Our Dermatology Online

Review Article

Evaluation and management of cardiovascular disease and metabolic syndrome in pediatric-adolescent patients with psoriasis

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ABSTRACT

Psoriasis is strongly associated with cardiovascular disease (CVD) and metabolic syndrome, with pediatric and adolescent patients having an increased risk of each compared to the general population. This increased risk is based on shared underlying genetic and cytokine profiles, as well as similar environmental risks. Many screening guidelines do not address the development of CVD and metabolic syndrome in these predisposed patients, particularly in the adolescent population. These deficits are evidenced by the absence of validated 10-year CVD risk calculators for pediatric and adolescent patients with chronic inflammatory diseases, as well as insufficient screening guidelines for insulin resistance in patients with psoriasis. This manuscript aims to contribute literature regarding allopathic and lifestyle recommendations to the most recent 2017 consensus guideline for the pediatric/adolescent population with psoriasis. PubMed, COCHRANE Database of Systematic Reviews and Google Scholar were reviewed by a panel of clinicians with clinical and research expertise in psoriasis and pediatric subspecialties. The patient-centered Strength of Recommendation Taxonomy (SORT) method was utilized to grade the quality of the evidence available. Updates in management surrounding the role of lipoprotein(a) in lipid panels, recommendations for exercise and weight management to decrease insulin resistance, as well as guidance for heart rate and blood pressure management were discussed. Screening and managing pediatric and adolescent patients with psoriasis for the associated comorbidities of CVD and metabolic syndrome is imperative. Future high-quality studies are needed to strengthen the evidence provided throughout this review, which acts as a framework for clinical practice.

Key words: Psoriasis, Comorbidity, Exercise, Treatment, Coronary heart disease

INTRODUCTION

Psoriasis is an independent risk factor for cardiovascular disease (CVD) and metabolic syndrome, with studies showing an increased prevalence of both conditions in pediatric and adolescent patients with psoriasis [1]. This increase in risk is attributed to underlying chronic inflammation, genetic predisposition, lifestyle and environmental risk factors. The risk of CVD is commonly underestimated in the psoriasis population, as current scoring criteria used to assess cardiovascular risk in the general population do not consider the underlying inflammation as an independent risk factor [2]. However, Flammer and Ruschitzka's theory of 'two plaques for one syndrome', highlights the similarity of the pro-inflammatory cytokines leading to psoriatic plaques and atherosclerotic plaques [3]. Oxidative stress, nitric oxide, angiotensin converting enzyme, renin and endothlin-1 all contribute to the systemic inflammation and subsequent hypertension, CVD and coronary microvascular dysfunction (CMD) [4]. CMD is the impairment of the coronary arteries' ability to vasodilate and/or alter coronary blood flow because of microvascular spasms. While CMD has

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been associated with severe psoriasis, its presence has also been demonstrated in young psoriatic patients with no evidence of CVD [5, 6]. Additionally, there appears to be a dose-response relationship between severity of psoriasis and prevalence of metabolic syndrome, secondary to metabolic dysfunction, oxidative stress and inflammation of adipocytes in patients with obesity. Yet, screening guidelines for insulin resistance are still widely debated in pediatric and adolescent patients [7]. Additionally, precise age-related criteria to define the metabolic syndrome in the pediatric patient are still lacking as well as precise guidelines for the management of these patients with the possibly intercepted comorbidities. The latest proposed guidelines regarding the comorbidities of psoriasis in the pediatric population available in the literature was by Osier et al in 2017 [8]. This article aims to expound on these guidelines by adding information about allopathic and lifestyle therapies for the screening and management of CVD and metabolic syndrome in pediatric and adolescent patients with psoriasis. A panel of clinicians with clinical and research expertise in psoriasis and pediatric subspecialties reviewed the available literature on multiple databases including PubMed and Google Scholar, as well as pooled their knowledge from clinical practice, to fulfill the above goal.

CURRENT AND PROPOSED SCREENING GUIDELINES

The American Heart Association (AHA) recommends stratification of cardiovascular risk in a stepwise approach [9]. The recommendations throughout this manuscript will be discussed with psoriasis being considered as a chronic inflammatory disease, and thereby making pediatric patients 'at risk'. In continuity with the latest 2017 systemic review, the patient-centered Strength of Recommendation Taxonomy (SORT) method was utilized to grade the quality of the evidence available (Table 1) [10]. The recommendations listed throughout this document are SORT level C, in keeping with the limited randomized controlled trials conducted to analyze the evidence provided. The bulk of recommendations discussed are based on consensus, usual practice, disease-oriented evidence, case series for studies of diagnosis, treatment, prevention, or screening and/or opinion.

Table 1: Strength of Recommendations Taxonomy (SORT) Outline. Adapted from Ebell et al [10]

Strength of Recommendation
A = Based on consistent and good quality patient-oriented evidence
B = Based on inconsistent or limited quality patient-oriented evidence
C = Based on consensus, usual practice, opinion, disease-oriented evidence or case series for studies of diagnosis, treatment, prevention or screening and/or opinion.

Screening for Hyperlipidemia in Children

In the pediatric assessment of lipid levels and subsequent cardiovascular risk, the approach to children is different from that of adults. Scoring systems, such as the Framingham risk score, are not available because robust outcome data is lacking [11, 12]. Therefore, it is not possible to accurately estimate a child's risk for ASCVD. Additionally, the '10-year' risk is presumably low in children and adolescents, so it may be more accurate to estimate the 'lifetime risk' instead.

The main concerns with prescribing statins in the pediatric population are not only related to the increased risk for myopathy and liver damage, but also the implications of decreased lipid synthesis [13]. Lipids are necessary for neurological development, and magnetic resonance imaging studies have demonstrated that the brain continues to mature throughout adolescence. Additionally, sterols are precursors of many steroid hormones that are integral in maturation and sexual development. However, clinicians may classify pediatric patients with familial hypercholesterolemia as being at high coronary risk due to LDL levels commonly >190mg/dL. Clinicians may therefore begin preventive efforts as early as childhood, with lifestyle therapy as the foundation of any regimen, and statin therapy as indicated [14]. In a systematic review evaluating the effect of statin therapy in pediatric populations aged 4.1-18 years old, apolipoprotein a and intima-media thickness (IMT) were significantly decreased across the target groups in most studies, in a positive dose response relationship. The statins under review were pravastatin, lovastatin, simvastatin, fluvastatin and atorvastatin to achieve an LDL <100mg/dL. CHD event prevention starts quickly, within 1 to 2 years of initiating statin therapy, suggesting that certain components of statin efficacy are attributable to plaque stabilization, anti-inflammatory effects, and other short-term pleiotropic mechanisms not directly related to arresting the long-term progression of atherosclerosis [13]. However, the long term duration and extent of decreased carotid IMT was directly associated with earlier initiation of statin therapy in the study by Rodenburg et al [15]. This finding therefore provides a basis for the preventative use of statin therapy in young patients upon initial diagnosis

of psoriasis, after evaluation and classification of either intermediate or high risk of CVD. Further research is still needed to access the impact of statin therapy on sex hormones such as DHEAS in adolescents, as well as the long-term effects on liver enzymes, as the average age of first onset of psoriasis is 15-20 years, an incremental time for steroidogenesis [13, 16].

The current recommendations are described below in Figure 1 [8, 9, 11, 17-24].

Screening for Diabetes Mellitus and Insulin Resistance in Children

Psoriasis is an independent risk factor for diabetes in adults (odds ratio][OR], 1.59 [95% CI, 1.38–1.83]]) and earlier age of psoriasis onset (<40 years old) and presence of psoriatic arthritis may impart an even greater risk of type 2 diabetes mellitus (T2DM) in adults [8]. However, the statistical increased risk of T2DM for children with psoriasis remains to be delineated; In a recent meta-analysis, Pietrzak et al. assessed metabolic disorder in children with psoriasis, analyzing data from seven studies with a total of 965 children [25]. Three of the seven studies assessed prevalence of metabolic syndrome, and in all three the rate of metabolic syndrome was significantly higher in cases of psoriasis. The authors also showed a significantly higher concentration of fasting glucose and a lower level of HDL cholesterol in patients with psoriasis but without reaching the abnormal cut-off [26]. Other studies reported higher plasma glucose levels, but without reaching the threshold for diabetes, and one reported a higher log-transformed HOMA, suggesting a link between insulin resistance and psoriasis. Meanwhile, Tollefson et al conducted a cohort study of 29,957 children (aged <19) with psoriasis and, independent of obesity status, noticed a statistically significant 40-75% increase of hyperlipidemia, hypertension, diabetes, metabolic syndrome, polycystic ovarian syndrome, non-alcoholic fatty liver disease (NAFLD) and elevated liver enzyme levels [27]. The risk of incident development of the comorbidities was also higher over the average 3.4 year cohort, with the highest hazard ratios being for NAFLD 1.64 (1.14-2.36) P=0.008, T2DM 1.63 (1.32-2.00) P<0.001 and HTN 1.57 (1.35-1.82) P<0.001.[27] The American Diabetes Association (ADA) guidelines recommend screening for T2DM or prediabetes in all asymptomatic children and adolescents ages 10 and older (or after the onset of puberty) who have an overweight or obese status and who have at least one of the following risk factors for diabetes: maternal history of gestational diabetes during the child's gestation; family history of type 2 diabetes in first or second degree relatives; American Indian, African American, Latino,

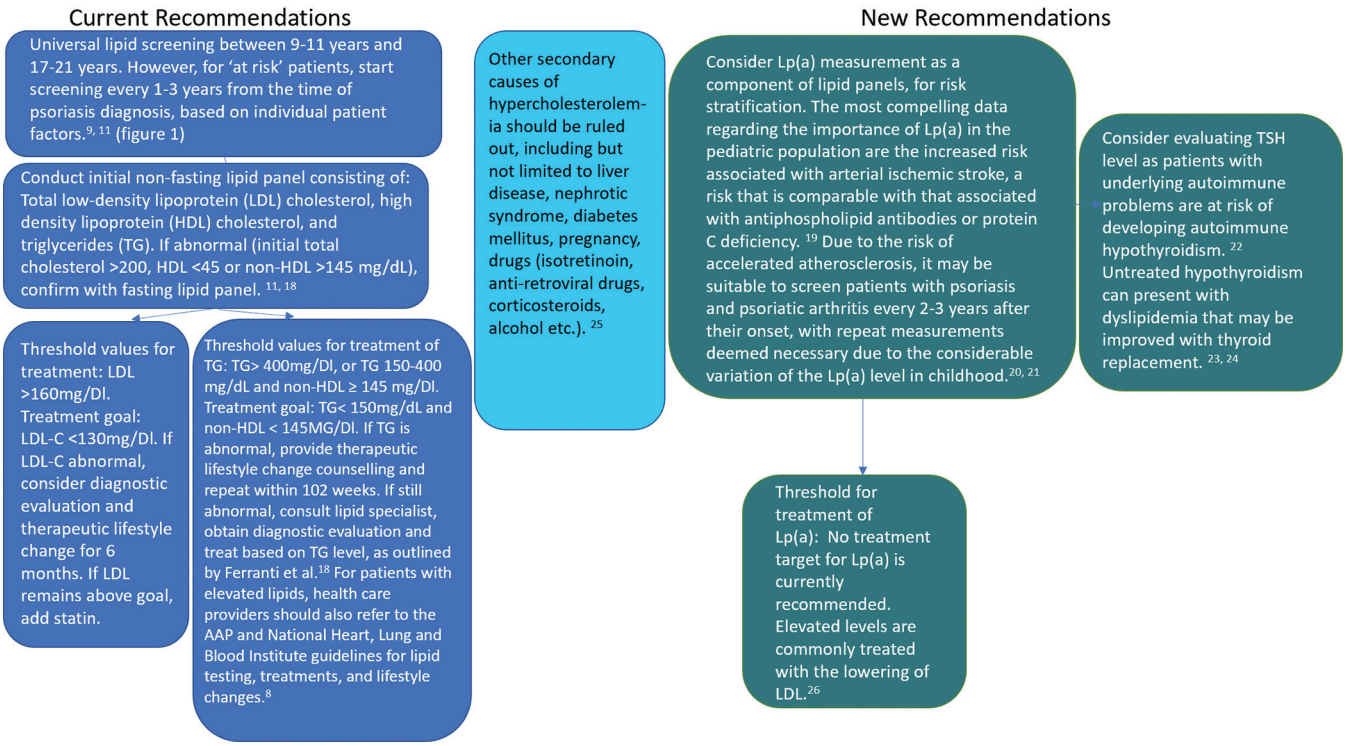

Figure 1: Current and new recommendations for hyperlipidemia screening in children and adolescents.

Asian American, or Pacific Islander race or ethnicity; or signs of insulin resistance or conditions associated with insulin resistance, specifically acanthosis nigricans, hypertension, dyslipidemia, polycystic ovarian syndrome, or small-for-gestational-age birth weight (Table 2) [28].

With the caveat of insulin resistance and metabolic syndrome in mind, inflammatory skin diseases such as psoriasis should also be considered. Therefore, these authors also propose earlier screening for T2DM in patients with psoriasis. However, current pediatric guidelines recommend the same screening for T2DM in children with and without psoriasis, thus indicating a potential for further guideline development [29].

The ADA recommends using a confirmatory approach (repeat testing or using a combination of elevated FPG and A1C in a single blood sample) if either one of the glycemic markers is elevated i.e FPG> 126 mg/dL or HbA1C ≥ 6.5%. [28] Additionally, cardiovascular risk factor associations such as obesity, metabolic syndrome and hypercholesterolemia were consistently stronger for HbA1c-defined hyperglycemia, with ORs ranging from 2.6 to 4.1, compared with FPG-defined hyperglycemia, in which ORs ranged from 1.5 to 3.0, so this finding gives strength for investigating both markers upon diagnosis as well. The current and new recommendations are described below in Figure 2 [8, 9, 30].

These authors recommend consultation with an endocrinologist in identifying ideal candidates for starting pharmacotherapy to ameliorate insulin resistance, and for optimal, individual dosage of the same. In adolescents, Sadovsky's metformin prescription for adolescent women with obesity and polycystic ovarian syndrome was 850mg once daily, with potential increase to twice daily pending tolerance [31]. However, 500mg once daily as a starting dose may be associated with improved tolerability in this population. Additionally, while the prior author concluded that the patients in the study had improved glucose tolerance and insulin sensitivity, controversy exists as to whether the insulin sensitivity is increased or glucose homeostasis is improved [32]. Additionally, Esmaeili et al observed a significant decrease in expression of catalase gene in patients with psoriasis ($P = 0.02$), likely as a result of sustained exposure to ROS leading to decreased expression of the catalase gene [33]. This finding could provide utility of PPARγ agonists, such as thiazolidinediones, as PPARγ regulates catalase production and is decreased in patients with

Table 2: Outlining the risk factors for T2DM. Adapted from the American Diabetes Association [30]

Risk Factors for Type 2 Diabetes Mellitus (T2DM)
Maternal history of diabetes or gestational diabetes during the child's gestation
First- or second-degree relative with T2DM
Race/ethnicity (Native American, African American, Latino, Asian American Pacific Islander)
Signs of insulin resistance or associated conditions (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovarian syndrome, small for gestational age birth weight)
Physical inactivity
HIV

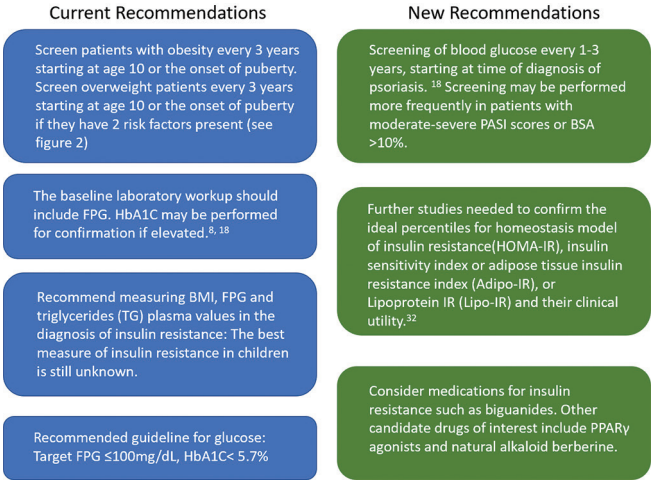

Figure 2: Current and new recommendations for the screening of type 2 diabetes mellitus and insulin resistance in children and adolescents.

psoriasis [34]. By virtue of this replacement, and the other characteristics of thiazolidinediones such as adipocyte differentiation, decreasing FFA, TNF-a and leptin, the mitochondrial regulation of PPARγ may have a role in the prevention of metabolic syndrome in patients with psoriasis [35]. Further studies are needed to reinforce this point. AMP-activated protein kinase (AMPK) dysfunction is also believed to be implicated in the pathogenesis of metabolic disorders; AMPK activates PGC1alpha within the mitochondria enhancing the biogenesis and inhibition of ROS, similar to the sirtuin pathway. Thiazolidinediones and biguanides share a common effect on AMPK potentiation and their potential clinical utility for insulin resistance treatment is being evaluated [36]. Additionally, berberine prevents the development of atherosclerosis, T2DM, and cardiovascular disorders by lowering blood glucose, hemoglobin A1c, TC, LDL-C and triglycerides, and reducing body weight and fat mass.[37] Further, it seems to have beneficial effects on endothelial function [37]. The principal mechanism responsible of its insulin sensitizing action is the upregulation of insulin receptor expression,

accompanied by activation of AMPK and inhibition of intestinal disaccharides. Multiple clinical trials are currently underway to determine optimal dosage and compare the efficacy against other agents such as biguanides [38].

For follow up of T2DM or insulin resistance, once diagnosed, use recommendations in keeping with Copeland et al and Tagi et al, respectively [39, 40].

Weight

Increased waist circumference has been directly correlated with the incidence of developing psoriasis and having increased PASI scores. This is likely due to the production of inflammatory cytokines in visceral obesity representing the link involved in the complex mechanisms leading to the exacerbation of psoriasis and psoriasis co-morbidities [41].

The current and new recommendations are described below in Figure 3 [41-48]:

Kim G et al found an inverse association between baseline skeletal muscle mass index (SMI) and metabolic syndrome development in a 7-year longitudinal follow-up study.[49] These findings were variable in subjects with obesity but consistent in subjects without obesity. However, an increase in relative muscle mass over a single year was significantly associated with low risk of metabolic syndrome even in people with obesity who have a high cardiometabolic risk, suggesting that an increase in relative skeletal muscle mass is a potent preventive parameter for metabolic syndrome. [49] Additionally, skeletal muscle hosts glucose transporter 4 (GLUT 4) and is a major site of postprandial glucose utilization. Overall, SMI changes were negatively correlated with changes in waist circumference, SBP, HOMA-IR, and concentrations of HbA_{1c}, fasting glucose, triglycerides, and LDL cholesterol, but not significantly so with CRP levels [49]. Lastly, it has been observed that the number of steps per day is directly related to insulin growth factor-1 (IGF-1) levels and inversely related to high sensitivity C-reactive protein (hsCRP) [39].

Further guidelines for exercise recommendations can be found in the Physical Activity Guideline for Americans, 2nd ed. [50].

Screening for Elevated Blood Pressure and Heart Rate

Blood pressure in normal-weight children with psoriasis has an association with stage 1 hypertension, independent of over-weight status [51].

Raised blood pressure is a major cause of both ASCVD and non-atherosclerotic CVD [particularly heart failure (HF)] [52]. In patients with psoriasis, raised PASI scores have been demonstrated as positively correlated with blood pressure levels.

The following recommendations for screening are below, with new recommendations denoted by the symbol '❖'

- Screen for hypertension yearly starting at 3 years of age, using age, sex, and height reference charts.

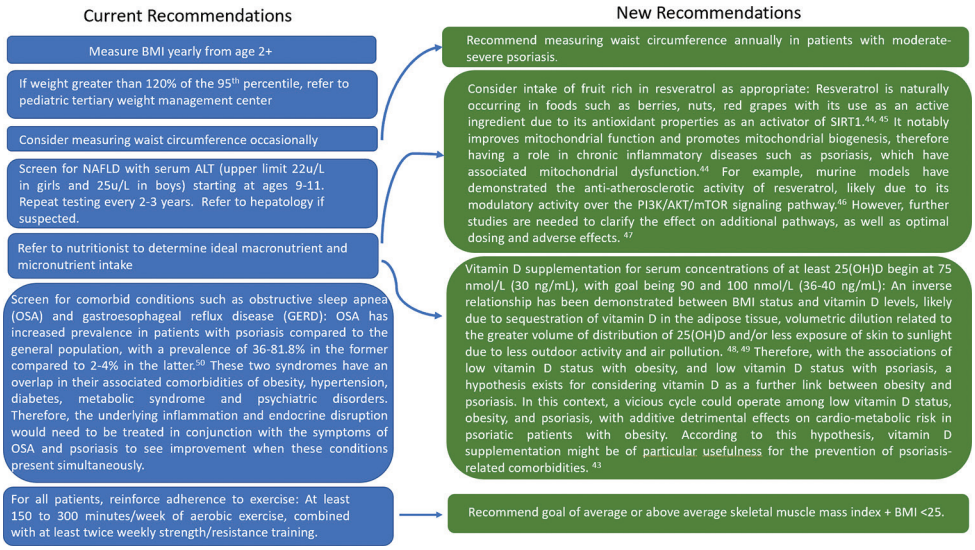

Figure 3: Current and new recommendations for weight management in the pediatric and adolescent population.

- Follow the AAP guidelines for annual blood pressure screening [53]. Screening should be performed using properly fitted equipment with the correct cuff size because this varies based on the size of the patient (the inflatable bladder should cover 80%–100% of the midpoint arm circumference). Initiate pharmacotherapy as per the AAP guidelines [9, 53].

Collaboration with a cardiologist is advised if hypertension is refractory.

❖ Consider evaluation of heart rate:
Age stratification shows that patients with psoriasis aged 20 to 39 years were at higher risk for arrhythmia (aHR 1.39; 95% CI 1.26-1.54) than middle-aged and elderly patients. For patients less than 20 years old HR 1.09 (0.86-1.39), the benefit of screening may be obsolete, but clinicians should nevertheless be aware of the risk of atrial fibrillation. The statistically non-significant finding could potentially have been due to small cohort of pediatric patients in study; the mean age of patients with psoriasis examined was 44.61 years [54].

❖ Screen for sleep dysfunction:
The recommended hours of sleep per 24 hours (including naps) on a regular basis for optimal health are: 8 to 10 hours for teenagers, 7 to 9 hours for young adults and adults, and 7 to 8 hours of sleep for older adults. [55] Non-restorative sleep and a sleep duration that varies significantly up or down from the optimum of 7 h are associated with increased CV risk [52]. Pruritus, variations in patient expectations, sleep hygiene or co-morbid depression and anxiety may result in transient physiological discomfort that impacts sleep and/or subsequent chronic insomnia. However, it should be noted that conditions such as restless leg syndrome and periodic limb movement disorder (PLMD) also have increased prevalence in patients with psoriasis [48]. Therefore, alternate causes of sleep disturbance should be considered and patient assessment of sleep disruption using qualitative QOL scoring criteria such as itch severity scale (ISS), insomnia severity index (ISI) or objective sleep studies such as polysomnography should be employed [56].

Mental Health Screening in Children

The risks of depression, anxiety, and suicidality are increased even among patients with mild psoriasis [57]. In fact, pediatric patients with psoriasis were found to have an approximately 25% to 30% higher risk of developing depression and/or anxiety compared to children without psoriasis. Mental disorders with either significant functional impairment or decreased use of healthcare systems should be considered as influencing total CVD risk. Additionally, treatment of an unhealthy lifestyle via exercise therapy, healthy dietary practices and abstinence from substance use reduces CVD risk as well as improves mental health. The recommendations for mental health screening in children are below:

- Screen yearly for depression and anxiety regardless of age.
- Screen yearly for substance abuse beginning at 11 years of age.
  - ❖ Screening can be done using tools such as the PHQ-4 or through clinical discussion. Refer to a mental health provider for formal evaluation if positive.
  - ❖ Consider performing child dermatology life quality index (CDLQI) yearly or when step-up therapy indicated.

DISCUSSION

Psoriasis is a chronic inflammatory disease with much potential for intervention to reduce the incidence and progression of associated co-morbidities such as CVD and metabolic syndrome. Thorough screening and management are essential for these patients at risk of insulin resistance, cardiovascular dysfunction, and psychiatric comorbidities. This manuscript provided background regarding the role of lipoprotein(a) in lipid panels, recommendations for exercise and weight management to decrease insulin resistance, as well as guidance for heart rate and blood pressure management. These supplements serve as a guide for future studies and reinforce the collaborative effort needed by clinicians to reduce the 'psoriatic march' and additional sequelae.

CONCLUSION

The evidence provided in this literature expounds on the existing consensus guidelines for comorbidity screening in pediatric patients with psoriasis. Future high-quality studies are needed to strengthen the evidence provided throughout this review, which serves primarily as a framework for screening and managing pediatric and adolescent patients with allopathic medications and lifestyle interventions for the reduction of CVD and metabolic syndrome.

ETHICS AND CONSENT STATEMENTS

This research did not require IRB approval/ethical approval because of the review nature of the study.

Informed consent for patient information to be published in this article was not obtained because no identifying patient information was included.

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