

# Comorbid Psoriasis and Metabolic Syndrome: Clinical Implications and Optimal Management

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**Purpose:** To review the literature on guidance on the follow-up of psoriasis and its comorbidities and to provide practical recommendations.

**Patients and Methods:** A PubMed search was conducted using MeSH terms and free text keywords related to “psoriasis”, “obesity”, “hypertension”, “diabetes”, “dyslipidemia”, “metabolic syndrome” and “Psoriatic arthritis”. The search was conducted between September 2021 and January 2022. References of selected articles were scanned to identify additional articles.

**Results:** Recommendations on the follow-up of hypertension, obesity, dyslipidemia, type 2 diabetes, metabolic syndrome, psoriatic arthritis, non-alcoholic fatty liver disease and inflammatory bowel disease in psoriasis patients were extracted from the included articles. These data are presented in summary tables for both adults and children. A practical and feasible approach for each comorbidity is discussed.

**Conclusion:** Awareness among dermatologists for relevant psoriasis-associated comorbidities is crucial. The dermatologist should function as gatekeeper and screen for comorbidities, in order to make timely referrals when indicated.

**Keywords:** psoriasis, comorbidities, metabolic syndrome, psoriatic arthritis, screening, atherosclerosis, liver disease, cardiovascular disease

## Introduction

Chronic plaque psoriasis is an inflammatory skin disease affecting 2% to 3% of the general adult population.<sup>1</sup> Psoriasis symptoms can occur at any age, however there are 2 peaks of onset: the first at age 20 to 30 years and the second at age 50 to 60 years.<sup>2</sup> Together with psoriatic arthritis, it comprises the psoriatic disease spectrum. However, it is a multimorbid condition: comorbidities including diabetes, dyslipidemia, arterial hypertension or metabolic associated fatty liver disease (MAFLD) (formerly known as nonalcoholic fatty liver disease (NAFLD)) have been described to be thoroughly associated with psoriatic disease. Since 1981, several morbidities (abdominal obesity, high triglyceride level, low HDL, high blood pressure, high fasting blood sugar) have been clustered into the concept of Metabolic Syndrome (MetS).<sup>3</sup> The prevalence of MetS in psoriasis patients ranges from 20% to 50%, this is up to three times higher compared to the general population.<sup>4-6</sup> Furthermore, obesity, dyslipidemia, and diabetes are associated with greater psoriasis disease severity and reduced response to treatment.<sup>7-9</sup> The pathogenesis of MetS is multifactorial, with a combination of nutritional, environmental, and genetic factors. Chronic low-grade inflammation together with visceral adipose tissue, adipocyte dysfunction, and insulin resistance plays a major role in the progression of the syndrome by impairing lipid and glucose homeostasis in insulin-sensitive tissues, such as the liver, muscle, and adipocytes.<sup>10</sup> To date, the exact mechanism that links MetS to psoriasis is not fully understood.

More than one decade ago, the concept of the psoriatic march has been proposed.<sup>11</sup> In this concept, it was suggested that psoriatic inflammatory cells predispose to cardiovascular disease, hence defining psoriasis as an independent cardiovascular risk factor.<sup>12,13</sup>

In recent years, the understanding of the underlying pathophysiology of psoriasis has increased exponentially, and IL-23 has been identified as the culprit for the pathogenic Th17-cells, which lead to the cutaneous psoriatic changes.<sup>14</sup> These

insights have subsequently led to multiple new treatment targets. Of interest, IL-17A, a cytokine released by TH17 cells, appears to play a central role in the pathophysiology/development of atherosclerotic plaques.<sup>15</sup> Furthermore, as in MAFLD, the IL23-Th17 axis has been identified as a crucial immunological pathway.<sup>16,17</sup> In addition, diabetes mellitus (DM), hypertension, dyslipidemia, obesity and insulin resistance share an upregulation of inflammatory cytokines like IFN- $\gamma$ , IL-23 and TNF- $\alpha$ .<sup>18</sup>

Dermatologists should play an important role in the early recognition and assessment of psoriasis associated comorbidities. Reassuringly, a recent survey among dermatologists in Belgium showed high awareness of these comorbidities, which is a prerequisite for screening.<sup>19</sup>

In this review, we present the existing literature on recommendations for the screening and prevention of psoriasis-associated comorbidities in patients of all ages. We aim to provide a practical overview and recommendation for implementation in daily practice.

## Materials and Methods

A PubMed search was conducted using MeSH terms and free text keywords related to “psoriasis”, “psoriatic arthritis”, “obesity”, “hypertension”, “diabetes”, “dyslipidemia”, and “metabolic syndrome”. Searches were limited to publications in the English language. After screening the title and abstract, relevant articles were included for full text assessment with no time frame. The search was conducted between September 2021 and January 2022. References of selected articles were scanned to identify additional articles.

## Results

### Arterial Hypertension/Cardiovascular Disease

#### Adults

A strong association between psoriasis and cardiovascular disease has been found in multiple studies.<sup>16,18</sup> Arterial hypertension (aHT) is a leading risk factor for cardiovascular morbidity and mortality.<sup>20</sup> aHT is defined as a blood pressure (BP) above 130/80 mmHg according to the ACC/AHA guidelines and 140/90 mmHg according to the ESC/ESH, NICE, and ISH guidelines.<sup>21</sup> Given that psoriasis patients have an inherently increased risk of developing aHT, dermatologists need to give special consideration to this comorbidity when following up and treating psoriasis patients.<sup>16</sup>

Current evidence does not support restrictions on the use of antihypertensive medication in patients with psoriasis.<sup>22</sup> However, it has been reported that long-term regular use of  $\beta$ -blockers may increase the risk of developing psoriasis.<sup>23</sup> Physicians should be aware of the potential for cyclosporine to induce hypertension, which should be treated preferably with amlodipine.<sup>22</sup>

Psoriasis cohort studies have shown a significantly lower risk of myocardial infarction in patients taking TNF inhibitors, oral agents (like methotrexate) and phototherapy in comparison to control groups treated with topical agents.<sup>24,25</sup> Table 1 shows some of the potential side effects of anti-psoriatic drugs on cardiovascular risk factors. We recommend regular

**Table 1** Potential Side Effects of Anti-Psoriatic Drugs on Cardiovascular Risk Factors

Drug	Toxicity/Benefit <sup>16</sup>
Acitretin	Coronary heart disease, dyslipidemia
Corticosteroids	Dyslipidemia, hyperglycemia, hypertension
Cyclosporine	Hypertension, hypercholesterolemia, dyslipidemia
Methotrexate	Decreases vascular risk

**Notes:** Adapted from Kakarala CL, Hassan M, Belavadi R, et al. Beyond the skin plaques: psoriasis and its cardiovascular comorbidities. *Cureus*. 2021;13(11):e19679. Copyright© 2021, Kakarala et al. This is an open access article distributed under the terms of the Creative Commons Attribution License.<sup>16</sup>

monitoring of the blood pressure as part of the dermatological follow-up of the psoriasis patient. Furthermore, we emphasize the importance of patient education about psoriasis-related cardiovascular risks and promoting a healthy lifestyle (smoking cessation, exercise and dietary changes are encouraged to achieve and maintain a normal BMI).<sup>26</sup>

### Children

Only one retrospective study supports the association between pediatric psoriasis and hypertension.<sup>27</sup> The American Academy of Pediatrics (AAP) expert panel guidelines recommend annual screening starting at the age of three. They state that primary prevention is best practiced at an early age.<sup>28</sup> When aHT is recorded or multiple risk factors are present for cardiovascular disease (CVD) (eg obesity, family history, DM, ...), a referral to the general practitioner (GP) or cardiologist is indicated.

## Dyslipidemia

### Adults

Dyslipidemia refers to the persistent elevation of serum cholesterol and/or triglycerides. Keye et al found in a case-control study that psoriasis patients hold a higher risk of dyslipidemia than controls without psoriasis.<sup>29</sup> In 2018, the American Heart Association and the American College of Cardiology categorized psoriasis as an atherosclerotic CVD risk-enhancing condition, favouring early intervention with a statin.<sup>30</sup> Elmetts et al recommend to screen patients with moderate-to-severe psoriasis periodically with fasting lipid tests (fasting total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides).<sup>22</sup> He also states that non-fasting screening is preferable to not screening at all. Patients with elevated fasting triglycerides or low-density lipoprotein cholesterol should be referred to their GP for further management.<sup>31</sup>

We recommend annual monitoring of non-fasting lipid panel. We consider more frequent screening useful in patients treated with lipid-altering medication, or with uncontrolled moderate-to-severe psoriasis.

### Children

According to international guidelines, having psoriasis does not warrant additional lipid screening beyond the general age-related recommendations for all children. Of interest, both the National Heart, Lung and Blood Institute and the AAP support universal screening for high blood lipids in all children, regardless of risk factors, between the ages of 9 and 11 years old and again at 17 and 21 years old.<sup>28</sup>

Outside of the specified age ranges, screening is also recommended in the presence of any additional cardiovascular risk factors (family history of cardiovascular disease (CVD), hypertension, smoking, obesity, HDL <40 mg/dL, Type 1 or 2 DM, renal disease, nephrotic syndrome, post-orthotopic heart transplant, Kawasaki disease with current or regressed aneurysms, HIV, chronic inflammatory disease).<sup>32</sup> Healthcare providers should be mindful of LDL-cholesterol variations in teens between 12 and 17 years old.<sup>33</sup>

We recommend annual monitoring of non-fasting lipid panel in children or adolescents with uncontrolled psoriasis. We consider more frequent screening in patients treated with lipid-altering medication.

## Obesity

### Adults

Similar to psoriasis, an upregulation of Th17 and Th1 helper cells has been shown in patients with obesity. Therefore, the co-occurring of both conditions could exacerbate each other.<sup>34</sup> For recommendations on obesity management, we refer to the MetS section.

### Children

Boccardi et al found an association between new-onset psoriasis and pre-existing overweight, especially in boys and children under the age of 10.<sup>35</sup> Children with obesity are more likely to have severe psoriasis compared to normal-weight psoriatic children.<sup>36</sup> Joint American Academy of Dermatology-National Psoriasis Foundation guidelines state that these children should be routinely assessed for obesity by either their dermatologist or primary care provider.<sup>37</sup>

## Metabolic Syndrome

### Adults

Metabolic syndrome (MetS) is a descriptive term for the co-occurrence (of at least three) of obesity, hypertension, hypertriglyceridemia, hypercholesterolemia and insulin resistance in an individual. MetS is associated with increased cardiovascular morbidity and mortality.<sup>38</sup> The prevalence of MetS is up to three times higher in patients with psoriasis compared to the general population, and this may impact the treatment of choice in certain patients.<sup>4–6</sup> For example, apremilast has been associated with weight loss, whereas etanercept and infliximab have been linked to weight gain.<sup>31</sup>

Furthermore, attention for possible drug interactions between MetS treatment and psoriasis treatment is required: the combination of cyclosporine and statins has a higher risk of rhabdomyolysis than statins alone. Additionally, awareness of drug-induced comorbidities (eg cyclosporine-induced hypertension and dyslipidemia) is warranted.<sup>39</sup>

In recent studies, the use of pioglitazone has been recommended in patients with metabolic syndrome because of its beneficial effect on weight and glucose levels. There is limited evidence that pioglitazone may also have a positive effect on psoriasis.<sup>40</sup>

The AAD guidelines encourage an annual measurement of the waist circumference by the dermatologist or primary care provider in patients with moderate-to-severe psoriasis. Additionally, these guidelines state that blood pressure measurement, fasting serum glucose, hemoglobin A1c and fasting lipid levels should be performed by the GP annually.<sup>31</sup> We refer to screening recommendations on the separate components of MetS. In addition, we promote educating psoriasis patients about the increased risk of MetS, its association with cardiovascular disease and preventive measures.

### Children

In recent years, the incidence of metabolic syndrome in children has increased significantly.<sup>41</sup>

Similar to adults with psoriasis, studies have suggested an association between the incidence of psoriasis and obesity in children. This association is even more significant in children with severe psoriasis, including adjustment for previous or active treatment with systemic immunosuppressants (including systemic corticosteroids).<sup>42</sup>

## Type 2 Diabetes

### Adults

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia induced by defects in insulin production or action. Chronic hyperglycemia is associated with long-term organ damage.<sup>43</sup> Since many diabetes-related complications can be prevented, early diagnosis and treatment are essential.

Type 2 diabetes was reported to be significantly more prevalent in a cohort with mild-moderate psoriasis (37.4%) versus a healthy control group (16%; aOR 3.137, 95% CI 2.675–3.68,  $P = 0.00001$ ). This association became even more apparent in patients with severe psoriasis (41%) compared with healthy controls (16%; OR 3.77, 95% CI 2.60–5.47,  $P = 0.00001$ ).<sup>44</sup>

These data suggest that severe psoriasis should be considered as an important risk factor for developing type 2 diabetes. We recommend annual screening for abnormal blood sugar (with HbA1c levels and fasting glucose) in all patients with moderate-to-severe psoriasis. Consider more frequent testing in patients with uncontrolled moderate-to-severe psoriasis. Patients with psoriasis who develop diabetes mellitus should be referred to their general practitioner for further assessment, lifestyle advice, treatment and follow-up.<sup>22</sup>

### Children

Similarly, the risk of developing insulin resistance in children with psoriasis is increased in comparison with unaffected children. Two studies by Augustin et al found that the prevalence of insulin resistance in children with psoriasis is twice as high compared to a normal population.<sup>2,45</sup> According to the American Diabetes Association, regular screening by measuring fasting serum glucose is advised every 3 years starting at 12 years in high-risk patients or 10 years in all obese pediatric patients. Risk factors (not including psoriasis) can be seen in [Table 2](#).<sup>33,37,46</sup> Since an association has been found between insulin resistance and psoriasis in children, it was suggested that psoriasis could be considered as an independent risk factor for developing type 2 diabetes mellitus.

**Table 2** Risk Factors for Developing Type 2 Diabetes in Children (Left Panel) and Adults (Right Panel)

Risk Factors for Type 2 Diabetes in Children <sup>33</sup>	Risk Factors for Type 2 Diabetes in Adults <sup>22</sup>
Body mass index $\geq$ 85th percentile	Body mass index $\geq$ 25 AND
Family history of type 2 diabetes in a first-degree or second-degree relative	Family history of type 2 diabetes in a first-degree relative
Native American, African American, Latino, Asian American, Pacific Islander race/ethnicity	Native American, African American, Latino, Asian American, Pacific Islander race/ethnicity
	Physical inactivity
Conditions associated with insulin resistance: polycystic ovary syndrome, acanthosis nigricans, hypertension, dyslipidemia, small-for-gestational-age birth weight	Conditions associated with insulin resistance: polycystic ovary syndrome, acanthosis nigricans, hypertension, dyslipidemia, small-for-gestational-age birth weight
Maternal history of diabetes or gestational diabetes during the child's gestation	Maternal history of diabetes or gestational diabetes during the child's gestation
	Severe obesity, hypertension, dyslipidemia, history of CVD

**Notes:** Reproduced from Elmetts CA, Leonardi CL, Davis DMR, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities. *J Am Acad Dermatol.* 2019;80(4):1073–1113. Copyright 2019, with permission from Elsevier.<sup>22</sup> Data from Osier et al.<sup>33</sup>

**Abbreviation:** CVD, cardiovascular disease.

## Psoriatic Arthritis

### Adults

Psoriatic arthritis (PsA) is one of the most common comorbidities in psoriasis patients. It is classified as a seronegative spondyloarthritis, with predominantly peripheral involvement. Symptoms of arthritis, enthesitis or dactylitis predominate the clinical presentation. Alinaghi et al reported a pooled PsA prevalence of 19.7% in patients with psoriasis. In adults, the prevalence of PsA was 21.6%, by contrast the prevalence was much lower in children and/or adolescents with psoriasis at 3.3%. Interestingly, there seems to be a correlation between disease severity and risk of PsA: the prevalence of PsA was reported to be significantly higher in the group with moderate-to-severe psoriasis compared to the group with mild psoriasis (24.6% vs 15.8%).<sup>47</sup>

Adult patients tend to develop cutaneous manifestations of psoriasis first, on average 8.5 years before arthritis symptoms.<sup>33</sup>

Dermatologists should conduct a thorough anamnesis and physical examination to distinguish PsA from degenerative joint disease (illustrated in [Table 3](#)). Imaging and laboratory tests to evaluate for signs of inflammation (erythrocyte sedimentation rate, C-reactive protein) can be helpful in distinguishing these 2 conditions. However, such testing is neither sensitive nor specific for PsA. When the diagnosis PsA is suspected, referral to a rheumatologist is warranted.<sup>31</sup>

**Table 3** Comparison of Inflammatory and Degenerative Pain Pattern

Inflammatory Arthritis	Degenerative/Osteoarthritis
Stiffness after a period of inactivity (30–60 min)	No significant period of stiffness after inactivity
Redness, warmth, swelling	Worsens with activity, end of the day
Subacute-chronic duration	Specific joint patterns (base of thumb)
Systemic symptoms (fatigue, uveitis etc.)	
Response to anti-inflammatory treatment	
Family history	

## Children

PsA can occur at any age, but the onset in children is more common between 2 to 3 years and 9 to 12 years of age. In contrast to adults, 80% of children with PsA develop arthritis 2 to 3 years prior to cutaneous manifestations.<sup>48</sup> In younger children, especially girls, PsA presents with an oligoarticular disease or dactylitis, while in older children, especially boys, it presents with enthesitis and axial joint involvement.<sup>33,49</sup> Those patients typically present with inflammatory joint pain, joint swelling and morning stiffness. Osier et al suggests that dermatologists question these symptoms in children and conduct a thorough clinical examination with attention to signs of dactylitis, enthesitis, joint swelling, and decreased axial mobility.<sup>33</sup> We recommend educating patients and parents about this comorbidity.

## Non-Alcoholic Fatty Liver Disease

### Adults

Non-Alcoholic Fatty Liver Disease (NAFLD) is defined by the presence of steatosis in 5% of hepatocytes or more. It is strongly associated with metabolic risk factors such as obesity or type 2 diabetes without a history of excessive alcohol consumption ( $\geq 30$  g per day for men and  $\geq 20$  g per day for women) or chronic liver disease. In time, NAFLD can progress to non-alcoholic steatohepatitis (NASH). Untreated, NASH can evolve to irreversible scarring of the liver tissue (cirrhosis).<sup>50</sup> The prevalence of NAFLD is estimated at a 25% in the general population and was seen 1.5 to 3 times more in psoriasis patients.<sup>51,52</sup>

While the exact underlying mechanisms are yet to be fully elucidated, both psoriasis and NAFLD are strongly associated with low-grade, chronic inflammation, insulin resistance and increased levels of oxidative stress.<sup>53–55</sup> When NAFLD is suspected, it is important to assess risk factors (Table 4) and to check for advanced fibrosis or cirrhosis. Elastography is a frequently used non-invasive measurement of liver fibrosis. Other non-invasive scores to determine if NAFLD is present are the NAFLD score (<http://naflscore.com>) and the FIB-4 index. The FIB-4 index uses a formula (<https://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4>) based on a combination of age, platelets, AST and ALT.<sup>52</sup>

When NAFLD is suspected, referral to a hepatologist for confirmation of the diagnosis is recommended. Patients without advanced fibrosis should be monitored with biochemistry and repeat elastography every 3 to 5 years.<sup>56</sup> Since ALT can remain normal for a long time in NAFLD, a degree of caution remains necessary.

Concerns about the toxicity of systemic medications (eg methotrexate or cyclosporine) have been raised: we recommend additional screening for NAFLD in psoriasis patients with risk factors.<sup>54,57</sup>

### Children

NAFLD is one of the most common chronic liver diseases in children and adolescents: Anderson et al reported a prevalence of 7.6% in the overall pediatric population, and 34.2% in obese children.<sup>58,59</sup> In a retrospective cohort study by Tollefson et al the rate of NAFLD in children with psoriasis was significantly higher compared to a healthy control group (HR, 1.76; 95% CI, 1.16–2.65).<sup>60</sup>

Osier et al advises ALT measurement as a screening tool for NAFLD in all overweight children with additional risk factors for insulin resistance (Table 2), starting at the age of 9–11 years. When initial assessment is normal, ALT measurement should be repeated every 2–3 years. Earlier reassessment may be needed if new risk factors develop. The upper limit of ALT is 22 U/L in girls and 25 U/L in boys.<sup>33</sup>

**Table 4** Risk Factors NAFLD<sup>56</sup>

Obesity
Type 2 diabetes, Insulin resistance
Dyslipidemia
Hypertension
Hypopituitarism

**Note:** Data from Powell et al.<sup>56</sup>

**Table 5** Comorbidity Screening Tool for Adult Psoriasis Patients

Comorbidity	Recommendations from the Literature	Practical Recommendation
Cardiovascular disease including hypertension	<ul style="list-style-type: none"> <li>Screen psoriasis patients with a family history of cardiovascular events<sup>63</sup></li> <li>Screening intervals may vary between patients on the basis of their individual risk factors and overall health<sup>22</sup></li> <li>Current evidence does not support restrictions on antihypertensive medications in patients with psoriasis<sup>31</sup></li> </ul>	<ul style="list-style-type: none"> <li>Measure blood pressure every visit</li> <li>Educate patient on the reason why you follow up on blood pressure</li> </ul>
Dyslipidemia	<ul style="list-style-type: none"> <li>Moderate to severe psoriasis patients are recommended to undergo periodic screening with lipid tests (eg fasting total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides)<sup>31</sup></li> </ul>	<ul style="list-style-type: none"> <li>Screen for blood lipids (Cholesterol, Triglycerides) 1/year, no fasting required<sup>64</sup></li> <li>Consider more frequent testing in uncontrolled psoriasis patients</li> <li>Consider fasting blood test when history of disturbed blood lipids</li> </ul>
Obesity	<ul style="list-style-type: none"> <li>BMI and waist circumference annually with moderate to severe psoriasis<sup>31</sup></li> <li>To encourage the measurement of blood pressure, waist, circumference, fasting blood glucose, hemoglobin A1C, and fasting lipid levels with their GP when indicated</li> </ul>	<ul style="list-style-type: none"> <li>Check weight/BMI every visit</li> <li>Encourage physical activities</li> </ul>
Type 2 diabetes	<ul style="list-style-type: none"> <li>BSA greater than 10%, should be targeted for diabetes prevention<sup>65</sup></li> <li>Regular monitoring of fasting blood glucose and/or hemoglobin A1C levels in patients with moderate to severe psoriasis is recommended<sup>31</sup></li> </ul>	<ul style="list-style-type: none"> <li>Screen for fasting glycemia and/or HbA1C 1/year</li> <li>Consider more frequent testing in uncontrolled psoriasis patients</li> </ul>
Metabolic syndrome	<ul style="list-style-type: none"> <li>Inform about risk and encourage to go to GP for the measurement of blood pressure, waist circumference, fasting blood glucose, hemoglobin A1C, and fasting lipid levels when indicated<sup>31</sup></li> <li>BMI and waist circumference annually in patients with moderate to severe psoriasis<sup>31</sup></li> </ul>	<ul style="list-style-type: none"> <li>Educate psoriasis patients about the increased risk of MetS, its association with cardiovascular disease and preventive measurements.</li> </ul>
Psoriatic arthritis	<ul style="list-style-type: none"> <li>Inflammation, RX, clinical examination and questionnaires<sup>22</sup></li> <li>Each visit asking for joint pain, stiffness and swelling<sup>31</sup></li> <li>Asses smoking (-cessation) status and BMI<sup>66</sup></li> </ul>	<ul style="list-style-type: none"> <li>Assess joint involvement during every visit</li> <li>Educate patients about associated rheumatological disease</li> </ul>
Nonalcoholic fatty liver disease (NAFLD)	<ul style="list-style-type: none"> <li>Abdominal ultrasonography, BMI, AST, ALT, glucose, lipids, blood pressure, low platelets.</li> <li>NAFLD fibrosis score (age, BMI, IFG and Diabetes, AST-to-ALT ratio, platelets and albumin) or FIB-4 score (age, AST, ALT and platelet)<sup>56</sup> They are simple to use and low scores have a good negative prediction for liver fibrosis</li> <li>retesting 3–5 years after initial assessment has been proposed</li> </ul>	<ul style="list-style-type: none"> <li>Multi-disciplinary approach with hepatologist</li> </ul>
IBD	<ul style="list-style-type: none"> <li>Patients should be informed of this relationship by their dermatologist; attention should be paid to signs and symptoms of bowel disease that would warrant further evaluation by the patient's primary care provider or gastroenterologist<sup>22</sup></li> </ul>	<ul style="list-style-type: none"> <li>Educate psoriasis patients about the increased risk of IBD</li> <li>Determine fecal calprotectin when Crohn's disease is suspected</li> </ul>

**Abbreviations:** BMI, body mass index; GP, general practitioner; MetS, metabolic syndrome; IFG, impaired fasting glycemia; ALT, alanine-amino-transferase; AST, aspartate-amino-transferase; IBD, inflammatory bowel disease.

## Inflammatory Bowel Disease

Patients with psoriasis have a higher risk of inflammatory bowel disease (IBD). Identified risk factors are onset of psoriasis at young age, low BMI, lower intestinal symptoms and smoking.<sup>61</sup> Patient education on this comorbidity is

warranted and anamnesis should target IBD.<sup>22</sup> For pediatric patients, a referral to a pediatrician with expertise in the field is advised.<sup>37</sup>

## Discussion

Psoriasis is a chronic inflammatory skin disease that manifests in genetically predisposed patients.<sup>55</sup> The current pathophysiologic model identifies the IL23-Th17 axis as the predominant immunologic cell-line involved. The high clinical response observed when targeting these immunological mediators seems an *in vivo* confirmation of this pathophysiological model.<sup>14</sup>

More than a decade ago the concept of the psoriatic march was introduced, referring to the clinical observation that psoriatic disease is often accompanied by metabolic diseases like diabetes mellitus, hypertension, dyslipidemia, obesity, insulin resistance and NAFLD.<sup>11</sup> Ultimately, these comorbidities lead to an increased risk of atherosclerosis and

**Table 6** Comorbidity Screening Tool for Children and Adolescents with Psoriasis

Comorbidity	Recommendations from the Literature	Practical Recommendation
Cardiovascular disease including hypertension	<ul style="list-style-type: none"> <li>Starting at 3 years of age, using age, sex, and height reference charts<sup>33</sup></li> <li>Starting at 3 years, yearly by their primary care provider<sup>37</sup></li> </ul>	<ul style="list-style-type: none"> <li>Measure blood pressure every visit</li> <li>Report high blood pressure to GP</li> <li>Encourage physical activities and weight reduction in first line</li> </ul>
Dyslipidemia	<ul style="list-style-type: none"> <li>Universal lipid screening should be performed during the following 2 age ranges: 9 to 11 years old and 17 to 21 years old<sup>33</sup></li> <li>Only screening if additional risk factor Family history of cardiovascular disease, hypertension, smoking, obesity, HDL &lt;40 mg/dL, Type 1 or 2 diabetes mellitus, renal disease, nephrotic syndrome, postorthotopic heart transplant, Kawasaki disease with current or regressed aneurysms, HIV, chronic inflammatory disease)<sup>33</sup></li> </ul>	<ul style="list-style-type: none"> <li>Consider testing in uncontrolled psoriasis patients</li> <li>Screen prior to initiation of (and during treatment with) blood lipid altering medication</li> </ul>
Obesity	<ul style="list-style-type: none"> <li>BMI as of the age of 2, yearly<sup>33</sup></li> </ul>	<ul style="list-style-type: none"> <li>Check weight/BMI every visit</li> <li>Encourage physical activities</li> </ul>
Type 2 Diabetes	<ul style="list-style-type: none"> <li>Fasting serum glucose from 10 years/year of onset puberty every 3 years if patient has obesity<sup>33</sup></li> </ul>	<ul style="list-style-type: none"> <li>Consider testing in uncontrolled psoriasis patients</li> </ul>
Metabolic syndrome	<ul style="list-style-type: none"> <li>Assessment among children and adolescents has not been as clear</li> <li>Central obesity, high blood pressure (Systolic or diastolic BP <math>\geq</math> 90% for age, sex, height, TG <math>\geq</math> 110 mg/dL, HDL <math>\leq</math> 40 mg/dL, Glucose <math>\geq</math> 100 mg/dL or known T2DM<sup>41</sup></li> </ul>	<ul style="list-style-type: none"> <li>See recommendations for dyslipidemia, obesity, type 2 diabetes</li> </ul>
Psoriatic arthritis	<ul style="list-style-type: none"> <li>Medical history and physical examination,<sup>33</sup> every check up</li> </ul>	<ul style="list-style-type: none"> <li>Assess joint involvement during every visit</li> <li>Educate psoriasis patients and parents about associated rheumatological disease</li> </ul>
Nonalcoholic fatty liver disease (NAFLD)	<ul style="list-style-type: none"> <li>All children who are overweight with additional risk factors (central adiposity, insulin resistance prediabetes or diabetes, dyslipidemia, obstructive sleep apnea or family history of NAFLD/ NASH) should be screened with ALT measurement starting at 9 to 11 years of age.<sup>33</sup></li> </ul>	<ul style="list-style-type: none"> <li>To our knowledge, there is currently no evidence supporting screening of patients with psoriasis with normal BMI</li> </ul>
IBD	<ul style="list-style-type: none"> <li>For patients who have decreased growth rate, unexplained weight loss, or symptoms consistent with inflammatory bowel disease (nausea, vomiting, abdominal pain, chronic diarrhea), formal gastrointestinal evaluation should be considered.<sup>33</sup></li> </ul>	<ul style="list-style-type: none"> <li>Educate psoriasis patients about the increased risk of IBD</li> </ul>

**Abbreviations:** BMI, body mass index; GP, general practitioner; AST, alanine-amino-transferase; IBD, inflammatory bowel disease; HDL, high-density lipoprotein; NASH, nonalcoholic steatohepatitis; BP, blood pressure.



cardiovascular mortality in psoriasis patients.<sup>16</sup> Notably, psoriasis severity was identified as an independent cardiovascular risk factor.

In recent years, the pathophysiological model of atherosclerosis and NAFLD has been elucidated and, interestingly, the IL23-Th17 axis seems to be involved in these processes. It seems feasible that patients with a genetic predisposition to upregulate the IL23-Th17 axis as part of a skin disease, might also display this upregulation in other organs (eg liver, artery wall, ...).<sup>17</sup> Indeed, these insights emphasize the importance of the dermatologist as gatekeeper who consequently screens for these comorbidities and timely refers when necessary. The GP who knows the patients' history as well as patients' family history is well placed to consequently follow-up and treat the comorbidities. This review aims to provide a literature overview on published recommendations, as well as a practical guide on how and when to screen for

**Table 7** Treatment Recommendations for Comorbidities in Adult Psoriasis Patients

Comorbidity	Recommendations from the Literature	Practical Recommendation UZ Leuven
Cardiovascular disease including hypertension	<ul style="list-style-type: none"> <li>Educate patients about the risk<sup>31</sup></li> <li>Physicians should be aware of the potential for cyclosporine to induce hypertension, which should be treated, specifically with amlodipine<sup>31</sup></li> <li>TNF-inh are contra-indicated with patients with New York Heart Association Class III or Class IV congestive heart failure<sup>22</sup></li> <li>ACE-I or ARB +/- CCB/thiazide diuretics<sup>67</sup></li> </ul>	<ul style="list-style-type: none"> <li>Report high blood pressure to GP</li> <li>Refer to GP for initiation of antihypertensive therapy</li> <li>Encourage physical activities and weight reduction</li> </ul>
Dyslipidemia	<ul style="list-style-type: none"> <li>Patients with elevated fasting triglycerides or LDL, cholesterol should be referred to their PCP for further management<sup>31</sup></li> </ul>	<ul style="list-style-type: none"> <li>Encourage physical activities</li> <li>Refer to nutritionist for education and support</li> </ul>
Obesity	<ul style="list-style-type: none"> <li>Stimulate weight loss<sup>31</sup></li> <li>Target waist circumference: 94cm for males; 80cm for females.<sup>68</sup></li> <li>Low energy diet (LED)<sup>69</sup></li> </ul>	<ul style="list-style-type: none"> <li>Aim for realistic weight reduction: - 0.5–1 kg/month</li> <li>Encourage physical activities</li> <li>Refer to nutritionist for education and support</li> </ul>
Type 2 Diabetes	<ul style="list-style-type: none"> <li>Patients who meet criteria for prediabetes or diabetes should be referred to their GP for further assessment and management</li> </ul>	<ul style="list-style-type: none"> <li>Refer to GP for initiation of treatment</li> </ul>
Metabolic syndrome	<ul style="list-style-type: none"> <li>See recommendations for dyslipidemia, obesity, type 2 diabetes</li> </ul>	<ul style="list-style-type: none"> <li>See recommendations for dyslipidemia, obesity, type 2 diabetes</li> </ul>
Psoriatic arthritis	<ul style="list-style-type: none"> <li>Imaging and laboratory tests to evaluate for signs of systemic inflammation (erythrocyte sedimentation rate, C-reactive protein).</li> <li>Full rheumatologic consultation is warranted in challenging cases.<sup>31</sup></li> <li>Ideally, dermatologists initiate treatment with a medication that is effective for both psoriasis and PsA<sup>70</sup></li> </ul>	<ul style="list-style-type: none"> <li>Refer to rheumatologist for rheumatological evaluation and treatment</li> <li>Consider systemic treatment effective for both cutaneous and articular psoriatic disease (eg methotrexate, biologics)</li> <li>Consider avoiding treatments not effective for articular disease (eg cyclosporine and/or acitretin)</li> </ul>
Nonalcoholic fatty liver disease (NAFLD)	<ul style="list-style-type: none"> <li>Weight loss of more than 5–7% reduces hepatic fat content and steatohepatitis, and, for weight loss in excess of 10%, even fibrosis is reduced in a large proportion of people<sup>56</sup></li> <li>A BMI &gt; 30 kg/m<sup>2</sup> increases the risk of NAFLD 9-fold compared to a BMI of 22<sup>71</sup></li> </ul>	<ul style="list-style-type: none"> <li>Weight reduction: -0.5kg/month</li> <li>Refer to nutritionist</li> </ul>
IBD	<ul style="list-style-type: none"> <li>Interleukin 17 inhibitor therapy should be avoided in patients with IBD.<sup>22</sup></li> <li>Referral GE and GP if complaints<sup>22</sup></li> </ul>	<ul style="list-style-type: none"> <li>Refer to GE</li> </ul>

**Abbreviations:** ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CCB, calcium channel blockers; BMI, body mass index; GP, general practitioner; MetS, metabolic syndrome; ALT, alanine-amino-transferase; AST, aspartate-amino-transferase; IBD, inflammatory bowel disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BP, blood pressure; GE, gastroenterologist; PsA, psoriatic arthritis.

**Table 8** Treatment Recommendations for Comorbidities in Children and Adolescents with Psoriasis

Comorbidity	Recommendations from the Literature	Practical Recommendation
Cardiovascular disease including hypertension	<ul style="list-style-type: none"> <li>Education, specialist referral<sup>37</sup></li> </ul>	<ul style="list-style-type: none"> <li>Report high blood pressure to GP/pediatrician</li> <li>Refer to GP/pediatrician for follow-up and/or treatment</li> <li>Encourage physical activities and weight reduction if in place</li> </ul>
Dyslipidemia	<ul style="list-style-type: none"> <li>Education on dyslipidemia, referral to their GP or an endocrinologist for further assessment and management.<sup>37</sup></li> </ul>	<ul style="list-style-type: none"> <li>Encourage physical activities</li> <li>Refer to nutritionist for education and support</li> <li>Refer to GP/pediatrician for follow-up and/or treatment</li> </ul>
Obesity	<ul style="list-style-type: none"> <li>Nutritional counseling, referral pediatric tertiary weight management center is particularly important for those children with a BMI greater than 120% of the 95th percentile.<sup>33</sup></li> </ul>	<ul style="list-style-type: none"> <li>Aim for realistic weight reduction: - 0.5–1 kg/month</li> <li>Encourage physical activities</li> <li>Refer to nutritionist for education and support</li> </ul>
Type 2 Diabetes	<ul style="list-style-type: none"> <li>Pediatric psoriasis patients with insulin resistance or diabetes mellitus should be referred to their primary care provider or an endocrinologist for further assessment and management.<sup>37</sup></li> </ul>	<ul style="list-style-type: none"> <li>Refer to GP/pediatrician for initiation of treatment</li> </ul>
MetS	<ul style="list-style-type: none"> <li>Pediatric patients with psoriasis who have been identified as having cardiovascular risk factors such as obesity, dyslipidemia, diabetes, hypertension, or metabolic syndrome should be referred to appropriate specialists for further evaluation and management.<sup>37</sup></li> </ul>	<ul style="list-style-type: none"> <li>See recommendations for dyslipidemia, obesity, type 2 diabetes</li> </ul>
Psoriatic arthritis	<ul style="list-style-type: none"> <li>Pediatric patients with psoriasis who show signs and symptoms of inflammatory arthritis should be referred to a rheumatologist with pediatric expertise, if available, for further evaluation and management.<sup>37</sup></li> </ul>	<ul style="list-style-type: none"> <li>Refer to rheumatologist for rheumatological evaluation and treatment</li> <li>Consider systemic treatment effective for both cutaneous and articular psoriatic disease (eg methotrexate, biologics)</li> <li>Consider avoiding treatments not effective for articular disease (eg cyclosporine and/or acitretin)</li> </ul>
Nonalcoholic fatty liver disease (NAFLD)	<ul style="list-style-type: none"> <li>Weight loss<sup>72</sup></li> <li>No medication or supplement is recommended for routine treatment of NAFLD<sup>72</sup></li> </ul>	<ul style="list-style-type: none"> <li>Weight reduction: -0.5kg/month</li> <li>Refer to nutritionist</li> </ul>
IBD	<ul style="list-style-type: none"> <li>Pediatric patients with psoriasis who show signs and symptoms of inflammatory bowel disease should be considered for consultation with a gastroenterologist with pediatric expertise, if available, for further evaluation and management.<sup>37</sup></li> </ul>	<ul style="list-style-type: none"> <li>Refer to GE</li> </ul>

**Abbreviations:** GP, general practitioner; BMI, body mass index; GE, gastroenterologist.

comorbidities in patients in daily practice (Tables 5–8). Furthermore, we recommend patient education and prevention, starting at the first symptoms of psoriatic disease.

For follow-up on hypertension and diabetes mellitus, the guidelines are unambiguous in terms of cutoff values. However, suggested screening intervals differ between the guidelines for both adults and children. We recommend to measure blood pressure during every patient visit across all ages since it is non-invasive and might convey an educational message to the patient. We recommend annual screening for diabetes through fasting blood sugar and/or HbA1c. In patients with uncontrolled psoriasis, more frequent monitoring (2x/year) should be considered.

Guidelines for the screening of dyslipidemia are somewhat conflicting when it comes to the fasting state of the patient. Here, we follow the guidelines and statements from Denmark, the United Kingdom, Europe, Canada, Brazil, and the United States which endorse non-fasting lipid profiles (total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol, and triglycerides) for routine screening.<sup>56,57</sup>

We emphasize the importance of educating the patient on the increased risk of PsA and IBD. Appropriate education of patients about the signs and symptoms of PsA and the potential consequences of delaying diagnosis and management is imperative to prevent permanent joint destruction. We recommend a targeted anamnesis every visit. When PsA is suspected, immediate referral to a collaborating rheumatologist is in place. Screening tools that may be of help are the Psoriasis Epidemiology Screening Tool, the Toronto Psoriatic Arthritis Screen, the Psoriatic Arthritis Screening and Evaluation, and the Early Arthritis for Psoriatic Patients questionnaire.<sup>58</sup> When IBD is suspected, we endorse determining fecal calprotectin as first-line screening.

Currently, NAFLD is a diagnosis of exclusion, rather than a diagnosis based on positive inclusive criteria that are present in the patient. In 2020, the term metabolic dysfunction-associated fatty liver disease (MAFLD) was proposed by an expert panel.<sup>62</sup> Even though the latter term is not the currently accepted nomenclature by the American Association for the Study of Liver Diseases or the European Association for the Study of Liver Diseases, we believe this term very accurately identifies the liver disease in the psoriatic population.<sup>49</sup> The dermatologist should be aware that weight reduction and physical activity are the cornerstones for prevention and treatment.

A limitation of this review is the non-systematic approach in literature search and inclusion of articles. Furthermore, some literature on the effect of anti-inflammatory therapy on comorbidities is available, however we deemed it outside the scope of this manuscript.

## Conclusion

The dermatologist is in charge of the psoriasis patient and its comorbidities. A holistic approach of this multimorbid disease is warranted. The dermatologist should function as gatekeeper and screen for comorbidities, in order to make timely referrals when a comorbidity is suspected or diagnosed.

## Abbreviations

AAP, American Academy of Pediatrics; ACE-I, angiotensin-converting enzyme inhibitor; aHT, arterial hypertension; ALT, alanine-amino-transferase; ARB, angiotensin receptor blockers; AST, aspartate-amino-transferase; BMI, body mass index; BP, blood pressure; CCB, calcium channel blockers; CVD, cardiovascular disease; DM, diabetes mellitus; GE, gastroenterologist; GP, general practitioner; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IBD, inflammatory bowel disease; IFG, Impaired fasting glycemia; LDL, low-density lipoprotein; MetS, metabolic syndrome; MAFLD, metabolic-associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PsA, psoriatic arthritis.

## Funding

No funding to report.

## Disclosure

The authors report no conflict of interest.

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