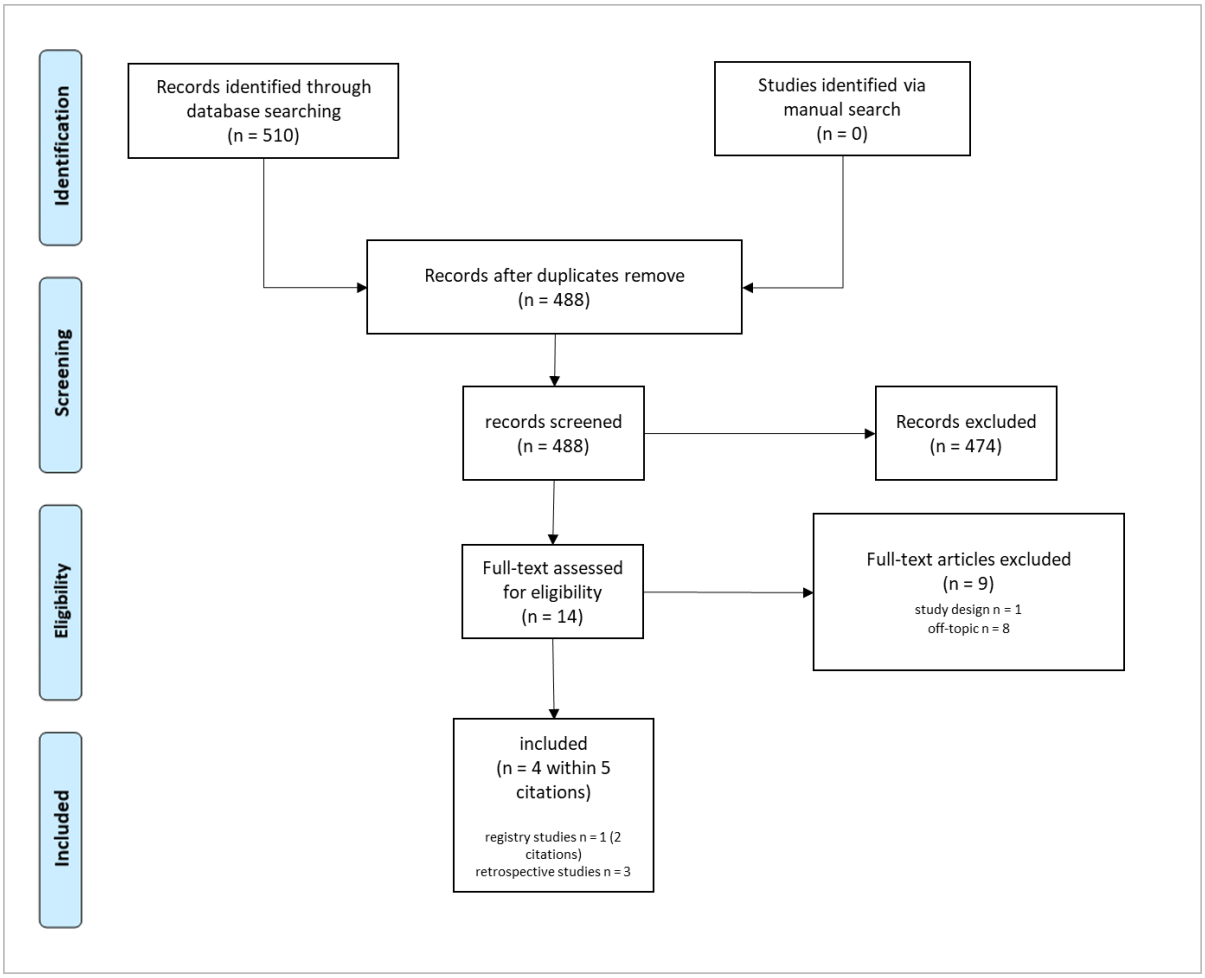
Methodological quality assessment/ Risk of bias assessment

We assigned Levels of Evidence for all studies included using the Center of Evidence Based Medicine Oxford recommendations. To assess risk of bias in uncontrolled prospective cohort studies, we applied and modified the IHE checklist [46]. We extended the possible answers in Item 13 by "not applicable" and in Item 10, 12 by "unclear".

Results

Our update search yielded 510 citations, 5 citations (4 studies) fulfilled the inclusion criteria [13, 40-43] (see Figure 1).

Figure 1: Study selection flowchart for the selection of studies for the review update 2 on psoriasis and diabetes mellitus



Based on the "Levels of Evidence - Center of Evidence Based Medicine Oxford recommendations" 5 prospective studies [30, 36, 42, 49, 52] were categorized level 2, 1 prospective study (2 citations) was categorized as level 3 [40, 41] and the retrospective studies [10, 13, 39, 42, 43, 50, 51] as level 3. Results of the additional assessment for prospective randomized studies with the Risk of Bias Tool 2 (RoB 2) and with the IHE checklist are shown in Figure 3 and Table 3, respectively.

Table 3 uncontrolled prospective cohort studies - results of the IHE checklist

reference	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Col/ Funding
Enos C. W., et al. Proportions of Biologic Discontinuation Among Psoriasis Patients With Metabolic Comorbidities. Journal of Psoriasis and Psoriatic Arthritis. 2022.	Y	Y	Y	N	Y	Y (Stroberet al.)	U	P	N	U	U	U	n.a.	U	Y	N	N	Y	P/Y	Y	funded by CorEvitas LLC CorEvitas has been supported through contracted subscriptions in the last two years by AbbVie, Amgen, Arena, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Chugai, Eli Lilly and Company, Genentech, Gilead, GSK, Janssen, LEO, Novartis, Ortho Dermatologics, Pfizer Inc., Regeneron, Sanofi,Sun and UCB
Enos C. W., et al. Comorbid obesity and history of diabetes are independently associated with poorer treatment response to biologics at 6 months: A prospective analysis in Corrona Psoriasis Registry. Journal of the American Academy of Dermatology. 2022	Y	Y	Y	N	Y	Y (Stroberet al.)	U	P	N	U	U	U	Y	U	Y	N	Y	N	Y	Y	Sponsored by CorEvitas (formerly Corrona) LLC CorEvitas has been supported through contracted subscriptions in the last 2 years by AbbVie, Amgen, ARENA, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Chugai, Eli Lilly and Company, Genentech, Gilead, GSK, Janssen, LEO, Novartis, Ortho Dermatologics, Pfizer Inc, Regeneron, Sanofi, SUN, and UCB. This study was supported through a partnership between CorEvitas and the National Psoriasis Foundation.
																					Y = Yes; N = No; P = Partial; U = Unclear; n.a. = not applicable

To appraise Item 6 of the IHE checklist [46] we identified a previous publication [54] via hand searching, in which the inclusion criteria are described more precisely.

Table 4 Prospective data from the included studies for the systematic review of the evidence on psoriasis treatment and diabetes mellitus (Update 2)

Titel	Author (Y)	Original study	Intervention	Duration of treatment (M)	Patients (n)	Patients with diabetes (n)	Follow up (M)	Age (Y) (Ø±SD)	♀ (%)	Poriasis-score at baseline (Ø±SD)	Qualtity of life at baseline (Ø±SD)	Diabetes parameters at baseline (Ø±SD)	Outcomes					overall RoB
													End of dollow up (M)	Psorias-Score e.g. PASI 75	Mean change of quality of life (Ø±SD)	Mean change of diabetes parameters (Ø±SD)	Adverse events	
Efficacy and safety of adalimumab among patients with moderate to severe psoriasis with co-morbidities: Subanalysis of results from a randomized, double-blind, placebo-controlled, phase III trial	Kimball, A. B. et al. (2011)	Menter, A. et al. (2008)	ADA (80mg/40mg)	4	814	73	13	47.2±12.4[1]	35%[1]	PASI 19.3±7.2	/	/	4	PASI 75 n=46 (63%)	DLQI -7.1±6.3	Glucose (mmol/L) -0.47	SAE not infectios n=2 (2.7%) SAE infectios n= 1 (1.4%) Dropout because of AE n=1 (1.4%)	low
			Placebo		398	52		48.8±12.6[1]	36%[1]	PASI 19.1±7.6				PASI 75 n=2 (3.8%)	DLQI -1.3±5.8	Glucose (mmol/L) -0.65	SAE not infectios n=2 (3.8%) SAE infectios n=0 (0%) Dropout because of AE n=2 (3.8%)	
Characterization of responder groups to secukinumab treatment in moderate to severe plaque psoriasis	Pinter, A. et al. (2019)	Blauvelt, A. et al. (2017) Langley, R.G. et al. (2014)	ETA (50mg)	4	298	27	4	43.6[1]	/	/			4	PASI100 n=1/27 (3.7%) PASI75 n=15/27 (55.6%) PASI50 n=8/27 (29.6%) <PASI50 n=3/27 (11.1%)	/	/	/	Blauvelt: low Langley: unclear
			SEC (300mg)		867	69		44.8[1]						PASI100 n=6.6/69 (9.6%) PASI75 n=50/69 (72.5%) PASI50 n=9.4/69 (13.6%) <PASI50 n=3/69 (4.3%)				
			UST (45/90mg)		318	97.5		44.8[1]						PASI100 n=23.5/97.5 (24.1%) PASI75 n=57/97.5 (58.5%) PASI50 n=9/97.5 (9.2%) <PASI50 n=8/97.5 (8.2%)				
Impact of etanercept therapy on glycemic	Koenig, A.S. et al.	Strohal, R. et al.	ETA (50mg/100mg)	3	273	35	3	44[1]	30[1]	21[1]	/	HbA1c (%) 7.0	3	/	/	HbA1c (%) -0.3	/	unclear

Table 4 continued

Titel	Author (Y)	Original study	Intervention	Duration of treatment (M)	Patients (n)	Patients with diabetes (n)	Follow up (M)	Age (Y) (Ø±SD)	♀ (%)	Poriasis-score at baseline (Ø±SD)	Qualtity of life at baseline (Ø±SD)	Diabetes parameters at baseline (Ø±SD)	Outcomes: End of dollow up (M)	Psorias-Score e.g. PASI 75	Mean change of quality of life (Ø±SD)	Mean change of diabetes parameters (Ø±SD)	Adverse events	overall RoB
Effects of tumor necrosis factor alpha inhibitors extend beyond psoriasis: insulin sensitivity in psoriasis patients with type 2 diabetes mellitus	Al-Mutairi, N., Shabaan, D. (2016)		ADA (n=14) ETA (n=8) IFX (n=12)	6	34 (35 randomised)	34 (35 randomised)	6	43.7±21.6	52.9% (18/34)	/	/	HbA1c (%) 8.4±0.38 FPG (mmol/L) 10±25 IS 5.9±0.52	6	/	/	HbA1c (%) -1.3 FPG (mmol/L) -2.74±0.34 IS 1.2±0.4	/	high
			Topic corticosteroids, calcipotriol (n=8) CsA (n=7) MTX (n=14)		29 (35 randomisedt)	29 (35 randomised)		47.7±14.2	51.7% (15/29)			HbA1c (%) 8.1±0.21 FPG (mmol/L) 11±0.4 IS 5.4±0.31				HbA1c (%) 0.2 FPG (mmol/L) -0.02±0.16 IS -0.3±0.12		
Glucagon-like peptide-1 receptor agonist liraglutide therapy for psoriasis patients with type 2 diabetes: a randomized-controlled trial	Lin, L. et al. (2020)		liraglutide 0.6mg - 1.8mg		11 (12 randomised)	11 (12 randomised)	12	56.73±8.27	9.1% (1/11)	PASI 14.02±10.67	DLQI 22.00±5.85	HbA1c (%) 7.80±2.55 FPG (mmol/l) 6.28±1.48 Fasting insulin (ug/ml) 10.61±4.39 Fasting C-peptide (ng/mL) 1.50±0.94 IR 2.96±1.35	3	PASI-Change -12.32±10.05 PASI50 90.91% (10/11) PASI75 72.73% (8/11)	DLQI-Change -18.18±5.86	HbA1c (%) -1.07±1.75 FPG (mmol/l) -0.55±1.50 Fasting insulin (ug/ml) -2.92±5.03 Fasting C-peptide (ng/mL) 0.43±0.38 IS -0.94±1.06	no SAE n = 1 nosebleed n = 6 gastrointestinal AE n=1 withdrawal due to adverse events	
			acitretin 30-50mg/d + calcipotriol ointment + metformin alone or + glimepirid or sitagliptin		13	13		55.23±7.84	15.4% (2/13)	PASI 13.57±5.49	DLQI 18.23±5.17	HbA1c (%) 7.30±1.88 FPG (mmol/l) 6.29±1.89 Fasting insulin (ug/ml) 11.79±7.84 Fasting C-peptide (ng/mL) 1.47±1.05 IP 3.69±3.20		PASI-Change -6.15±3.43 PASI50 38.46% (5/13) PASI75 7.69 (1/13)	DLQI-Change -8.54±5.33	HbA1c (%) -0.82±0.73 FPG (mmol/l) -0.20±1.49 Fasting insulin (ug/ml) 0.86±4.81 Fasting C-peptide (ng/mL) 0.06±0.37 IS 0.37±2.09	no SAE no AW	unclear
Proportions of Biologic Discontinuation Among Psoriasis Patients With Metabolic Comorbidities. Journal of Psoriasis and Psoriatic Arthritis.	Enos C. W., et al. (2022)		TNF-α inhibitors	initiation in the past 12 months	2924	96	6	56.9 ± 11,9[3]	252/507 (49.7)[3]	PASI 9.1 ± 7.2[3]	/	/	6	/	/	/	discontinuation of therapy patients with diabetes: n= 33/96 (34.4%) patients without diabetes: n= 111/455 (24.4%)	
			IL-17 inhibitors			219											discontinuation of therapy patients with diabetes: n= 44/219 (20.1%) patients without diabetes: n= 155/1011 (15.3%)	
			IL-23 / IL-12/23 inhibitors			192											discontinuation of therapy patients with diabetes: n= 25/192 (13.0%) patients without diabetes: n= 78/950 (8.2%)	

Table 4 continued

Titel	Author (Y)	Original study	Intervention	Duration of treatment (M)	Patients (n)	Patients with diabetes (n)	Follow up (M)	Age (Y) (Ø±SD)	♀ (%)	Poriasis-score at baseline (Ø±SD)	Qualtity of life at baseline (Ø±SD)	Diabetes parameters at baseline (Ø±SD)	Outcomes				overall RoB
													End of dollow up (M)	Psorias-Score e.g. PASI 75	Mean change of quality of life (Ø±SD)	Mean change of diabetes parameters (Ø±SD)	Adverse events	
Comorbid obesity and history of diabetes are independently associated with poorer treatment response to biologics at 6 months: A prospective analysis in Corrona Psoriasis Registry. Journal of the American Academy of Dermatology.	Enos C. W., et al. (2022)		TNF-α inhibitors	initiation in the past 12 months	2924	96	6	50.0 ± 14.4[2]	268 (48.6)[2]	PASI 7.8 ± 6.9[2]	/	/	6	**achieving PASI75** (patients with vs. without diabetes) 43.8% (42/96) vs. 53.0% (241/455) aOR 0.72 (95%CI 0.44, 1.18)[§] **achieving PASI90** (patients with vs. without diabetes) 29.2% (28/96) vs. 36.5% (166/455) aOR 0.81 (95%CI 0.47, 1.38)[§]	/	/	/	
			IL-17 inhibitors			219		51.2 ± 13.8[2]	576 (46.8)[2]	PASI 8.4 ± 7.7[2]				**achieving PASI75** (patients with vs. without diabetes) 47.5% (104/219) vs. 60.6% (613/1011) aOR 0.61 (95%CI 0.45, 0.85)[§] **achieving PASI90** (patients with vs. without diabetes) 33.8% (74/219) vs. 44.4% (449/1011) aOR 0.69 (95% CI 0.49, 0.96)[§]				
			IL-23 / IL-12/23 inhibitors			192		49.8 ± 15.0[2]	534 (46.8)[2]	PASI 8.9 ± 7.5[2]				**achieving PASI75** (patients with vs. without diabetes) 52.6% (101/192) vs. 62.3% (592/950) aOR 0.77 (95%CI 0.55, 1.09)[§] **achieving PASI90** (patients with vs. without diabetes) 39.1% (75/192) vs. 45.6% (433/950) aOR 0.92 (95%CI 0.65, 1.30)[§]				

Abbreviation:
1 = refers to all patients; 2 = refers to all patients in the subgroup; 3= refers to all patients with diabetes; a = adjusted; ADA = Adalimumab; AE = Adverse Event; APR = Apremilast; BSA = body surface area (%); CI = Confidence intervall; CsA = Cyclosporine A; DLQI = Dermatology Life Qulity Index; ETA = Etanercept; FPG = Fasting Plasma Glucose; GOL = Golimumab; HbA1c = Haemoglobin A1c; IFX = Infliximab; IS = Insuline Sensitivity measured by HOMA (Homeostasis Modell Assessment); M = Month; MTX = Methotrexate; Ø±SD = Mean ± standard deviation; OR = Odds ratio; PASI = Psoriasis area severity index; PASI 100/90/75/50 = 100%/90%/75%/50% improvement in PASI; PI = Plasma Insuline; SAE = Severe Adverse Event; SEC = Secukinumab; TNFi = Tumour Necrosis Factor inhibitor; UST = Ustekinumab; Y = Year; blue = new studies update 2022; § = Odds ratio adjusted for: age, sex, race, smoking, education, duration of psoriasis, psoriatic arthritis, number of prior biologics, and obesity

EUROGUIDERM GUIDELINE FOR THE TREATMENT OF PSORIASIS VULGARIS. SYSTEMIC TREATMENT

EUROPEAN CENTRE FOR GUIDELINES DEVELOPMENT

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Table 5 Retrospective data from the included studies for the systematic review of the evidence on psoriasis treatment and diabetes mellitus (Update 2)

	Titel	Author (Y)	Intervention	Duration of treatment (M)	Patients (n)	Patients with diabetes (n)	Age (Y) (Ø±SD)	♀ (%)	Outcomes							Oxford Levels of Evidence
									Poriasis-score at baseline (Ø±SD)	Quality of life at baseline (Ø±SD)	Diabetes parameters at baseline (Ø±SD)	End of dollow up (M)	Psorias-score e.g. PASI 75	Mean change of quality of life (Ø±SD)	Mean change of diabetes parameters (Ø±SD)	Adverse events
Registrydata	Risk of Serious Infection With Biologic and Systemic Treatment of Psoriasis: Results From the Psoriasis Longitudinal Assessment and Registry (PSOLAR)	Kalb, R. E. et al. (2015)	ADA (n=331) ETA (n=221) IFX (n=161) UST (n=440)	21[1]	11461	1459 (12.7%[1])	48.5±13.8[1]	44.9%[1]	/	/	/	/	/	/	/	"presence of diabetes mellitus was found to be a significant predictor of serious infection" (HR, 1.7; 95% CI, 1.25-2.23; p < 0.001)	3
			Non-MTX/Non-biologics (n=204)													/	
	Risk factors for increased serum creatinine level in patients with psoriasis treated with cyclosporine in a real-world practice	Hong, J. R. et al. (2019)	CsA	3	398	37 (9.3%)	45.3±15.6[1]	44.2%[1] (176/398)	PASI 11.5[1]	/	/	/	/	/	/	"relative risk of a greater than 10% increase in serum creatinine levels was increased in diabetic patients" (HR 2.34; 95% CI, 1.59–3.45; p <0 .001)	3
Retrospektivestudies	No association between TNF inhibitor and methotrexate therapy versus methotrexate in changes in hemoglobin A1C and fasting glucose among psoriasis, psoriatic arthritis, and rheumatoid arthritis patients	Wu, J. J. et al. (2015)	MTX + TNFi (ADA/ ETA/IFX)/GoI	12	118	99 (83.9%[2])	59.4±9.43[2]	70.3%[2] (83/118)	/	/	HbA1c (%) 6.9±1.7	1 - 12	/	/	HbA1c (%) -0.1±1.0	/	3
					121	34 (28.1%[2])	57.7±9.78[2]	73.9%[2] (86/121)			FPG (mg/dl) 102.5±22.1				FPG (mg/dl) 3.7±18.6		
			MTX		344	247 (71.8%[2])	64.7±10.36[2]	67.2%[2] (231/344)	/	/	HbA1c (%) 6.7±1.2				HbA1c (%) 0.0±0.8		
					524	92 (17.6%[2])	64.7±11.16[2]	73.9%[2] (387/524)			FPG (mg/dl) 104.1±28.1				FPG (mg/dl) 1.3±24.5		
	Initiation of TNF inhibitor therapy and change in physiologic measures in psoriasis	Wu, J. J. et al. (2014)	TNFi	12	1274	209/1274 (16.4%[2])	46.7±13.8[2]	48.5%[2] (618/1274)	/	/	/	6	/	/	FPG (mg/dl; n=35 diabetes patients) 1.5±40.7	/	3
			MTX		979	163/979 (16.7%[2])	50.9±14.4[2]	52.3%[2] (512/979)							FPG (mg/dl; n=43 diabetes patients) -15.6±54		
			Photo-therapy		4309	711/4309 (16.5%[2])	52±15.9[2]	47.1%[2] (2029/4309)							/		
	Persistence, effectiveness, and real-world outcomes in psoriasis patients treated with secukinumab in Portugal.	Mendes-Bastos P., et al. (2022)	SEC	>3	302	24/302 (7.9%[1])	48.4 ± 13.4[1]	41.7%[1] (126/302)	PASI Median (IQR) 16.6[1] (11.8; 24.0)	DLQI score Median (IQR) 16.0[1] (12.0; 20.5)	/	104 weeks	/	/	/	Drug persistence (= time since initiation until its discontinuation or last medical contact) "diabetes mellitus patients presented a significantly higher persistence in secukinumab than patients who were not diabetic (p = 0.007)"	3
	Incidence and Risk Factors of Hepatic Fibrosis in Psoriatic Patients Receiving Methotrexate with Concomitant Acitretin Therapy and Methotrexate Monotherapy.	Rattanakaemakorn P., et al. (2021)	MTX	/	128	25/128 (19.5%[2])	age of disease onset: Median (IQR) 33.0[2] (28–81)	50.8%[2] (65/128)	8.5[2] (6.3)	/	/	1604.37 person-years	/	/	/	Hepatic Fibrosis "Cumulative incidence of hepatic fibrosis at 5 years was estimated to be 16% in the MTX-ACI group and 17% in the MTX group." "multivariate regression analysis showed that T2DM (aHR = 2.40, 95% CI: 1.05–5.51; p = 0.04) and […] increased the probability of developing hepatic fibrosis" no information identified, what the HR is adjusted for	3
			MTX-ACI		32	8/32 (25.0%[2])	age of disease onset: Median (IQR) 26.0[2] (23–78)	40.6%[2] (13/32)	8.9[2] (6.1)			108.65 person-years					
	Real-world Data Reveal Long Drug Survival for Guselkumab in Patients with Plaque Psoriasis.	Van Muijen M. E., et al. (2022)	GUS	Inclusion was allowed during the entire study period, leading to various lengths in follow-up duration	195	26/195 (13.3%[1])	at GUS initiation 49.4[1] ± 14.2 (missing values: n= 31)	43.6%[1] (85/195)	Psoriasis Area and Severity Index Median (IQR) 9.2[1] (9.3) (missing values: n= 71)	Dermatology Life Quality Index 14.3[1] ± 8.0 (missing values: n= 148)	/	various lengths in follow-up duration; ≥ 1 follow-up visit after GUS initiation	/	/	/	Drug survival[5] "The multivariable model showed a significant association between diabetes mellitus type 2 (T2DM) and a shorter drug survival (HR 3.69 (95% CI 1.14–11.98) (p = 0.030) due to ineffectiveness."	3

Abbreviation:
1 = refers to all patients; 2 = refers to all patients in the subgroup; a = adjusted; ACI = Acitrin; ADA = Adalimumab; AE = Adverse Event; CsA = Cyclosporine A; DLQI = Dermatology Life Quility Index; ETA = Etanercept; FPG = Fasting Plasma Glucose; GOL = Golimumab; GUS = Guselkumab; HbA1c = Haemoglobin A1c; IFX = Infliximab; IS = Insuline Sensitivity measured by HOMA (Homeostasis Modell Assessment); HR = Hazard ratio; M = Month; MTX = Methotrexate; ØSD = Mean ± standard deviation; PASI = Psoriasis area severity index; PASI 100/90/75/50 = 100%/90%/75%/50% improvement in PASI; PI = Plasma Insuline; SAE = Severe Adverse Event; SEC = Secukinumab; T2DM = Diabetes mellitus, type 2; TNFi = Tumour Necrosis Factor Inhibitor; UST = Ustekinumab; Y = Year; 5 = "Temporary treatment interruptions for any reason were allowed if <90 days. This 90day gap was prolonged up to 1 year if patients discontinued due to fear of COVID-19 or due to remission" blue = new study update 2022

Appendix

Search strategy

Databases: Embase Classic+Embase 1947 to 2022 October 26

Ovid MEDLINE(R) ALL 1946 to October 26, 2022

Search date: October 27, 2022

Hits: 482 + 0 Deucra (Embase)

28 + 0 Deucra (MEDLINE)

Table 6 Search strategy for the review update 2 on psoriasis and diabetes mellitus (Embase via Ovid)

1.	exp Psoriasis/ or Psoria*.mp.
2.	pustulosis palmaris et plantaris.ti,ab.
3.	(pustulosis and palm and soles).ti,ab.
4.	palmoplantar* pustulosis.ti,ab.
5.	1 or 2 or 3 or 4
6.	Urea/ or Urea*.mp.
7.	uric acid.mp. or Uric Acid/
8.	salicyl* acid.mp. or Salicylic Acid/
9.	Calcineu* inhibito*.mp. or Calcineurin Inhibitors/
10.	Tacrolimus/ or Pimecrolim*.mp.
11.	dithranol*.mp. or Anthralin/
12.	Cortisone/ or cortiso*.mp.
13.	Betamethasone/ or Betametha*.mp.
14.	mometaso*.mp. or Glucocorticoids/ or Mometasone Furoate/
15.	Retinoids/ or tazarot*.mp.
16.	coal tar.mp. or Coal Tar/
17.	vit d3.mp or Cholecalciferol/
18.	calcipotrio*.mp.
19.	tacalcito*.mp.
20.	Calcitriol/ or calcitrio*.mp.
21.	phototherap*.mp. or exp Phototherapy/
22.	PUVA Therapy/ or Photochemotherapy/ or PUVA.mp.
23.	exp Ultraviolet Therapy/ or UV-B therap*.mp.
24.	photodynamic therap*.mp.
25.	photochemotherap*.mp.
26.	light therap*.mp.
27.	photoradiation therap*.mp.
28.	BBUVB.mp.
29.	NBUVB.mp.
30.	BB-UVB.mp.
31.	NB-UVB.mp.
32.	broad band uvb.mp.
33.	broad band ultraviolet.mp.
34.	narrow band uvb.mp.
35.	narrow band ultraviolet.mp.
36.	psoralen ultraviolet a.mp.

37.	psoralen uva.mp.
38.	Laser therap*.mp. or Laser Therapy/
39.	Ciclospori*.mp. or Cyclosporine/
40.	cyclospor*.mp.
41.	fumar*.mp. or exp Fumarates/
42.	fumaderm.mp.
43.	dimethylfumara*.mp.
44.	fae.ti,ab.
45.	dmf.ti,ab.
46.	exp Methotrexate/ or MTX.mp.
47.	methotrexa*.mp.
48.	amethopterin.mp.
49.	mexate.mp.
50.	acitretin.mp. or Acitretin/
51.	Retinoids/
52.	Phosphodiesterase 4 Inhibitors/ or apremilast.mp.
53.	(etanercep* or enbrel).mp. or Etanercept/
54.	(Infliximab* or remicade).mp. or Infliximab/
55.	ustekinumab.mp. or Ustekinumab/
56.	CNTO 1275.mp.
57.	stelara.mp.
58.	secukinumab.mp.
59.	guselkumab.mp.
60.	adalimumab*.mp. or Adalimumab/
61.	(d2e7 or humira).mp.
62.	exp Antibodies, Monoclonal/
63.	monoclonal antibod*.mp.
64.	exp Interleukin-23/ or exp Interleukin-12/
65.	brodalumab.mp.
66.	ixekizumab.mp.
67.	bimekizumab.mp.
68.	(tumor necrosis factor-alpha or tumour necrosis factor-alpha).mp.
69.	certolizuma*.mp.
70.	risankizumab.mp.
71.	tildrakizumab.mp.
72.	anti tnf.mp.
73.	(tumor necrosis factor antibod* or tumour necrosis factor antibod*).mp.
74.	(antitumor necrosis factor or antitumour necrosis factor).mp.
75.	(anti tumor necrosis factor or anti tumour necrosis factor).mp.
76.	(tnf antibod* or tnf alpha antibod*).mp.
77.	climate therap*.mp. or Climatotherapy/
78.	Psychotherapy/ or psychosocial therap*.mp.
79.	exp Tumor Necrosis Factor-alpha/
80.	deucravacitinib.mp.
81.	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or

	55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 78 or 79 or 80
82.	5 and 81
83.	Diabetes mellitus.mp. or Diabetes mellitus/
84.	Diabetes Mellitus, Type 1/ or Diabetes Mellitus, Type 2/ or diabetes mellitus type 1.mp.
85.	DM.ti,ab.
86.	(Type 1 diabetes mellitus or type 2 diabetes mellitus).ti,ab.
87.	(type 1 DM or type 2 DM).ti,ab.
88.	83 or 84 or 85 or 86 or 87
89.	82 and 88

Additional time-frame filters:

("202106*" or "202107*" or "202108*" or "202109*" or "202110*" or "202111*" or "202112*" or "2022*").dc. (Embase)

("202106*" or "202107*" or "202108*" or "202109*" or "202110*" or "202111*" or "202112*" or "2022*").dt. (Medline)

1.	exp Psoriasis/ or Psoria*.mp.
2.	pustulosis palmaris et plantaris.ti,ab.
3.	(pustulosis and palm and soles).ti,ab.
4.	palmoplantar* pustulosis.ti,ab.
5.	1 or 2 or 3 or 4
6.	deucravacitinib.mp.
7.	5 and 6
8.	Diabetes mellitus.mp. or Diabetes mellitus/
9.	Diabetes Mellitus, Type 1/ or Diabetes Mellitus, Type 2/ or diabetes mellitus type 1.mp.
10.	DM.ti,ab.
11.	(Type 1 diabetes mellitus or type 2 diabetes mellitus).ti,ab.
12.	(type 1 DM or type 2 DM).ti,ab.
13.	8 or 9 or 10 or 11 or 12
14.	7 and 13

Additional time-frame filters:

("202101*" or "202102*" or "202103*" or "202104*" or "202105*").dc. (Embase)

("202101*" or "202102*" or "202103*" or "202104*" or "202105*").dt. (Medline)

Table 7 Excluded full texts for the review update 2 on psoriasis and diabetes mellitus

Citation	Reason
Chen C. B., et al. Real-World Effects of Biologics on Renal Function in Psoriatic Patients: A Retrospective Study. BioDrugs. 2022.36(5):657-666.	off-topic
Enos C. W., et al. Cardiometabolic multimorbidity is common among patients with psoriasis and is associated with poorer outcomes compared to those without comorbidity. Journal of Dermatological Treatment. 2022.	off-topic
Fitzgerald T., et al. Characteristics of Patients Initiating Guselkumab for Plaque Psoriasis in the Symphony Health Claims Database. Journal of Drugs in Dermatology: JDD. 2021.20(10):1127-1131.	off-topic
Gottlieb A. B., et al. Clinical efficacy and safety of secukinumab in patients with psoriasis and comorbidities: pooled analysis of 4 phase 3 clinical trials. Journal of Dermatological Treatment. 2022.33(3):1482-1490.	off-topic

Citation	Reason
Liles J. E., et al. Association of IL-17 Inhibitor and SGLT2 Inhibitor with Candida Pyelonephritis. American Journal of Medicine. 2021.134(11):e561-e562.	case report
Nguyen H. T., et al. Secukinumab Demonstrated High Effectiveness in Vietnamese Patients with Moderate-To-Severe Plaque Psoriasis in a Real-World Clinical Setting: 16 Week Results from an Observational Study. Dermatology and Therapy. 2021.11(5):1613-1621.	off-topic
Setyawan J., et al. Risk of Thromboembolic Events and Associated Risk Factors, Including Treatments, in Patients with Immune-mediated Diseases. Clinical Therapeutics. 2021.43(8):1392-1407.e1.	off-topic
Tsuruta N., et al. Establishment of the Western Japan Psoriasis Registry and first cross-sectional analysis of registered patients. Journal of Dermatology. 2021.48(11):1709-1718.	off-topic
Zhou Y., et al. Anti-tumor Necrosis Factor-Alpha Therapy and Hypoglycemia: A Real-World Pharmacovigilance Analysis. Drug Safety. 2022.45(9):951-959.	off-topic

Update 1

Authors: M. Kinberger, R. Jakubzyk

Inclusions criteria

Apart from the newly included drugs, bimekizumab, certolizumab pegol, risankizumab and tildrakizumab we did not change the search strategy and the inclusion criteria of the previous version. Only briakinumab and cdp571 were no longer searched for.

Table 8 Eligibility criteria for the review update 1 on psoriasis and diabetes mellitus

Patients	Inclusion: adult patients with a clinical diagnosis of psoriasis and a concomitant diabetes mellitus of any type being treated for psoriasis Exclusion: patients with psoriatic arthritis only
Intervention	Conventional systemic treatment (acitretin, apremilast, ciclosporin, fumarates, methotrexate) and biologicals (TNFi: adalimumab, etanercept, certolizumab pegol (new), infliximab; anti-IL12/23: ustekinumab; anti-IL17: bimekizumab (new), brodalumab, ixekizumab, secukinumab; anti-IL23: guselkumab, risankizumab (new), tildrakizumab (new)
Comparator	Comparisons with another included drug and/or placebo
Outcomes	Change in skin lesions based on PASI (Psoriasis Area Severity Index) or PGA (Physician Global Assessment) or another study specific assessment. Fasting plasma glucose, HbA1c or insulin sensitivity measured by HOMA (Homeostasis Modell Assessment) or other study specific outcomes Type and proportion of other adverse events Quality of life based on SF-36 (The Short Form (36) Health Survey), DLQI (Dermatology Life Quality Index) or another study specific assessment.
Study Design	Inclusion: randomized controlled trials, clinical trials (with and without comparison group), cohort studies, case control studies and cross sectional studies Exclusion: case series, case reports, retrospective studies with with less than 100 patients

Information sources

The search strategy was updated and the databases MEDLINE Ovid from 1946 and Embase Ovid from 1974 were searched for the period 2019 to 2 June 2021. Furthermore, we examined the reference lists of included studies to identify references to relevant trails. The full search strategy is shown below (Table 11). We screened all identified abstracts/titles for eligibility. Included title/abstracts were then screened as full texts based on the above listed eligibility criteria.

Data collection, statistical analysis and evaluation

We performed the screening and did the data extraction using a standardized form. We recorded all full-texts excluded and the primary reason for exclusion (Table 12).

Methodological quality assessment/ Risk of bias assessment

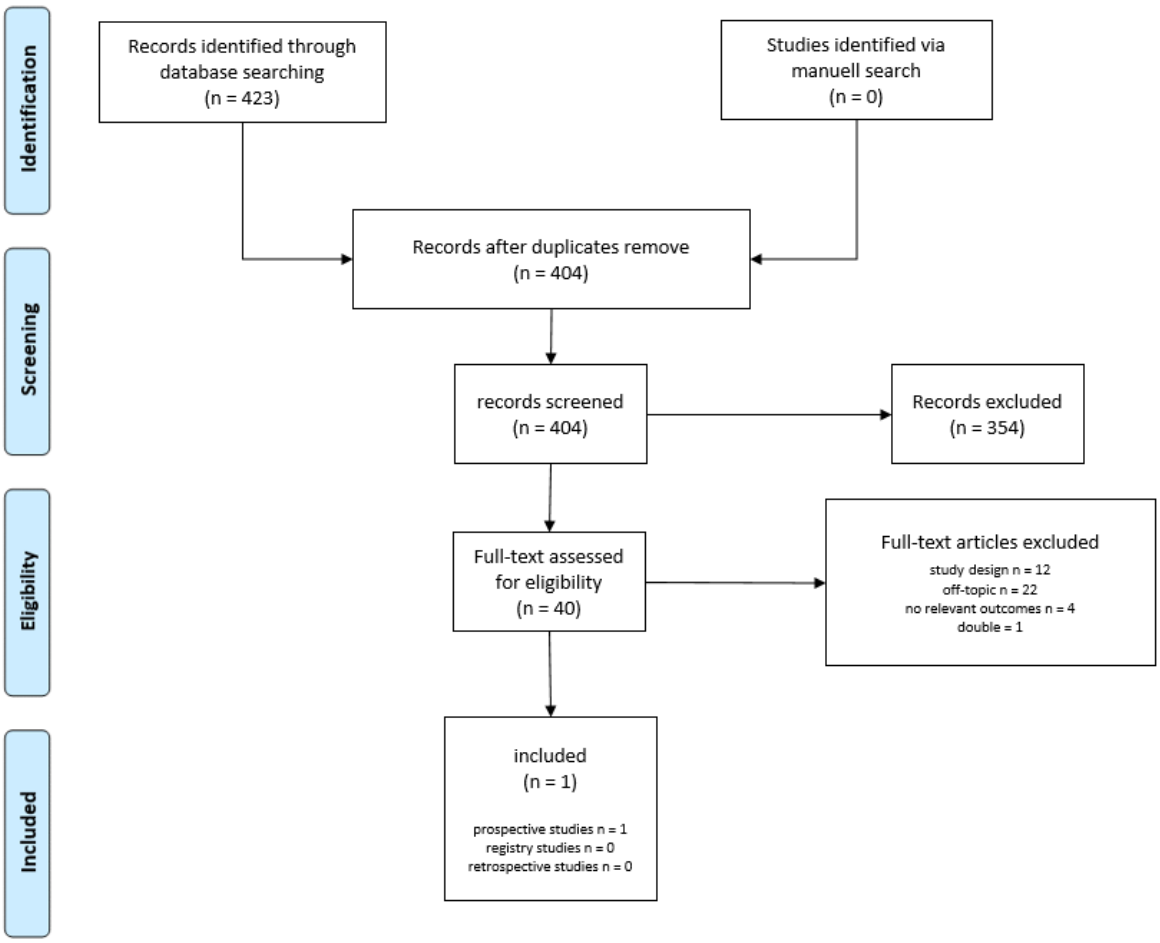
We assigned Levels of Evidence for all studies included using the Center of Evidence Based Medicine Oxford recommendations. To assess risk of bias in randomized trials we additionally used the RoB 2.0 tool [45].

Results

Our update search yielded 423 citations, one fulfilled the inclusion criteria [49] (Figure 2).

We did not find any studies on systemic treatment with apremilast, bimekizumab, certolizumab pegol, brodalumab, fumarates, guselkumab, ixekizumab, risankizumab, tildrakizumab that reported diabetes mellitus outcomes neither in the original search nor in the update.

Figure 2 Study selection flowchart for the selection of studies for the review update 1 on psoriasis and diabetes mellitus



Based on the "Levels of Evidence - Center of Evidence Based Medicine Oxford recommendations" prospective studies [30, 36, 47, 49, 52] were categorized level 2 and retrospective studies [10, 39, 50, 51] level 3.

Results of the additional assessment for prospective randomized studies with Risk of Bias Tool 2 (RoB 2) are shown in Figure 3.

Figure 3 Risk of bias in prospective studies (Update 1).

Author (Year)	Orginal study	Randomization process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall risk of bias
Al-Mutairi, N., Shabaan, D. (2016)		⊕	⊖	⊕	⊖	?	⊕
Kimball, A. B. et al. (2011)	Menter, A. et al. (2008)	⊖	⊖	⊖	⊖	⊖	⊖
Koenig, A. S. et al. (2011)	Strohal, R. et al. (2013)	?	⊖	⊖	⊖	⊖	?
Pinter, A. et al. (2019)	Blauvelt, A. et al. (2017)	⊖	⊖	⊖	⊖	⊖	⊖
	Langley, R.G. e al. (2014)	?	?	⊖	?	⊖	?
Lin, L. et al. (2020)		?	?	⊖	?	⊖	?

Abbreviation: ⊕ = high risk of biaso ? = some concerns ⊖ = low risk of bias

Data for patients with psoriasis and diabetes mellitus were extracted. Summarized results, sorted by study type are shown below in Table 9 and Table 10.

Table 9 Prospective data from the included studies for the systematic review of the evidence on psoriasis treatment and diabetes mellitus (Update 1)

	Titel	Author (Y)	Original study	Intervention	Duration of treatment (M)	Patients (n)	Patients with diabetes (n)	Follow up (M)	Age (Y) (Ø±SD)	♀ (%)	Poriasis-score at baseline (Ø±SD)	Qualtity of life at baseline (Ø±SD)	Diabetes parameters at baseline (Ø±SD)	Outcomes				
														End of dollow up (M)	Psorias-Score e.g. PASI 75	Mean change of quality of life (Ø±SD)	Mean change of diabetes parameters (Ø±SD)	Adverse events
Prospektive Studien	Efficacy and safety of adalimumab among patients with moderate to severe psoriasis with co-morbidities: Subanalysis of results from a randomized, double-blind, placebo-controlled, phase III	Kimball, A. B. et al. (2011)	Menter, A. et al. (2008)	ADA (80mg/40mg)	4	814	73	13	47.2±12.4[1]	35%[1]	PASI 19.3±7.2	/	/	4	PASI 75 n=46 (63%)	DLQI -7.1±6.3	Glucose (mmol/L) -0.47	SAE not infectios n=2 (2.7%) SAE infectios n= 1 (1.4%) Dropout because of AE n=1 (1.4%)
				Placebo		398	52		48.8±12.6[1]	36%[1]	PASI 19.1±7.6				PASI 75 n=2 (3.8%)	DLQI -1.3±5.8	Glucose (mmol/L) -0.65	SAE not infectios n=2 (3.8%) SAE infectios n=0 (0%) Dropout because of AE n=2 (3.8%)
	Characterization of responder groups to secukinumab treatment in moderate to severe plaque psoriasis	Pinter, A. et al. (2019)	Blauvelt, A. et al. (2017) Langley, R.G. et al. (2014)	ETA (50mg)	4	298	27	4	43.6[1]	/	/			4	PASI100 n=1/27 (3.7%) PASI75 n=15/27 (55.6%) PASI50 n=8/27 (29.6%) <PASI50 n=3/27 (11.1%)	/	/	/
				SEC (300mg)		867	69		44.8[1]						PASI100 n=6.6/69 (9.6%) PASI75 n=50/69 (72.5%) PASI50 n=9.4/69 (13.6%) <PASI50 n=3/69 (4.3%)			
				UST (45/90mg)		318	97.5		44.8[1]						PASI100 n=23.5/97.5 (24.1%) PASI75 n=57/97.5 (58.5%) PASI50 n=9/97.5 (9.2%) <PASI50 n=8/97.5 (8.2%)			

Titel	Author (Y)	Original study	Intervention	Duration of treatment (M)	Patients (n)	Patients with diabetes (n)	Follow up (M)	Age (Y) (Ø±SD)	♀ (%)	Poriasis-score at baseline (Ø±SD)	Quality of life at baseline (Ø±SD)	Diabetes parameters at baseline (Ø±SD)	Outcomes				
													End of dollow up (M)	Psorias-Score e.g. PASI 75	Mean change of quality of life (Ø±SD)	Mean change of diabetes parameters (Ø±SD)	Adverse events
Impact of etanercept therapy on glycemic control in a cohort of psoriatic patients: The pristine trial	Koenig, A.S. et al. (2011)	Strohal, R. et al. (2013, Studienende 2010)	ETA (50mg/100mg)	3	273	35	3	44[1]	30[1]	21[1]	/	HbA1c (%) 7.0 FPG (mmol/l) 6.8 IS 5.3 PI (mcU/mL) 14.0	3	/	/	HbA1c (%) -0.3 FPG (mmol/l) 0.1 IS 1.1 PI (mcU/mL) 3.0	/
Effects of tumor necrosis factor alpha inhibitors extend beyond psoriasis: insulin sensitivity in psoriasis patients with type 2 diabetes mellitus	Al-Mutairi, N., Shabaan, D. (2016)		ADA (n=14) ETA (n=8) IFX (n=12)	6	34 (35 randomised)	34 (35 randomised)	6	43.7±21.6	52.9% (18/34)	/	/	HbA1c (%) 8.4±0.38 FPG (mmol/L) 10±25 IS 5.9±0.52	6	/	/	HbA1c (%) -1.3 FPG (mmol/L) -2.74±0.34 IS 1.2±0.4	/
			Topic corticosteroids, calcipotriol (n=8) CsA (n=7)		29 (35 randomisedt)	29 (35 randomised)		47.7±14.2	51.7% (15/29)			HbA1c (%) 8.1±0.21 FPG (mmol/L) 11±0.4 IS 5.4±0.31				HbA1c (%) 0.2 FPG (mmol/L) -0.02±0.16 IS -0.3±0.12	
Glucagon-like peptide-1 receptor agonist liraglutide therapy for psoriasis patients with type 2 diabetes: a randomized-controlled trial	Lin, L. et al. (2020)		acitretin 30-50mg/d + calcipotriol ointment + metformin allone or + glimepirid or sitagliptin		13	13	12	55.23±7.84	15.4% (2/13)	PASI 13.57±5.49	DLQI 18.23±5.17	HbA1c (%) 7.30±1.88 FPG (mmol/l) 6.29±1.89 Fasting insulin (ug/ml) 11.79±7.84 Fasting C-peptide (ng/mL) 1.47±1.05 IP 3.69±3.20	3	PASI-Change -6.15±3.43 PASI50 38.46% (5/13) PASI75 7.69 (1/13)	DLQI-Change -8.54±5.33	HbA1c (%) -0.82±0.73 FPG (mmol/l) -0.20±1.49 Fasting insulin (ug/ml) 0.86±4.81 Fasting C-peptide (ng/mL)-0.06±0.37 IS 0.37±2.09	no SAE no AW

Abbreviation:
ADA = Adalimumab; AE = Adverse Event; APR = Apremilast; BSA = body surface area (%); CsA = Cyclosporine A; DLQI = Dermatology Life Quality Index; ETA = Etanercept; FPG = Fasting Plasma Glucose; GOL = Golimumab; HbA1c = Haemoglobin A1c; IFX = Infliximab; IS = Insuline Sensitivity measured by HOMA (Homeostasis Modell Assessment); M = Month; MTX = Methotrexate; Ø±SD = Mean ± standard deviation; PASI = Psoriasis area severity index; PASI100/90/75/50 = 100%/90%/75%/50% improvement in PASI; PI = Plasma Insuline; SAE = Severe Adverse Event; SEC = Secukinumab; TNFi = Tumour Necrosis Factor inhibitor; UST = Ustekinumab; Y = Year

Table 10 Retrospective data from the included studies for the systematic review of the evidence on psoriasis treatment and diabetes mellitus (Update 1)

	Titel	Author (Y)	Intervention	Duration of treatment (M)	Patients (n)	Patients with diabetes (n)	Age (Y) (Ø±SD)	♀ (%)	Poriasis-score at baseline (Ø±SD)	Qualtity of life at baseline (Ø±SD)	Diabetes parameters at baseline (Ø±SD)	Outcomes: End of dollow up (M)	Outcomes: Psorias-score e.g. PASI 75	Outcomes: Mean change of quality of life (Ø±SD)	Outcomes: Mean change of diabetes parameters (Ø±SD)	Outcomes: Adverse events
Registry data	Risk of Serious Infection With Biologic and Systemic Treatment of Psoriasis: Results From the Psoriasis Longitudinal Assessment and Registry (PSOLAR)	Kalb, R. E. et al. (2015)	ADA (n=331) ETA (n=221) IFX (n=161) UST (n=440)	21[1]	11461	1459 (12.7%[1])	48.5±13.8[1]	44.9%[1]	/	/	/	/	/	/	/	"presence of diabetes mellitus was found to be a significant predictor of serious infection" (HR, 1.7; 95% CI, 1.25-2.23; p < 0.001)
			Non-biologics (n=204)													/
	Risk factors for increased serum creatinine level in patients with psoriasis treated with cyclosporine in a real-world practice	Hong, J. R. et al. (2019)	CsA	3	398	37 (9.3%)	45.3±15.6[1]	44.2%[1] (176/398)	PASI 11.5[1]	/	/	/	/	/	/	"relative risk of a greater than 10% increase in serum creatinine levels was increased in diabetic patients" (HR 2.34; 95% CI, 1.59–3.45; p <0 .001)
Retrospektive studies	No association between TNF inhibitor and methotrexate therapy versus methotrexate in changes in hemoglobin A1C and fasting glucose among psoriasis, psoriatic arthritis, and rheumatoid arthritis patients	Wu, J. J. et al. (2015)	MTX + ADA/ ETA/IFX/GoI	12	118	99 (83.9%[2])	59.4±9.43[2]	70.3%[2] (83/118)	/	/	HbA1c (%) 6.9±1.7	1 - 12	/	/	HbA1c (%) -0.1±1.0	/
					121	34 (28.1%[2])	57.7±9.78[2]	73.9%[2] (86/121)			FPG (mg/dl) 102.5±22.1				FPG (mg/dl) 3.7±18.6	
			MTX		344	247 (71.8%[2])	64.7±10.36[2]	67.2%[2] (231/344)	/	/	HbA1c (%) 6.7±1.2				HbA1c (%) 0.0±0.8	
					524	92 (17.6%[2])	64.7±11.16[2]	73.9%[2] (387/524)			FPG (mg/dl) 104.1±28.1				FPG (mg/dl) 1.3±24.5	
	Initiation of TNF inhibitor therapy and change in physiologic measures in psoriasis	Wu, J. J. et al. (2014)	TNFi	12	1274	209/1274 (16.4%[2])	46.7±13.8[2]	48.5%[2] (618/1274)	/	/	/	6	/	/	FPG (mg/dl; n=35 diabetes patients) 1.5±40.7	/
			MTX		979	163/979 (16.7%[2])	50.9±14.4[2]	52.3%[2] (512/979)							FPG (mg/dl; n=43 diabetes patients) -15.6±54	
			Photo-therapie		4309	711/4309 (16.5%[2])	52±15.9[2]	47.1%[2] (2029/4309)							/	

Abbreviation:
ADA = Adalimumab; AE = Adverse Event; CsA = Cyclosporine A; DLQI = Dermatology Life Qulity Index; ETA = Etanercept; FPG = Fasting Plasma Glucose; GOL = Golimumab; HbA1c = Haemoglobin A1c; IFX = Infliximab; IS = Insuline Sensitivity measured by HOMA (Homeostasis Modell Assessment); M = Month; MTX = Methotrexate; Ø±SD = Mean ± standard deviation; PASI = Psoriasis area severity index; PASI100/90/75/50 = 100%/90%/75%/50% improvement in PASI; PI = Plasma Insuline; SAE = Severe Adverse Event; SEC = Secukinumab; TNFi = Tumour Necrosis Factor Inhibitor; UST = Ustekinumab; Y = Year

Appendix

Table 11 Search strategy for the review update 1 on psoriasis and diabetes mellitus (Embase via Ovid)

1.	exp Psoriasis/ or Psoria*.mp.
2.	pustulosis palmaris et plantaris.ti,ab.
3.	(pustulosis and palm and soles).ti,ab.
4.	palmoplantar* pustulosis.ti,ab.
5.	1 or 2 or 3 or 4
6.	Urea/ or Urea*.mp.
7.	uric acid.mp. or Uric Acid/
8.	salicyl* acid.mp. or Salicylic Acid/
9.	Calcineu* inhibito*.mp. or Calcineurin Inhibitors/
10.	Tacrolimus/ or Pimecrolim*.mp.
11.	dithranol*.mp. or Anthralin/
12.	Cortisone/ or cortiso*.mp.
13.	Betamethasone/ or Betametha*.mp.
14.	mometaso*.mp. or Glucocorticoids/ or Mometasone Furoate/
15.	Retinoids/ or tazarot*.mp.
16.	coal tar.mp. or Coal Tar/
17.	vit d3.mp or Cholecalciferol/
18.	calcipotrio*.mp.
19.	tacalcito*.mp.
20.	Calcitriol/ or calcitrio*.mp.
21.	phototherap*.mp. or exp Phototherapy/
22.	PUVA Therapy/ or Photochemotherapy/ or PUVA.mp.
23.	exp Ultraviolet Therapy/ or UV-B therap*.mp.
24.	photodynamic therap*.mp.
25.	photochemotherap*.mp.
26.	light therap*.mp.
27.	photoradiation therap*.mp.
28.	BBUVB.mp.
29.	NBUVB.mp.
30.	BB-UVB.mp.
31.	NB-UVB.mp.
32.	broad band uvb.mp.
33.	broad band ultraviolet.mp.
34.	narrow band uvb.mp.
35.	narrow band ultraviolet.mp.
36.	psoralen ultraviolet a.mp.
37.	psoralen uva.mp.
38.	Laser therap*.mp. or Laser Therapy/
39.	Ciclospori*.mp. or Cyclosporine/
40.	cyclospor*.mp.
41.	fumar*.mp. or exp Fumarates/
42.	fumaderm.mp.
43.	dimethylfumara*.mp.
44.	fae.ti,ab.
45.	dmf.ti,ab.
46.	exp Methotrexate/ or MTX.mp.
47.	methotrexa*.mp.
48.	amethopterin.mp.

49.	mexate.mp.
50.	acitretin.mp. or Acitretin/
51.	Retinoids/
52.	Phosphodiesterase 4 Inhibitors/ or apremilast.mp.
53.	(etanercep* or enbrel).mp. or Etanercept/
54.	(Infliximab* or remicade).mp. or Infliximab/
55.	ustekinumab.mp. or Ustekinumab/
56.	CNTO 1275.mp.
57.	stelara.mp.
58.	secukinumab.mp.
59.	guselkumab.mp.
60.	adalimumab*.mp. or Adalimumab/
61.	(d2e7 or humira).mp.
62.	exp Antibodies, Monoclonal/
63.	monoclonal antibod*.mp.
64.	exp Interleukin-23/ or exp Interleukin-12/
65.	brodalumab.mp.
66.	ixekizumab.mp.
67.	bimekizumab.mp.
68.	(tumor necrosis factor-alpha or tumour necrosis factor-alpha).mp.
69.	certolizuma*.mp.
70.	risankizumab.mp.
71.	tildrakizumab.mp.
72.	anti tnf.mp.
73.	(tumor necrosis factor antibod* or tumour necrosis factor antibod*).mp.
74.	(antitumor necrosis factor or antitumour necrosis factor).mp.
75.	(anti tumor necrosis factor or anti tumour necrosis factor).mp.
76.	(tnf antibod* or tnf alpha antibod*).mp.
77.	climate therap*.mp. or Climatotherapy/
78.	Psychotherapy/ or psychosocial therap*.mp.
79.	exp Tumor Necrosis Factor-alpha/
80.	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 78 or 79
81.	5 and 80
82.	Diabetes mellitus.mp. or Diabetes mellitus/
83.	Diabetes Mellitus, Type 1/ or Diabetes Mellitus, Type 2/ or diabetes mellitus type 1.mp.
84.	DM.ti,ab.
85.	(Type 1 diabetes mellitus or type 2 diabetes mellitus).ti,ab.
86.	(type 1 DM or type 2 DM).ti,ab.
87.	82 or 83 or 84 or 85 or 86
88.	81 and 87

Additional time filters:
("2019*" or "2020*" or "2021*").dc. (Embase)
("2019*" or "2020*" or "2021*").dt. (Medline)

Table 12 Excluded full-texts for the review update 1 on psoriasis and diabetes mellitus

R. Abramczyk	2020	study design
M. Aksentijevich	2020	study design

J. P. Allam	2019	off-topic
A.G. Ashbaugh	2020	study design
F. Assan	2021	off-topic
M. Augustin	2020	off-topic
I. Belinchon-Romero	2021	off-topic
F. Bellinato	2019	off-topic
F. Benhadou	2020	off-topic
K. P. Botelho	2020	no relevant outcomes
F. Diotallevi	2020	off-topic
C. V. Fricke	2019	study design
J. M. Gelfand	2020	off-topic
S. Gerdes	2020	no relevant outcomes
N. Goolam Mahyoodeen	2019	off-topic
A. B. Gottlieb	2021	off-topic
R. Greenberg	2021	off-topic
A. Grodner	2021	off-topic
M. Hajiebrahimi	2020	off-topic
N. Joseph	2020	off-topic
K. Kamiya	2021	off-topic
E. Kapniari	2020	no relevant outcomes
E. Kapniari	2020	study design
E. H. Klujszo	2020	study design
J. L. W. Lambert	2020	study design
M. G. Lebwohl	2021	off-topic
M. G. Lebwohl	2021	study design
L. Legiawati	2020	off-topic
M. Lynch	2021	study design
M. Lynch	2021	double
M. Lynch	2021	off topic
S. Mazzilli	2020	no relevant outcomes
J. Nowowiejska	2020	study design
S. Pannu	2021	study design
L. Rodriguez Fernandez-Freire	2020	off-topic
R. Ruiz-Villaverde	2021	off topic
B. W. Schwarz	2020	off topic
M. Teklu	2021	off topic
E. von Stebut	2020	study design

Original version

We conducted a "Systematic review of the efficacy, effectiveness and safety of topical and systemic treatments for psoriasis in patients with diabetes mellitus", for which a protocol was published on for which a protocol was published on PROSPERO (CRD42018087908). For the guideline, the recommendations focus on the systemic treatment options licensed for plaque type psoriasis.

Inclusion criteria

We included all studies on adult patients with a clinical diagnosis of psoriasis and a concomitant diabetes mellitus of any type being treated for psoriasis.

The interventions were specified to be topical treatment (urea, salicylic acid, calcineurin-inhibitors (pimecrolimus, tacrolimus), dithranol, corticosteroids (betamethasone, mometasonfuroat), tazaroten, coal tar, vitamin D3 derivate (calcipotriol, tacalcitol, calcitriol, calcipotriol and betamethasone) or systemic treatment (aciretin, ciclosporin, fumarates, methotrexate, apremilast) for psoriasis including biologicals (TNFi: etanercept, infliximab, adalimumab; anti-IL12/23: ustekinumab; Anti-IL17: secukinumab, ixekizumab, brodalumab; Anti-IL23). We included studies comparing the intervention to placebo or another treatment and those without comparator.

The following outcomes were of interest:

Change in skin lesions based on PASI (Psoriasis Area Severity Index) or PGA (Physician Global Assessment) or another study specific assessment.

Fasting plasma glucose, HbA1c or insulin sensitivity measured by HOMA (Homeostasis Modell Assessment) or other study specific outcomes

Type and proportion of other adverse events

Quality of life based on SF-36 (The Short Form (36) Health Survey), DLQI (Dermatology Life Quality Index) or another study specific assessment.

Wherever possible, we evaluated the outcomes at different timings, based on what was reported in the publications (e.g. short-term, long-term).

Included were randomized controlled trials, clinical trials (with and without comparison group), cohort studies, case control studies and cross sectional studies. We used a step-wise approach for including studies (for each study drug and comparator) following the hierarchy of evidence [55].

We excluded studies on patients with psoriatic arthritis only because of the different pathophysiology and treatment options. We also excluded studies with less than 100 patients to minimize bias.

Information sources

Three databases were searched systematically (MEDLINE Ovid from 1946, Embase Ovid from 1974 and The Cochrane Central Register of Controlled Trials (CENTRAL); updated last in September 2019. Furthermore, we examined the reference lists of included studies to identify references to relevant trials. The full search strategy is shown in Table 15.

Data collection, statistical analysis and evaluation

We screened all identified abstracts/titles for eligibility. Included title/abstracts were then screened as full texts based on the above listed eligibility criteria.

Data collection and reporting

Endnote was used to manage all records. One reviewer performed the screening and did the data extraction using a standardized form. A second reviewer checked the screening. We recorded all full-texts excluded and the primary reason for exclusion (see Table 16).

The following items were extracted: Author, year of publication, country in which the study took place, study design, inclusion and exclusion criteria, baseline characteristics of the included patients, details of the interventions, details of any co-interventions, number and reasons for drop-out, type of adverse events and proportion of patients experiencing adverse events and serious adverse events, proportion of patients who experienced worsening of diabetes parameters, proportion of patients who showed an improvement in skin lesions, proportion of patients who showed an improvement in quality of life, time of assessment of endpoints and number/rate of patients assessed.

Methodological quality assessment/ Risk of bias assessment

We assigned Levels of Evidence for all studies included using the Center of Evidence Based Medicine Oxford recommendations [44]. To assess risk of bias in randomized trials we additionally used the RoB 2.0 tool [45]. We planned to use the ROBINS-I tool for controlled non-randomized studies of interventions but none of these type were included [56].

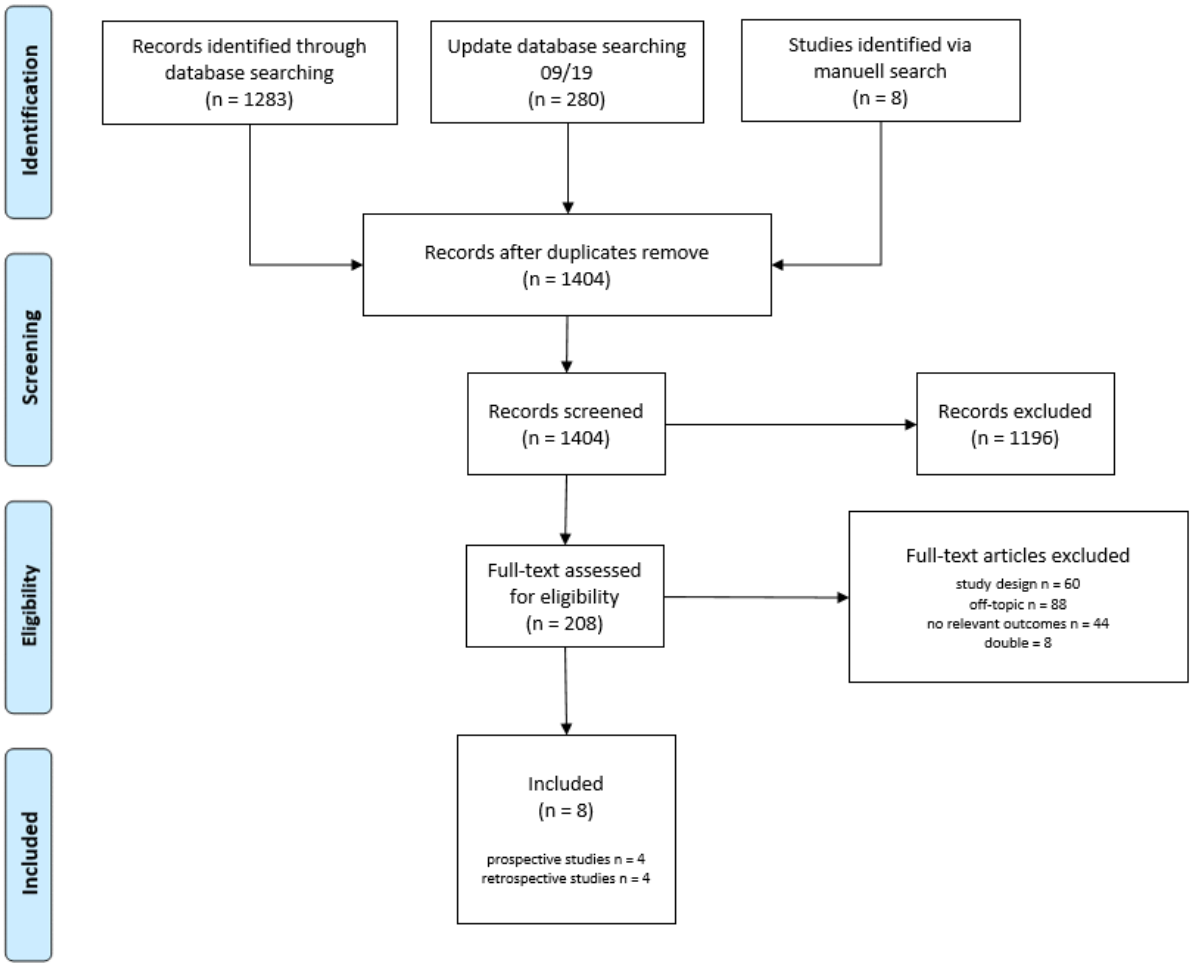
Data was summarized and sorted by study type (see Table 13 and Table 14).

Results

Our search yielded 1404 citations, eight of which fulfilled the inclusion criteria (September 2019; see Figure 4). Four prospective studies [30, 36, 47, 52], one study based on registry data [50] and three retrospective studies [10, 39, 51] were included.

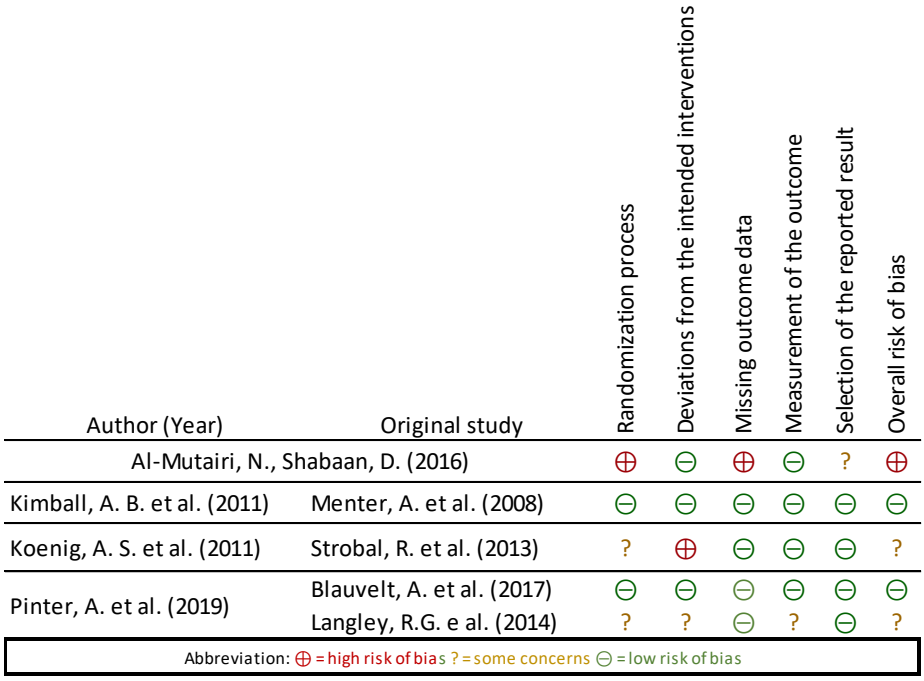
We did not find any studies on acitretin, apremilast, brodalumab, fumarates, guselkumab, ixekizumab, risankizumab, tildrakizumab that reported diabetes mellitus outcomes.

Figure 4 Study selection flowchart for the selection of studies for the original review on psoriasis and diabetes mellitus



Based on the "Levels of Evidence - Center of Evidence Based Medicine Oxford recommendations" [44] four prospective studies were categorized level 2 [30, 36, 47, 52] and four retrospective studies level 3 [10, 39, 50, 51]. Results of the additional assessment [45] for prospective randomized studies are shown in Figure 5 [30, 36, 47, 48, 52, 57-59].

Figure 5 Risk of Bias in prospective studies (original review)



Author (Year)	Original study	Randomization process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall risk of bias
Al-Mutairi, N., Shabaan, D. (2016)		⊕	⊖	⊕	⊖	?	⊕
Kimball, A. B. et al. (2011)	Menter, A. et al. (2008)	⊖	⊖	⊖	⊖	⊖	⊖
Koenig, A. S. et al. (2011)	Strobal, R. et al. (2013)	?	⊕	⊖	⊖	⊖	?
Pinter, A. et al. (2019)	Blauvelt, A. et al. (2017)	⊖	⊖	⊖	⊖	⊖	⊖
	Langley, R.G. e al. (2014)	?	?	⊖	?	⊖	?

Abbreviation: ⊕ = high risk of bias ? = some concerns ⊖ = low risk of bias

Data for overall 3503 patients with psoriasis and diabetes mellitus was extracted. Summarized results, sorted by study type are shown in Table 13 and Table 14.

Table 13 Prospective data from the included studies for the systematic review of the evidence on psoriasis treatment and diabetes mellitus (original)

	Title	Author (Y)	Original study	Intervention	Duration of treatment (M)	Patients (n)	Patients with diabetes (n)	Follow-up (M)	Age (Y) (Ø±SD)	♀ (%)	Psoriasis-score at baseline (Ø±SD)	Quality of life at baseline (Ø±SD)	Diabetes parameters at baseline (Ø±SD)	Outcomes: End of follow-up (M)	Outcomes: Psorias-score e.g. PASI 75	Outcomes: Mean change of quality of life (Ø±SD)	Outcomes: Mean change of diabetes parameters (Ø±SD)	Outcomes: Adverse events
Prospective studies	Efficacy and safety of adalimumab among patients with moderate to severe psoriasis with co-morbidities: Subanalysis of results from a randomized, double-blind, placebo-controlled, phase III trial	Kimball, A. B. et al. (2011)	Menter, A. et al. (2008)	ADA (80mg/40mg)	4	814	73	13	47.2±12.4[1]	35%[1]	PASI 19.3±7.2	/	/	4	PASI75 n=46 (63%)	DLQI -7.1±6.3	Glucose (mmol/L) -0.47	SAE not infectios n=2 (2.7%) SAE infectios n= 1 (1.4%) Dropout because of AE n=1 (1.4%)
				Placebo		398	52		48.8±12.6[1]	36%[1]	PASI 19.1±7.6				PASI75 n=2 (3.8%)	DLQI -1.3±5.8	Glucose (mmol/L) -0.65	SAE not infectios n=2 (3.8%) SAE infectios n=0 (0%) Dropout because of AE n=2 (3.8%)
	Characterization of responder groups to secukinumab treatment in moderate to severe plaque psoriasis	Pinter, A. et al. (2019)	Blauvelt, A. et al. (2017) Langley, R.G. et al. (2014)	SEC (300mg)	4	867	69	4	44.8[1]	/		/	/	4	PASI100 n=6.6/69 (9.6%) PASI75 n=50/69 (72.5%) PASI50 n=9.4/69 (13.6%) <PASI50 n=3/69 (4.3%)	/	/	/
				UST (45/90mg)		318	97.5		44.8[1]	/					PASI100 n=23.5/97.5 (24.1%) PASI75 n=57/97.5 (58.5%) PASI50 n=9/97.5 (9.2%) <PASI50 n=8/97.5 (8.2%)			
				ETA (50mg)		298	27		43.6[1]						PASI100 n=1/27 (3.7%) PASI75 n=15/27 (55.6%) PASI50 n=8/27 (29.6%) <PASI50 n=3/27 (11.1%)			
	Impact of etanercept therapy on glycemic control in a cohort of psoriatic patients: The pristine trial	Koenig, A.S. et al. (2011)	Strobal, R. et al. (2013)	ETA (50mg/100mg)	3	273	35	3	44[1]	30[1]	21[1]	/	HbA1c (%) 7.0 FPG (mmol/l) 6.8 IS 5.3 PI (mcU/mL) 14.0	3	/	/	HbA1c (%) -0.3 FPG (mmol/l) 0.1 IS 1.1 PI (mcU/mL) 3.0	/
	Effects of tumor necrosis factor alpha inhibitors extend beyond psoriasis: insulin sensitivity in psoriasis patients with type 2 diabetes mellitus	Al-Mutairi, N., Shabaan, D. (2016)		ADA (n=14) ETA (n=8) IFX (n=12)	6	34 (35 randomised)	34 (35 randomised)	6	43.7±21.6	52.9% (18/34)	/	/	HbA1c (%) 8.4±0.38 FPG (mmol/L) 10±25 IS 5.9±0.52	6	/	/	HbA1c (%) -1.3 FPG (mmol/L) -2.74±0.34 IS 1.2±0.4	/
				Topic cortikosteroids, calcipotriol (n=8) CsA (n=7) MTX (n=14)		29 (35 randomised)	29 (35 randomised)		47.7±14.2	51.7% (15/29)			HbA1c (%) 8.1±0.21 FPG (mmol/L) 11±0.4 IS 5.4±0.31				HbA1c (%) 0.2 FPG (mmol/L) -0.02±0.16 IS -0.3±0.12	

Table 14 Retrospective data from the included studies for the systematic review of the evidence on psoriasis treatment and diabetes mellitus (Original review)

	Title	Author (Y)	Intervention	Duration of treatment (M)	Patients (n)	Patients with diabetes (n)	Age (Y) (Ø±SD)	♀ (%)	Psoriasis-score at baseline (Ø±SD)	Quality of life at baseline (Ø±SD)	Diabetes parameters at baseline (Ø±SD)	Outcomes: End of follow-up (M)	Outcomes: Psorias-score e.g. PASI 75	Outcomes: Mean change of quality of life (Ø±SD)	Outcomes: Mean change of diabetes parameters (Ø±SD)	Outcomes: Adverse events
Registry data	Risk of Serious Infection With Biologic and Systemic Treatment of Psoriasis: Results From the Psoriasis Longitudinal Assessment and Registry (PSOLAR)	Kalb, R. E. et al. (2015)	ADA (n=331) ETA (n=221) IFX (n=161) UST (n=440)	21[1]	11461	1459 (12.7%[1])	48.5±13.8[1]	44.9%[1]	/	/	/	/	/	/	/	"presence of diabetes mellitus was found to be a significant predictor of serious infection" (HR, 1.7; 95% CI, 1.25-2.23; p < 0.001)
			Non-MTX/Non-biologics (n=204)													/
Retrospective studies	Risk factors for increased serum creatinine level in patients with psoriasis treated with cyclosporine in a real-world practice	Hong, J. R. et al. (2019)	CsA	3	398	37 (9.3%)	45.3±15.6[1]	44.2%[1] (176/398)	PASI 11.5[1]	/	/	/	/	/	/	"relative risk of a greater than 10% increase in serum creatinine levels was increased in diabetic patients" (HR 2.34; 95% CI, 1.59–3.45; p <0 .001)
	No association between TNF inhibitor and methotrexate therapy versus methotrexate in changes in hemoglobin A1C and fasting glucose among psoriasis, psoriatic arthritis, and rheumatoid arthritis patients	Wu, J. J. et al. (2015)	MTX + TNFi (ADA, ETA,IFX)/GOL	12	118	99 (83.9%[2])	59.4±9.43[2]	70.3%[2] (83/118)	/	/	HbA1c (%) 6.9±1.7	1-12	/	/	HbA1c (%) -0.1±1.0	/
					121	34 (28.1%[2])	57.7±9.78[2]	73.9%[2] (86/121)			FPG (mg/dl) 102.5±22.1				FPG (mg/dl) 3.7±18.6	
			MTX		344	247 (71.8%[2])	64.7±10.36[2]	67.2%[2] (231/344)	/	/	HbA1c (%) 6.7±1.2				HbA1c (%) 0.0±0.8	
					524	92 (17.6%[2])	64.7±11.16[2]	73.9%[2] (387/524)			FPG (mg/dl) 104.1±28.1				FPG (mg/dl) 1.3±24.5	
	Initiation of TNF inhibitor therapy and change in physiologic measures in psoriasis	Wu, J. J. et al. (2014)	TNFi	12	1274	209/1274 (16.4%[2])	46.7±13.8[2]	48.5%[2] (618/1274)	/	/	/	6	/	/	FPG (mg/dl; n=35 diabetes patients) 1.5±40.7	/
			MTX		979	163/979 (16.7%[2])	50.9±14.4[2]	52.3%[2] (512/979)							FPG (mg/dl; n=43 diabetes patients) -15.6±54	
			Phototherapy		4309	711/4309 (16.5%[2])	52±15.9[2]	47.1%[2] (2029/4309)							/	

Abbreviation:
ADA = Adalimumab; AE = Adverse Event; CsA = Cyclosporine A; DLQI = Dermatology Life Quality Index; ETA = Etanercept; FPG = Fasting Plasma Glucose; GOL = Golimumab; HbA1c = Haemoglobin A1c; IFX = Infliximab; IS = Insuline Sesitivity measured by HOMA (Homeostasis Modell Assessment); M = Month; MTX = Methotrexate; Ø±SD = Mean ± standard deviation; PASI = Psoriasis Area Severity Index; PASI100/75/50 = 100%/75%/50% improvement in PASI; PI = Plasma Insuline; SAE = Severe Adverse Event; SEC = Secukinumab; TNFi = Tumor Necrosis Factor Inhibitor; UST = Ustekinumab; Y = Year

Appendix

Table 15 Search strategy for the review on psoriasis and diabetes mellitus (Embase via Ovid)

1. exp Psoriasis/ or Psoria*.mp.	34. narrow band uvb.mp.
2. pustulosis palmaris et plantaris.ti,ab.	35. narrow band ultraviolet.mp.
3. (pustulosis and palm and soles).ti,ab.	36. psoralen ultraviolet a.mp.
4. palmoplantar* pustulosis.ti,ab.	37. psoralen uva.mp.
5. 1 or 2 or 3 or 4	38. Laser therap*.mp. or Laser Therapy/
6. Urea/ or Urea*.mp.	39. Ciclospori*.mp. or Cyclosporine/
7. uric acid.mp. or Uric Acid/	40. cyclospor*.mp.
8. salicyl* acid.mp. or Salicylic Acid/	41. fumar*.mp. or exp Fumarates/
9. Calcineu* inhibito*.mp. or Calcineurin Inhibitors/	42. fumaderm.mp.
10. Tacrolimus/ or Pimecrolim*.mp.	43. dimethylfumara*.mp.
11. dithranol*.mp. or Anthralin/	44. fae.ti,ab.
12. Cortisone/ or cortiso*.mp.	45. dmf.ti,ab.
13. Betamethasone/ or Betametha*.mp.	46. exp Methotrexate/ or MTX.mp.
14. mometaso*.mp. or Glucocorticoids/ or Mometasone Furoate/	47. methotrexa*.mp.
15. Retinoids/ or tazarot*.mp.	48. amethopterin.mp.
16. coal tar.mp. or Coal Tar/ 17. vit d3.mp or Cholecalciferol/	49. mexate.mp.
18. calcipotrio*.mp.	50. acitretin.mp. or Acitretin/
19. tacalcito*.mp.	51. Retinoids/
20. Calcitriol/ or calcitrio*.mp.	52. Phosphodiesterase 4 Inhibitors/ or apremilast.mp.
21. phototherap*.mp. or exp Phototherapy/	53. cdp571.mp.
22. PUVA Therapy/ or Photochemotherapy/ or PUVA.mp.	54. (etanercep* or enbrel).mp. or Etanercept/
23. exp Ultraviolet Therapy/ or UV-B therap*.mp.	55. (Infliximab* or remicade).mp. or Infliximab/
24. photodynamic therap*.mp.	56. ustekinumab.mp. or Ustekinumab/
25. photochemotherap*.mp.	57. (briakinumab or ABT-874).mp.
26. light therap*.mp.	58. CNTO 1275.mp.
27. photoradiation therap*.mp.	59. stelara.mp.
28. BBUVB.mp.	60. secukinumab.mp.
29. NBUVB.mp.	61. guselkumab.mp.
30. BB-UVB.mp.	62. adalimumab*.mp. or Adalimumab/
31. NB-UVB.mp.	63. (d2e7 or humira).mp.
32. broad band uvb.mp.	64. exp Antibodies, Monoclonal/
33. broad band ultraviolet.mp.	65. monoclonal antibod*.mp.

65. monoclonal antibod*.mp.

66. exp Interleukin-23/ or exp Interleukin-12/
67. brodalumab.mp.
68. ixekizumab.mp.
69. (tumor necrosis factor-alpha or tumour necrosis factor-alpha).mp.
70. anti tnf.mp.
71. (tumor necrosis factor antibod* or tumour necrosis factor antibod*).mp.
72. (antitumor necrosis factor or antitumour necrosis factor).mp.
73. (anti tumor necrosis factor or anti tumour necrosis factor).mp.
74. (tnf antibod* or tnf alpha antibod*).mp.
75. climate therap*.mp. or Climatotherapy/
76. Psychotherapy/ or psychosocial therap*.mp.
77. exp Tumor Necrosis Factor-alpha/
78. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 79. 5 and 78 80. Diabetes mellitus.mp. or Diabetes mellitus/ 81. Diabetes Mellitus, Type 1/ or Diabetes Mellitus, Type 2/ or diabetes mellitus type 1.mp. 82. DM.ti,ab. 83. (Type 1 diabetes mellitus or type 2 diabetes mellitus).ti,ab. 84. (type 1 DM or type 2 DM).ti,ab. 85. 80 or 81 or 82 or 83 or 84 86. 79 and 85

Table 16 Excluded full-texts for the original review on psoriasis and diabetes mellitus

A. Abdelmaksoud	2019	off-topic
K. Abuabara	2010	off-topic
T. Ahern	2013	off-topic
E. Akasaka	2013	no relevant outcomes
J. Alcantara-Gonzalez	2012	study design
N. Al-Mutairi	2014	double
M. Amy de la Breteque	2017	off-topic
Anonymous	1973	no relevant outcomes
Anonymous	2018	no relevant outcomes
Y. Arakawa	2019	off-topic
A. Armstrong and E. Levi	2017	study design
A. W. Armstrong	2013	no relevant outcomes
D. Arps	2013	study design
F. Augey	2004	study design
R. S. Azfar	2012	off-topic
R. S. Azfar	2012	off-topic
P. Babakinejad	2018	off-topic
P. Balasubramaniam	2004	off-topic
J. Belzunegui	2001	off-topic
I. Ben-Skowronek	2013	off-topic
T. Bhutani	2013	no relevant outcomes
P. B. Bookstaver	2008	study design
P. B. Bookstaver	2008	study design
Y. B. Brauchli	2008	off-topic
E. I. Brokalaki	2012	study design
B. A. Buckingham and C. I. Sandborg	2000	off-topic
S. O. Bulic	2018	study design
S. Burillo-Martinez	2016	off-topic
R. E. Burns and F. W. Whitehouse	1973	off-topic
A. Campanati	2013	off topic
T. M. Capusan	2018	study design

A. Carija	2019	study design
J. C. Cather	2017	no relevant outcomes
H. H. Chen	2017	off-topic
Y. J. Chen	2012	no relevant outcomes
D. Cheung and M. Bryer-Ash	2009	study design
Y. Y. Chin	2013	no relevant outcomes
C. H. Chu and C. Davis	2017	study design
L. Costa	2014	off-topic
W. H. Crown	2004	no relevant outcomes
M. Daghem and D. Newby	2018	off-topic
E. Dantes	2018	study design
C. De Simone	2010	study design
T. Dehpouri	2019	off-topic
K. Eisendle and P. Fritsch	2005	study design
J. El Khalifa	2013	study design
H. Escande	2013	no relevant outcome
M. Esposito	2008	study design
M. Esposito	2019	off-topic
R. Eswaran	2018	study design
J. Fleming and S. Bashir	2012	study design
S. Foster	2015	no relevant outcomes
P. Freire	2016	off-topic
S. Gerdes	2008	no relevant outcomes
P. Gisondi	2013	off-topic
P. Gisondi	2013	off-topic
P. Gisondi	2011	no relevant outcomes
P. Gisondi	2013	no relevant outcomes
P. Gisondi	2008	off-topic
P. Gisondi	2019	off-topic
A. B. Gottlieb	2017	off-topic
C. E. M. Griffiths	2017	off-topic
E. Guevara	2015	study design

W. Gulliver and S. Gulliver	2018	study design
W. P. Gulliver	2016	off-topic
R. Gupta	2014	no relevant outcomes
K. A. Haitz and R. E. Kalb	2007	off-topic
K. M. Halprin	1982	off-topic
P. Helliwell	2018	off-topic
C. Herz	2017	off-topic
R. Hillson	2019	off-topic
Y. Hongo	2017	study design
Y. Hongo	2017	study design
W. D. Hoover	2007	study design
W. Hussain	2008	study design
S. Imafuku	2016	off-topic
S. Imafuku	2016	off-topic
I. Y. Iskandar	2015	no relevant outcomes
T. Ito	2018	off-topic
A. Jacobi	2013	no relevant outcomes
E. C. Johns and R. M. Reynolds	2019	study design
R. Kalb	2015	double
R. E. Kalb	2015	double
A. Kimball	2009	double
A. B. Kimball	2014	off-topic
A. B. Kimball	2008	no relevant outcomes
B. Kirby	2013	double
M. Kobayashi	2018	study design
K. Kofoed	2012	off-topic
M. Kojanova	2017	no relevant outcomes
A. J. Krentz and P. S. Friedmann	2006	off-topic
J. Lachaine	2011	off-topic
C. P. Lee and B. Bt Khalid	2015	off-topic
J. J. Lee	2011	study design
M. S. Lee	2014	off-topic

M. S. Lee	2014	off-topic
O. Leonard	2012	study design (n < 100)
C. Leonardi	2015	no relevant outcomes
C. Leonardi	2019	off-topic
C. H. Loo	2015	no relevant outcomes
S. K. F. Loo	2010	study design
A. Lopez-Ferrer	2013	no relevant outcome
M. T. A. Loste	2019	off-topic
M. Lynch	2017	study design
M. Lynch	2017	off-topic
T. Mabuchi	2013	off-topic
A. W. L. Macewen	2011	study design
A. D. Maderal	2018	study design
D. A. Malatjalian	1996	no relevant outcome
V. Manfreda	2019	off-topic
P. Mansueto	2011	study design
P. Mansueto	2012	study design
S. Mantravadi	2018	study design
M. Marra	2007	off-topic
C. E. Martinez	2017	study design
C. E. Martinez	2017	study design
E. Martinez-Abundis	2007	off-topic
C. Martinez-Peinado	2016	study design
T. A. Maurer	1994	study design
A. Menter	2010	double
A. Menter	2017	no relevant outcome
A. Michalska-Bankowska	2019	study design (n < 100)
A. Michalska-Bankowska	2018	no relevant outcomes
A. Michalska-Bankowska	2019	off-topic
G. H. Millward-Sadler and T. J. Ryan	1974	study design
R. Mittal	2009	off-topic
H. Miyachi	2017	off-topic

H. Miyachi	2017	off-topic
A. Morita	2018	off-topic
U. Mrowietz	2009	no relevant outcomes
N. Mumoli	2014	study design
T. Nakamura-Wakatsuki and T. Yamamoto	2014	off-topic
T. Narang	2012	study design (n < 100)
T. Nishioka	2012	off-topic
D. Norris	2017	off-topic
D. Norris	2017	double
R. O'Connor	2015	off-topic
E. Ojaimi	2012	off-topic
Y. Okubo	2019	off-topic
E. Papadavid	2010	off-topic
K. Papp	2018	off-topic
S. Parisi	2019	off-topic
L. Patricia	2014	no relevant outcomes
P. Patro and V. Agarwal	2018	off-topic
C. M. Peinado	2016	study design
A. Perez-Plaza	2017	off-topic
E. C. Pfeifer	2017	study design
E. C. Pfeifer	2017	study design
S. Piel and J. Dissemond	2008	study design
T. Pina Murcia	2014	off topic
T. Pina	2015	off-topic
T. Pina	2015	off-topic
M. Pirowska	2019	off-topic
L. Puig	2010	no relevant outcomes
L. Puig	2015	off-topic
J. Qiang	2016	no relevant outcomes
E. Rallis and V. Anyfantakis	2008	study design
B. Rao	2015	study design

K. Reich	2013	no relevant outcomes
K. Reich	2013	no relevant outcomes
P. Rimbaud and J. Meynadier	1968	off-topic
C. Riquelme-Mc Loughlin	2018	study design
H. H. Roenigk Jr	1971	off-topic
C. C. Romero	2010	no relevant outcomes
R. M. Romero-Jimenez	2018	no relevant outcome
P. Rosenberg	2007	study design (n < 100)
L. S. Sauter	1971	off-topic
L. Selvarajah	2016	study design
A. Shahbaz	2017	no relevant outcomes
A. Shahbaz	2017	no relevant outcomes
J. Shapiro	2007	off-topic
V. Singh	2019	off-topic
V. M. Smith and V. Goulden	2014	study design
D. H. Solomon	2011	off-topic
B. Strober	2017	off-topic (no DM)
B. Strober	2018	no relevant outcomes
J. Takeshita	2015	no relevant outcomes
M. Tokuyama	2019	off-topic
H. Trattner	2017	off-topic
H. Trattner	2017	no relevant outcomes
S. Troyanova-Slavkova and L. Kowalzick	2019	study design
E. Tula	2017	double
Y. Umezawa	2015	study design
F. Ursini	2010	study design
D. A. Vekic and J. W. Frew	2018	off-topic
R. Vender	2013	off-topic
C. G. Wambier	2009	study design
K. C. Wei and P. C. Lai	2015	off-topic
J. Wu	2012	double

J. J. Wu and K. Y. T. Poon	2013	no relevant outcome
J. J. Wu and T. F. Tsai	2008	study design
K. Xu	2010	study design
T. Yamaguchi	2017	off-topic
T. Yamaguchi	2017	off-topic
Z. Yao	2018	off-topic
B. Yazdani-Biuki	2006	off-topic
C. M. Yeo	2009	no relevant outcomes
P. D. Yesudian	2016	no relevant outcomes
Y. Zhu	2009	no relevant outcomes
L. Zisova	2012	no relevant outcomes

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