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Integrated Approach to Comorbidity in Patients With Psoriasis

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KEYWORDS
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Cancer;
Lymphoma;
Inflammatory bowel disease;
Anxiety;
Depression;
Smoking;

Abstract The relationship between psoriasis and associated diseases has drawn particular interest in recent years. To provide appropriate management of psoriasis from an early stage, it is necessary to include prompt diagnosis of concomitant disease and to prevent and treat any comorbidity found. Such an integrated approach also serves to ensure that the drugs used to treat associated diseases do not interfere with the management of psoriasis, and vice versa.

This clinical practice guideline on the management of comorbidity in psoriasis has been drawn up to help dermatologists to achieve an integrated approach to this inflammatory disease. The guide focuses primarily on the diseases most often found in patients with psoriasis, which include psoriatic arthritis, cardiovascular disease, nonalcoholic fatty liver disease, inflammatory bowel disease, lymphoma, skin cancer, anxiety, and depression. Cardiovascular disease is approached through the study of its major risk factors (obesity, diabetes mellitus, hypertension, dyslipidemia, and metabolic syndrome). Other cardiovascular risk factors related to lifestyle, such as smoking and alcohol consumption, are also discussed.

The overall aim of this guide is to provide the dermatologist with a precise, easy-to-use tool for systematizing the diagnosis of comorbidity in these patients and to facilitate decisions regarding referral and treatment once associated diseases have been found. The specific objectives are as follows: *a)* to review the most common diseases

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Alcohol consumption

associated with psoriasis, including the prevalence of each one and its importance to the dermatologist; *b)* to provide guidelines for the physical examination, diagnostic tests, and clinical criteria on which to base a preliminary diagnosis; *c)* to establish criteria for the appropriate referral of patients with suspected comorbidity; *d)* to provide information on how therapies for psoriasis may modify the course of associated diseases, and *e)* to provide information concerning treatments prescribed for associated diseases that may have an impact on the course of psoriasis.

This guide has been written by a working group of guideline methodologists and clinical experts. The selection of the diseases included was based on a systematic review of the literature and a summary of available evidence; information on the prevalence of each comorbidity was also taken from the literature. The recommendations on diagnostic criteria are based on the main clinical practice guidelines for each of the diseases discussed and on the recommendations of the expert advisory group. The information regarding the repercussions of psoriasis treatments on comorbid diseases was obtained from the summary of product characteristics of each drug. The statements concerning the impact on psoriasis of the associated diseases and their treatment are based on the review of the literature.

PALABRAS CLAVE
Psoriasis;
Comorbilidades;
Artritis psoriásica;
Diabetes mellitus;
Obesidad;
Enfermedad cardiovascular;
Hipertensión arterial;
Dislipemia;
Síndrome metabólico;
Hígado graso;
Cáncer;
Linfoma;
Enfermedad inflamatoria intestinal;
Ansiedad;
Depresión;
Tabaco;
Alcohol

Abordaje integral de la comorbilidad del paciente con psoriasis

Resumen En los últimos años, se está prestando especial importancia a la relación de la psoriasis con otras enfermedades concomitantes. El manejo temprano y adecuado del paciente con psoriasis se ha de contemplar, por tanto, desde un punto de vista integral, tanto para el diagnóstico temprano de la comorbilidad, como para su prevención y tratamiento, así como para evitar que los medicamentos utilizados en las enfermedades asociadas puedan interferir el curso de la psoriasis, o viceversa.

Como ayuda a este abordaje integral de la psoriasis, se plantea la elaboración de esta guía de práctica clínica enfocada específicamente hacia el manejo de la comorbilidad, y dirigida especialmente a dermatólogos. Esta guía se centra en las enfermedades más prevalentes en la psoriasis: artritis psoriásica, enfermedad cardiovascular a través del estudio de sus principales factores de riesgo (obesidad, diabetes mellitus, hipertensión arterial, dislipemia y síndrome metabólico), hígado graso no alcohólico, enfermedad inflamatoria intestinal, linfoma y cáncer de piel, ansiedad y depresión. También se consideran otros factores de riesgo cardiovascular relacionados con los hábitos de vida, como el consumo de tabaco y de alcohol.

El objetivo principal de esta guía es proporcionar al dermatólogo una herramienta ágil y precisa que protocolice el diagnóstico de la comorbilidad y le facilite la toma de decisiones en relación con la derivación y el tratamiento del paciente con alguna enfermedad asociada. Los objetivos específicos son: *a)* documentar sobre la comorbilidad más frecuente en psoriasis, aportando datos sobre la prevalencia y la importancia de cada una de estas enfermedades en el ámbito de la consulta de dermatología; *b)* orientar en el protocolo de exploración física, pruebas diagnósticas y criterios clínicos que permitan realizar un diagnóstico de sospecha de estas enfermedades; *c)* establecer los criterios de derivación de los pacientes con sospecha de comorbilidad al especialista correspondiente; *d)* informar sobre los tratamientos utilizados en el manejo de la psoriasis que modifican el curso de cada una de las enfermedades asociadas, e *e)* informar sobre los tratamientos utilizados en el manejo de estas enfermedades que pueden influir en el curso de la psoriasis.

La guía ha sido elaborada por un grupo de trabajo constituido por metodólogos y expertos. La selección y la documentación sobre las enfermedades a incluir y los datos de prevalencia de cada una se han basado en una revisión sistemática de la bibliografía científica y en la síntesis de la evidencia disponible. Las recomendaciones sobre criterios diagnósticos se han basado en las principales guías de práctica clínica de cada una de las enfermedades y en recomendaciones del grupo de expertos. La información sobre las repercusiones terapéuticas de la psoriasis en la comorbilidad se ha obtenido a partir de la ficha técnica de los diferentes fármacos, y de las diferentes enfermedades en la psoriasis a partir de los artículos encontrados en la revisión.

Abbreviations Used

ALT: alanine aminotransferase
AST: aspartate aminotransferase
BMI: body mass index
CAGE: Cut-down, Annoyed, Guilty, Eye-opener
CASPAR: Classification Criteria for Psoriatic Arthritis
GGT: gamma-glutamyltransferase
GRAPPA: Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
HR: hazard ratio
IBD: inflammatory bowel disease
IL: interleukin
MCV: mean corpuscular volume
MINI: Mini International Neuropsychiatric Interview
MRI: magnetic resonance imaging
NAFLD: nonalcoholic fatty liver disease
NASH: nonalcoholic steatohepatitis
NMSC: non-melanoma skin cancer
NYHA: New York Heart Association
PAPPS: Preventive Activities and Health Promotion Program
PAQ: Psoriasis and Arthritis Questionnaire
PASE: Psoriatic Arthritis Screening and Evaluation
PASI: Psoriasis Area and Severity Index
PEST: Psoriasis Epidemiology Screening Tool
PsA: psoriatic arthritis
PUVA: psoralen-UV-A
SPC: summary of product characteristics
TNF: tumor necrosis factor

I. INTRODUCTION

I.1. Comorbidity in Psoriasis

The relationship between psoriasis and comorbid diseases has attracted particular interest in recent years.[1] In a cohort of almost 3000 patients, an association was found between psoriasis and the following diseases: diabetes mellitus (hereafter referred to as diabetes), obesity, heart disease, and hypertension.[2] More recently, metabolic syndrome (abdominal obesity, hypertension, hyperglycemia, and dyslipidemia) has been identified as the comorbidity most often associated with psoriasis,[1] and associations have also been found between psoriasis and Crohn disease, cancer, and depression. Associations between psoriasis and other risk factors for heart disease, such as smoking[3] and alcohol consumption,[4] have also been found. It has been suggested that some of these associations may be related to the patient's genetic profile or that they could be explained by the inflammatory process that leads to psoriasis, which can also cause insulin resistance.[5,6]

Early detection and appropriate treatment of these comorbid diseases are important in terms of preventing progression to more advanced stages. Psoriatic arthritis (PsA) and rheumatoid arthritis are similar in that they both lead to joint destruction and loss of function, and in both cases early treatment can slow disease progression.[7] Consequently, a number of questionnaires have been developed to aid early diagnosis of PsA, including the Toronto Psoriatic Arthritis Screen (ToPAS),[8] the Psoriatic Arthritis Screening and Evaluation (PASE) tool,[9] and the Psoriasis Epidemiology Screening Tool (PEST).[10] In the case of the other diseases associated with psoriasis, various groups have published monitoring protocols that use patient characteristics in addition to clinical and laboratory parameters to detect comorbid disease in psoriasis patients.[11,12]

It is also important to remember that some of the drugs used to treat psoriasis may aggravate certain comorbid diseases (for example, acitretin may increase serum lipid levels and ciclosporin may increase blood pressure), and that the drugs used to treat such diseases may affect psoriasis (eg, β-blockers, angiotensin-converting enzyme inhibitors, interferon, and diuretics).

Therefore, appropriate management of psoriasis requires an integrated approach to ensure prompt diagnosis of concomitant disease and to prevent and treat comorbidity. Integrated management will also ensure that the drugs used to treat associated diseases do not interfere with the management of psoriasis, and vice versa. This clinical practice guideline on the management of comorbidity in psoriasis has been drawn up to help dermatologists to achieve an integrated approach to this inflammatory disease.

I.2. Diseases Covered in the Guideline

This guideline focuses primarily on the diseases most often found in conjunction with psoriasis: PsA, cardiovascular disease through the study of its major risk factors (obesity, diabetes, hypertension, dyslipidemia, and metabolic syndrome), nonalcoholic fatty liver disease, inflammatory bowel disease, lymphoma, skin cancer, anxiety, and depression. Lifestyle-related cardiovascular risk factors, such as tobacco use and alcohol consumption, are also discussed.

II. OBJECTIVES

II.1. General Objective

The overall aim of this guide is to provide the dermatologist with a precise, easy-to-use tool for systematizing the diagnosis of comorbidity in patients with psoriasis and to facilitate decisions regarding referral and treatment once associated diseases have been found.

II.2. Specific Objectives

The specific objectives were as follows:

1. To review the most common diseases associated with psoriasis, including their importance to the dermatologist and the data on the prevalence of each one;

2. To provide guidelines on history taking, physical examination, diagnostic tests, and clinical criteria on which to base a preliminary diagnosis;
3. To establish criteria for the appropriate referral of patients with suspected comorbidity;
4. To provide information on how psoriasis therapies may modify the course of associated diseases;
5. To provide information concerning the treatments prescribed for associated diseases that may have an impact on the course of psoriasis.

III. METHODS

This guide has been written by a working group of guideline methodologists and clinical experts. The selection of diseases for inclusion was based on a systematic review of the literature and a summary of available evidence; information on the prevalence of each comorbidity was also taken from the literature. The recommendations on diagnostic criteria are based on the foremost clinical practice guidelines for each of the diseases discussed and on the recommendations of the expert advisory group.

The information regarding the repercussions of psoriasis treatments on comorbid diseases was obtained from the summary of product characteristics (SPC) of each drug. The statements concerning the possible impact on psoriasis of the associated diseases and their treatment are based on the review of the literature. Before the definitive version was finalized, the guideline was reviewed and endorsed by an expert panel of 16 dermatologists and was likewise evaluated by all the members of the Spanish Psoriasis Group of the Spanish Academy of Dermatology and Venereology.

III.1. Description of the Working Group

The guideline working group was made up of a team of researchers, who were advised and supervised by a multidisciplinary advisory group and a panel of experts in psoriasis.

- Research team: 3 researchers and 1 information professional from TAISS (Técnicas Avanzadas de Investigación en Servicios de Salud)
- Advisory group: 4 dermatologists, 1 internist, 1 rheumatologist, and 1 psychiatrist
- Expert panel: 12 dermatologists with particular expertise in psoriasis

III.2. Summary of Evidence

To fulfill the first objective, the evidence on the prevalence of the diseases associated with psoriasis was reviewed and summarized.

III.2.a. Literature Search for Scientific Evidence

The following databases were searched for scientific evidence: EMBASE, MEDLINE, Índice Médico Español (IME, the Spanish medical index), MEDES (MEDicina en ESpañol, a database of medical texts in the Spanish language), and the Cochrane Library Plus. The search was limited to documents published between 1999 and 2010 in Spanish or English.

- The search strategy used for MEDLINE was as follows: (psoriasis) AND (comorbidit* OR arthritis OR diabetes OR obesity OR hypertension OR dyslipemia OR dyslipidemia OR hyperlipidemia OR hypercholesterolemia OR metabolic syndrome OR inflammatory bowel disease OR crohn OR ulcerative colitis OR anxiety OR depression OR *vascular OR vascular OR infarct OR stroke OR coronary heart disease OR ischemic OR atherosclerosis OR smok* OR tobacco OR cigarett* OR alcohol OR overweight OR skin cancer OR skin tumor OR lymphoma OR hepatopathy OR liver diseases OR fatty liver disease OR hepatic steatosis OR hyperuricemia OR hyperuricaemia OR homocysteine OR hyperhomocysteinemia). Limits Activated: Clinical Trial, Meta-Analysis, Practice Guideline, Randomized Controlled Trial, Review, Consensus Development Conference, Consensus Development Conference NIH, Controlled Clinical Trial, Corrected and Republished Article, Evaluation Studies, Government Publications, Guideline, Journal Article, Multicenter Study, Patient Education Handout, Published Erratum, Technical Report, Validation Studies, English, Spanish, Publication Date from 1999/01/01, Field: Title/Abstract. In total, 2358 articles were found (April 29, 2010).
- The search strategy used for EMBASE was as follows: psoriasis:ab,ti AND (comorbidit*:ab,ti OR arthritis:ab,ti OR diabetes AND mellitus:ab,ti OR obesity:ab,ti OR hypertension:ab,ti OR dyslipidemia:ab,ti OR hyperlipidemia:ab,ti OR hypercholesterolemia:ab,ti OR metabolic AND syndrome:ab,ti OR enteritis:ab,ti OR crohn AND disease:ab,ti OR ulcerative AND colitis:ab,ti OR anxiety:ab,ti OR depression:ab,ti OR vascular:ab,ti OR infarction:ab,ti OR stroke:ab,ti OR ischemic AND heart AND disease:ab,ti OR ischemia:ab,ti OR atherosclerosis:ab,ti OR smok*:ab,ti OR tobacco:ab,ti OR cigarett*:ab,ti OR alcohol:ab,ti OR skin AND cancer:ab,ti OR skin AND tumor:ab,ti OR lymphoma:ab,ti OR hepatopathy:ab,ti OR liver AND diseases:ab,ti OR fatty AND liver:ab,ti OR hyperuricemia:ab,ti OR homocysteine:ab,ti OR hyperhomocysteinemia:ab,ti) AND ([english]/lim OR [spanish]/lim) AND [embase]/lim AND [1999-2010]/py. In total, 78 references were found (May 10, 2010).
- The search strategy used for IME was as follows: (TI has “psoriasis”) AND (TI has “comorbilidad”) OR (TI has “comorbilidades”) OR (TI has “artritis”) OR (TI has “diabetes”) OR (TI has “obesidad”) OR (TI has “hipertensión”) OR (TI has “dislipemia”) OR (TI has “dislipemias”) OR (TI has “dislipidemia”) OR (TI has “dislipidemias”) OR (TI has “hiperlipidemia”) OR (TI has “hiperlipidemias”) OR (TI has “hipercolesterolemia”) OR (TI has “síndrome metabólico”) OR (TI has “enfermedad inflamatoria intestinal”) OR (TI has “crohn”) OR (TI has “crohn-colitis”) OR (TI has “colitis”) OR (TI has “ansiedad”) OR (TI has “ansiedad-depresión”) OR (TI has “depresión”) OR (TI has “vascular”) OR (TI has “infarto”) OR (TI has “enfermedad coronaria”) OR (TI has “isquemia”) OR (TI has “aterosclerosis”) OR (TI has “arteriosclerosis”) OR (TI has “tabaco”) OR (TI has

"fumar") OR (TI has "cigarro") OR (TI has "alcohol") OR (TI has "sobrepeso") OR (TI has "cáncer de piel") OR (TI has "linfoma") OR (TI has "hepatopatía") OR (TI has "esteatosis") OR (TI has "hígado graso") OR (TI has "hiperuricemia") OR (TI has "hiperuricemias") OR (TI has "homocisteína") OR (TI has "homocisteinemia") OR (TI has "hiperhomocisteinemia"). Limits: Year of publication = 1999:2010. Field: Title in Spanish. In total, 2 references were found (May 5, 2010).

- The search strategy used for MEDES was as follows: (psoriasis) AND (comorbilidad* OR artritis OR diabetes OR obesidad OR hipertensión OR dislipemia OR dislipidemia OR hiperlipidemia OR hipercolesterolemia OR síndrome metabólico OR enfermedad inflamatoria intestinal OR crohn OR colitis ulcerosa OR ansiedad OR depresión OR vascular OR infarto OR enfermedad coronaria OR isquemi* OR aterosclerosis OR ateriosclerosis OR arteriosclerosis OR tabaco OR fumar OR cigarr* OR alcohol OR sobrepeso OR cáncer de piel OR linfoma OR hepatopatía OR esteatosis hepática OR hígado graso OR hiperuricemia OR homocisteína OR homocisteinemia OR hiperhomocisteinemia). Limits: Field: Title and Abstract. In total, 27 articles were found (May 6, 2010).
- The search strategy used for the Cochrane Library Plus was: (psoriasis) AND (comorbidit* OR arthritis OR diabetes OR obesity OR hypertension OR dyslipemia OR dyslipidemia OR hyperlipidemia OR hypercholesterolemia OR metabolic syndrome OR inflammatory bowel disease OR crohn OR ulcerative colitis OR anxiety OR depression OR vascular OR infarct OR stroke OR coronary heart disease OR ischemic OR atherosclerosis OR smok* OR tobacco OR cigarett* OR alcohol OR overweight OR skin cancer OR skin tumor OR lymphoma OR hepatopathy OR liver diseases OR fatty liver disease OR hepatic steatosis OR hyperuricemia OR hyperuricaemia OR homocysteine OR hyperhomocysteinemia):TA. Limits: date range 1999-2010 In: Title and Abstract (TA). In total, 97 articles were found (May 6, 2010).
- Finally, the Google search engine was used to find articles published in Spanish that were not indexed on IME or MEDES. In this case the search strategy used was more specific to avoid spurious data. The following combination of keywords was used: "prevalencia AND comorbilidad AND psoriasis AND España". The search returned 1630 results (May 12, 2010), of which, the first 100 results were reviewed. All but 1 of these 100 results had already been found by the IME and MEDES searches. Thus, only 1 additional reference was added.

All the references found with these different search strategies were captured using the bibliography management software Reference Manager. Once duplicate references had been eliminated, 2419 articles remained for review by the researchers.

III.2.b. Study Selection Process

In the first phase of the selection process, the researchers read the titles of all the articles. If a document could not be excluded on the basis of its title, the abstract was read. If it still could not be excluded, the full text was read.

III.2.c. Results of the Selection Process

Of the 2419 references, 1939 were eliminated on the basis of the title. Of the 480 remaining references, 135 were rejected on the basis of their abstracts. A further 345 articles were rejected after a full text reading, leaving 112 for final review.

III.3. Other Documents Used

For each of the diseases studied, the expert panel proposed up-to-date clinical practice guidelines recommended by the leading scientific societies for each specialty. The diagnosis and referral criteria (the second and third objectives of these guidelines) were based on these clinical practice guidelines and the opinion of the expert panel.

When drafting each chapter, the authors also made use of an additional bibliography, including, for example, articles referenced in the documents identified by the systematic literature review and articles published after the initial search.

Altogether, taking into account clinical practice guidelines and the additional bibliography, another 192 references were included.

III.4. Implications of Treatment

With respect to the fourth objective, the warnings and remarks concerning the repercussions that common psoriasis treatments may have on comorbid diseases were primarily taken from the SPC for each drug. In Spain, these documents are available from the online drug information center of the Agencia Española de Medicamentos y Productos Sanitarios (Spanish Agency for Drugs and Healthcare Products). Only very common (≥ 1/10) and common (1/10 to 1/100) adverse events were described. The adverse events described for a particular drug are those observed in clinical trials and do not necessarily have a causal relationship with the drug, given that there was often no statistically significant difference between the effects observed in the group receiving the drug and the control group. The warnings and remarks on the repercussions that the treatments for the comorbid diseases analyzed may have on psoriasis were taken from articles found in the literature review.

III.5. Structure of the Chapters on Comorbid Diseases

The issues addressed for each comorbid disease are as follows:

a) An introduction discussing the importance of the disease and its diagnostic criteria.

b) Scientific evidence of the association between psoriasis and the disease in question. The discussion of the scientific evidence is supplemented by a table summarizing the results of the studies reviewed. Also included are data on the prevalence of the disease in the general population and in patients with psoriasis. When available, data on the association between psoriasis and

the disease are presented both unadjusted and adjusted for confounding factors.

c) Recommendations for the clinical management of the disease in the dermatology office, including a targeted medical history, physical examination, the diagnostic tests required to establish a suspected diagnosis, and recommendations on the frequency of screening.

d) Referral criteria based on the clinical practice guidelines and the opinion of the expert panel.

e) The implications of comorbidity on treatment. This section provides information on how the drugs used in the treatment of psoriasis may modify the course of the comorbid disease, and which drugs prescribed for the comorbidity may affect the course of psoriasis.

III.6. Summary Algorithm

This guide also includes an algorithm providing an easy-to-read graphic summary of its content. The algorithm contains information on the medical history, physical examination, and diagnostic tests required to identify suspected comorbidity, as well as referral criteria and the repercussions of comorbidity on treatment.

III.7. Validation of the Guide

The guide has been reviewed and endorsed by an expert panel of 16 potential users (dermatologists) and evaluated by the Spanish Psoriasis Group of the Spanish Academy of Dermatology and Venereology.

IV. ARTHROPATHY IN PSORIASIS

IV.1. Psoriatic Arthritis

IV.1.a. Introduction

PsA is an inflammatory disease of the joints found in association with psoriasis, although its severity does not necessarily correlate with the extent of the patient's cutaneous lesions. It affects both sexes equally and can develop at any age, even in childhood, but in most cases onset occurs between the ages of 30 and 50 years.[13] PsA is an inflammatory arthropathy that presents with pain, swelling, and heat. Patients experience difficulty in moving the inflamed joint and, over time, the condition may even lead to permanent deformity and joint damage. It is a chronic recurrent condition that takes the form of periodic flares, with periods of inactivity interspersed with episodes of pain and inflammation. A number of different forms of PsA have been described, the most common being asymmetrical oligoarticular arthritis affecting up to 3 joints in the limbs. Other forms of presentation are as follows: *a)* symmetric polyarticular arthritis with a course similar to that of rheumatoid arthritis; *b)* distal interphalangeal arthritis primarily affecting the hands; *c)* arthritis mutilans, a less common form that is extremely destructive and deforming; and *d)* arthritis affecting the spinal bones and the pelvic or sacroiliac joints, with a course similar to that of ankylosing spondylitis. Since many patients present with an overlapping combination of the symptoms of these different clinical forms, the clinical spectrum is very wide and presentation differs in each case. Oligoarticular forms of the disease can progress to polyarticular disease in later stages.[14]

PsA frequently affects other anatomical structures such as tendons, ligaments, and bones. Lesions tend to develop mainly at the points at which tendons and ligaments insert into bone (the entheses). Inflammation is common at the point where the Achilles tendon (Achilles tendonitis) and the plantar fascia (plantar fasciitis) insert into the heel bone.

The etiology of PsA is multifactorial and poorly understood. What is known is that the condition is due to a combination of genetic, immunologic, and environmental factors. Genetic studies have identified common risk factors shared by psoriasis and PsA. The genetic predisposition to psoriasis and PsA is strongly associated with the HLA class 1 region. Other risk factors involve the interleukin (IL) 23 pathway and the induction and regulation of helper T (T_H) 17 cells in the pathogenesis of both diseases. The secretion of cytokines, such as IL-22 and IL-17, could trigger hyperproliferation of keratinocytes and synoviocytes and lead to a vicious cycle of cell proliferation and inflammation of the skin and joints.[15]

IV.1.b. Diagnostic Criteria for Psoriatic Arthritis

One of the characteristics of PsA is that it generally develops in patients previously affected by psoriasis. It is estimated that in approximately 70% of cases of PsA, skin involvement precedes the onset of arthropathy, while arthropathy precedes skin disease in 15% of cases, and both occur simultaneously in the remaining 15%.[16] In a cross-sectional study in Spain and Portugal, only 5% of patients developed arthritis before developing skin lesions, and the average interval between the diagnosis of psoriasis and the development of PsA was 17 years.[17] This lengthy interval between the onset of psoriasis and that of arthritis affords dermatologists a unique opportunity to ensure early diagnosis of arthropathy in these patients, that is, the opportunity to diagnose recent-onset PsA. A number of classification criteria for PsA have been proposed for this purpose. In 1973, Moll and Wright[18] were the first authors to identify PsA as a clinical entity distinct from other rheumatologic diseases, and they coined the characteristic definition of the disease: seronegative inflammatory arthritis associated with psoriasis. Several authors have proposed new classification criteria,[19-25] and questionnaires have been developed for use as screening tools to identify patients with psoriasis and symptoms of inflammatory arthritis. These tools include the Psoriasis and Arthritis Questionnaire (PAQ),[26] ToPAS,[8] PASE,[27] and PEST.[10] It is unclear which set of criteria best represents the broad spectrum of the disease, and none of the questionnaires cited has achieved sufficient consensus to be universally accepted, either because of disagreement on clinical issues or, in some cases, because the use of the tool is unwieldy in clinical practice. However, the Classification Criteria for Psoriatic Arthritis (CASPAR) is the tool that has gained the most acceptance for use in daily clinical practice.[25,28]

The CASPAR criteria were proposed in 2006 by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), an international group of researchers with proven experience in the study of PsA. They based the criteria on the results of a large prospective multicenter study carried out in 13 countries. The study included data from 588 patients diagnosed with PsA and 536 controls, who had other forms of inflammatory arthritis (rheumatoid arthritis, ankylosing spondylitis, connective tissue disorders, or undifferentiated arthritis).[25] The CASPAR criteria have a sensitivity of 91.4% and a specificity of 98.7% for diagnosing PsA. An important limitation of the study on which they are based, however, is that the mean disease duration on enrolment of the patients was 12.5 years. Different results were later obtained in several studies that enrolled patients with a shorter disease duration. In a retrospective study of 107 patients with recent-onset PsA (defined as a disease duration < 2.5 years) recruited over a 14-year period at a clinic specializing in PsA, 106 patients satisfied the CASPAR criteria (sensitivity of 99.1%).[29] However, in a later prospective study of 44 patients with a mean disease duration of 15.8 weeks (half of whom had a disease duration of < 12 weeks), the sensitivity of the CASPAR criteria was only 77.3%.[30] This reduced sensitivity could be due to another limitation of the CASPAR criteria, namely that, to satisfy the criteria, the patient must have inflammatory articular disease (joint, spine, or entheseal) and this component is not always evident, especially in the early stages of PsA.[16] In addition to inflammatory articular disease, the patient must score 3 or more points in the 5 categories relating to the clinical, serologic, and radiographic manifestations of the disease (Table 1).

One advantage of the CASPAR criteria is that they are simple, quick, and easy to apply. The tool has also made 2 very important contributions. Firstly, it enables physicians to classify patients as having PsA even when they do not have psoriasis at the time of diagnosis, since the 3 points required to detect PsA can be obtained from the other criteria or even from a family history of psoriasis. Secondly, it can diagnose PsA in patients with a positive rheumatoid factor so long as they score 3 points in the other categories. However, in such cases the titers of rheumatoid factor are usually low.

Thus, although in principle the CASPAR criteria were developed for use in the context of clinical research and, in general, classification criteria should not be used for diagnostic purposes in routine clinical practice,[31] the advantages discussed above, together with the high sensitivity and specificity of the tool, make the CASPAR criteria very useful in clinical practice (Table 1).

Table 1 CASPAR Criteria[25]

To meet the CASPAR criteria, the patient must have inflammatory articular disease (joint, spine, or entheseal) and score 3 or more points from the following 5 categories:

1. Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis
   - Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist[a]
   - A personal history of psoriasis is defined as a history of psoriasis that may be obtained from the patient, a family physician, dermatologist, rheumatologist, or other qualified health care provider
   - A family history of psoriasis is defined as a history of psoriasis in a first- or second-degree relative according to patient report
2. Psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination
3. A negative test result for the presence of rheumatoid factor by any method except latex but preferably by enzyme-linked immunosorbent assay or nephelometry, using the local laboratory reference range
4. Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist
5. Radiographic evidence of juxtaarticular new bone formation near joint margins. This appears as poorly defined ossification (excluding osteophyte formation) on plain radiographs of the hand or foot.

[a]Current psoriasis is assigned a score of 2; all other features are assigned a score of 1. The 3 subsections of category 1 are mutually exclusive.

IV.1.c. Scientific Evidence

Appendix 1 summarizes the data from the studies reviewed on the prevalence of PsA in patients with psoriasis and shows the 95% CIs. When no CI was reported in the original study, it was calculated using Epidat version 3.1. The prevalence of PsA in psoriasis patients varied enormously across the studies, partly due to differences in the diagnostic criteria used. In some studies, psoriasis was diagnosed on the basis of a physical examination in the dermatology office, while in others the diagnosis was identified by a code in a database. Furthermore, the criteria used to establish a diagnosis of PsA were very varied and included the following: diagnosis by a rheumatologist, targeted questionnaires, distinction between joint pain alone and joint pain in conjunction with arthritis, and database codes. In addition, a number of different validated tools were used, including the Moll and Wright[18] criteria, the European Study Spondylarthropathy Study Group criteria,[22] and the CASPAR criteria.[25]

In view of the great heterogeneity of the sources from which the data were obtained and of the diagnostic criteria used in the studies reviewed, and given that prevalence varies with the severity of psoriasis,[32] there would be little sense in calculating a combined estimate of the prevalence of PsA.[33] The reported prevalence of PsA in psoriatic patients was between 2.0% and 29.6% in all but 2 studies, which reported a prevalence of 46% and 48%.[34,35] However, the study that reported the highest prevalence

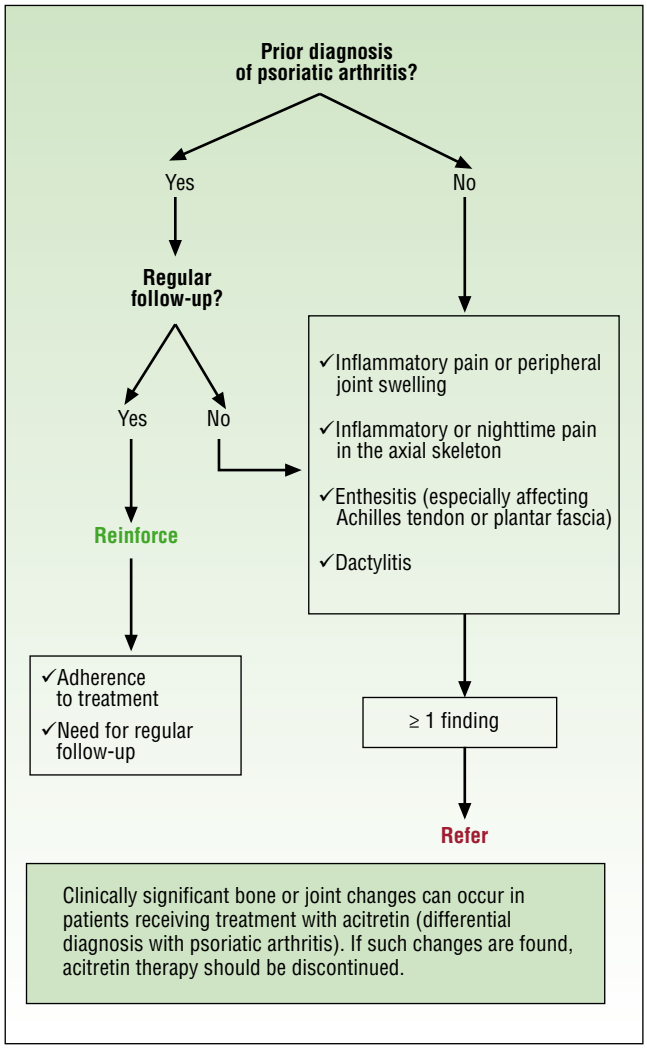

Figure 1. Management of psoriatic arthritis.

(48%)[35] was very probably affected by a selection and classification bias because the patients were volunteers and the authors based their diagnosis on a combination of physical and radiological findings and PAQ scores[26] rather than on validated diagnostic criteria.[33] The other high prevalence (46%) was reported by a study conducted in Pakistan,[34] in which there is also a high probability of selection bias because patients with positive rheumatoid factor were excluded. In a sample of 1774 patients with psoriasis in Spain, PsA was found in 9.4%, although 17.3% reported joint problems.[36] In a later study carried out by 332 dermatologists in Spain and Portugal, 12.8% of 3320 patients with moderate to severe psoriasis had PsA.[17] In another international multicenter study of 1560 patients with plaque psoriasis carried out in Spain, the United Kingdom, Italy, France, and Germany, the prevalence of PsA was 8.1%.[37] When only studies that used validated criteria were considered and excluding the study in Pakistan, the prevalence of PsA in patients with psoriasis ranged from 5.9% (United States) to 29.6% (Italy).

IV.1.d. Management of PsA in the Dermatology Office

Figure 1 is an algorithm for the clinical management of PsA in the dermatology office.

IV.1.d.a. Targeted History

Patients should be asked about the current presence of inflammatory pain or swelling of the joints, with special emphasis on the areas where joint involvement is more frequent, namely, the knees, ankles, and small joints of the hands. Patients should also be asked specifically about inflammatory or nighttime pain in the axial skeleton (the spine and sacroiliac joints) and at tendon insertions, especially in the heel (Achilles tendon) or the soles of the feet (plantar fascia).

IV.1.d.b. Specific Physical Examination

The physical examination should include visual inspection (for redness) and exploration (for swelling, heat, limited mobility, and pain) of painful or swollen joints. Particular attention should be paid to the most typically affected tendon insertions or entheses (the Achilles tendon and plantar fascia), which are the signs most often overlooked by nonrheumatologists. The limbs should be examined to identify the following signs: *a)* nail dystrophy, onycholysis, pitting and hyperkeratosis; and *b)* dactylitis ("sausage digits" or inflammation of an entire finger or toe).

IV.1.d.c. Specific Additional Tests

None required.

IV.1.d.d. Frequency of Screening

Patients receiving local treatment for their psoriasis should be screened annually and those on systemic treatment every 6 months.

IV.1.d.e. Referral Criteria for Patients with Suspected Psoriatic Arthritis

To date, none of the questionnaires developed to diagnose PsA (PAQ, ToPAS, PASE, and PEST) have been validated for Spain. Once validated, any of them might prove to be good tools for this purpose. Nevertheless, they are sometimes not very easy to use because they can be time consuming and awkward to administer.

Because it requires the diagnosis of inflammatory articular disease and radiographic evidence of juxtaarticular new bone formation (excluding osteophytes), it is difficult to apply the CASPAR classification outside of a rheumatology practice.[38] In this guide, we propose criteria for referral to a rheumatologist based on the CASPAR criteria, but adapted to the nonrheumatology setting. These criteria are only indicative of suspected PsA, and it will be the task of the rheumatologist to confirm the diagnosis.

Since the patients in question all have psoriasis, PsA should be suspected if theany of following conditions are fulfilled: *a)* inflammatory pain (Table 2) or peripheral joint swelling; *b)* inflammatory or nighttime pain in the axial skeleton; *c)* evidence of enthesitis (particularly affecting the Achilles tendon or plantar fascia); or *d)* current dactylitis (defined as swelling of

an entire digit) or a history of dactylitis recorded by a rheumatologist.

IV.1.d.f. Recommended Action in Patients Diagnosed With Psoriatic Arthritis

If the patient has PsA and is currently being monitored regularly by a primary care physician or specialist, stress the importance of adherence to the prescribed treatment and regular follow-up visits. Patients who are not being regularly monitored for their PsA should be referred to the appropriate specialist.

IV.1.d.g. Implications of Psoriasis Treatment in Psoriatic Arthritis

Certain drugs used to treat psoriasis may benefit the course of PsA. Methotrexate is indicated for severe PsA (SPC). The anti-tumor necrosis factor (TNF) biologic agents currently used to manage psoriasis (adalimumab, etanercept, and infliximab) are also indicated for the treatment of active and progressive PsA in adults when the response to treatment with disease-modifying antirheumatic drugs has not been adequate.[39] In patients with PsA, these 3 anti-TNF agents have been shown to improve physical function and reduce the rate of progression of peripheral joint damage measured by radiographic ultrasound, and magnetic resonance imaging (MRI) evidence in patients with polyarticular symmetric subtypes of the disease (SPCs).

According to their SPCs, ciclosporin and acitretin are not indicated for the treatment of PsA. Ustekinumab has been shown to be effective in the treatment of PsA,[40,41] although its use in this disease has not yet been approved. Phase III studies are currently underway for this indication.

Any patient who displays atypical musculoskeletal symptoms during treatment with acitretin must be rapidly assessed to exclude possible drug-related bone changes. If significant changes are found in the bones or joints, treatment should be discontinued (SPC).

Table 2 Characteristics of Inflammatory Pain in all Types of Arthritis (Also Applicable in Psoriatic Arthritis)[38]

- Painful all day, sometimes more painful on waking up
- Pain increases with activity and exercise
- Pain at rest and even at night
- Morning stiffness and swelling > 30 minutes
- Good response to nonsteroidal anti-inflammatory drugs
- More or less evident signs of inflammation and absence of cracking joints

V. CARDIOVASCULAR COMORBIDITY IN PSORIASIS

V.1. CARDIOVASCULAR DISEASE AND PSORIASIS

V.1.a. Introduction

Cardiovascular disease was the direct cause of death of more than 4 million people in Europe in 2004; of these, 1.9 million were in the European Union.[42] In recent decades, there has been a growing awareness of an association between psoriasis and a number of cardiovascular risk factors (metabolic syndrome, obesity, hypertension, dyslipidemia, and type 2 diabetes) and, consequently, with cardiovascular disease. The exact mechanism of this association is unclear, but it may involve humoral and cellular inflammatory mediators,[43] which are also involved in arteriosclerosis and other cardiovascular risk factors.

Arteriosclerosis has many points in common with psoriasis and other inflammatory diseases (eg, rheumatoid arthritis, inflammatory bowel disease, and lupus erythematosus); these relate to the immune process and the profile of the mediators and immune cells involved in the pathogenesis of all of these diseases.[44,45] Inflammatory markers are high at both local and systemic levels. Specifically in psoriasis, the inflammatory process is accompanied by abnormalities in ILs and elevated TNF-α and C-reactive protein, alterations that also play a role in the genesis of arteriosclerosis.

Other cardiovascular risk factors also share common pathogenic mechanisms with psoriasis. In metabolic syndrome, for example, obesity gives rise to a cytokine imbalance when adipocytes trigger excessive secretion of the most deleterious cytokines from the vascular point of view (IL-6, IL-18, TNF-α, and leptin) and downregulate the secretion of protective cytokines, such as adiponectin.[46] Some authors have suggested that the apolipoprotein E4 variant may have a pathogenic role in psoriasis.[47] The same variant is also associated with certain types of dyslipidemia.[48]

In addition to the common pathogenetic mechanisms, other factors may also play a role in the strong association between psoriasis and cardiovascular disease. Firstly, they share common risk factors, including excessive alcohol and tobacco consumption. Obesity and a sedentary lifestyle are also more common in patients with psoriasis than in individuals who do not have this condition. Secondly, some of the drugs routinely used to manage psoriasis may give rise to or aggravate certain cardiovascular risk factors. For example, acitretin can cause dyslipidemia, and ciclosporin can cause dyslipidemia and high blood pressure (SPC).[49]

V.1.b. Scientific Evidence

We reviewed 15 studies carried out during the last decade that examined the association between cardiovascular disease and psoriasis (Appendix 2). These studies included the following cardiovascular diseases: arteriosclerosis, ischemic heart disease, myocardial infarction, cerebrovascular disease, cerebral infarction, transient ischemic attack, and peripheral vascular disease. Many of the studies found a significant association between 1 or more of these diseases and psoriasis, and frequently the measures of risk calculated were adjusted for variables such as age, sex, and other cardiovascular risk factors. Eight of these studies were based on data from large institutional databases in Germany, the United Kingdom, the United

States, and Israel. The General Practice Research Database in the United Kingdom was used in 4 of these studies. All the database studies were cohort studies except for 1 case-control study carried out by Kimball et al[50] in the United States. The rest of the articles reviewed were case-control studies except for 1 carried out by Pearce et al,[51] which had a cross-sectional design.

The prevalence of myocardial infarction in psoriasis patients varied considerably across the different studies, ranging from 0.9% (odds ratio [OR] = 1.07; 95% CI, 0.92-1.23) to 1.6% (OR = 1.22; 95% CI, 1.08-1.39) according to data from 2 databases in the United States[50] and the results of a study in China.[52] Prevalence rose to 6% (OR = 1.72; 95% CI, 1.29-2.30) after adjusting for age, sex, diabetes, hypertension, hyperlipidemia, and tobacco use in patients with mild psoriasis, and to 8.01% (OR = 2.01; 95% CI, 1.45-2.79) after adjusting for age, sex, diabetes, hypertension, hyperlipidemia, and tobacco use in patients with severe psoriasis. According to these studies, ischemic heart disease is the most prevalent cardiovascular disease in psoriasis, with a prevalence ranging from 4.6% (OR = 1.19; 95% CI, 1.11-1.29) to 7.8% (OR = 1.18; 95% CI, 1.12-1.25). The authors also highlighted cerebrovascular disease, with a prevalence ranging from 3.1% (OR = 1.19; 95% CI, 1.11-1.29) to 6.5% (OR = 1.13; 95% CI, 1.06-1.20) and peripheral vascular disease, with a prevalence ranging from 2.7% (OR = 1.25; 95% CI, 1.15-1.41) to 4.9% (OR = 1.26; 95% CI, 1.17-1.35).

In the cohort studies, the measure of risk most often used was the hazard ratio (HR). For myocardial infarction, an HR of 1.21 (95% CI, 1.10-1.42) was found for patients with psoriasis of unspecified severity and without adjusting for cardiovascular risk factors.[53] In another study, in which the data was stratified according to severity and adjusted for cardiovascular risk factors, the authors found an HR of 1.54 (95% CI, 1.24-1.91) in mild psoriasis and of 7.08 (95% CI, 3.06-16.36) in severe psoriasis.[54] For cerebral infarction, an HR of 1.12 (95% CI, 1.00-1.25) was found in patients with psoriasis of unspecified severity without adjusting for cardiovascular risk factors.[53] In the study in which the data were stratified by severity and adjusted for cardiovascular risk factors, the authors found an HR of 1.06 (95% CI, 1.01-1.11) in mild psoriasis and of 1.43 (95% CI, 1.10-1.87) in severe psoriasis.[55] Two studies analyzed ischemic heart disease, but only 1 found a significant association (HR = 1.20; 95% CI, 1.12-1.29). Results similar to those of this last study have been found for arteriosclerosis and peripheral vascular disease. For cardiovascular disease mortality in patients with severe psoriasis, the HR reported was 1.57 (95% CI, 1.26-1.96).

V.1.c. Management of Cardiovascular Disease in the Dermatology Office

The aim of this guide was not to discuss the diagnosis or treatment of cardiovascular diseases (myocardial infarction, angina, stroke, transient ischemic attack, or peripheral vascular ischemia), but rather to provide guidelines for the identification of psoriasis patients at risk for these comorbidities. Since the symptoms are generally obvious, patients with cardiovascular disease are usually diagnosed promptly and treated by the appropriate clinicians. However, the aim is to advocate the diagnosis of cardiovascular risk factors and primary prevention of cardiovascular disease. Since these risk factors are more common in patients with psoriasis, the role of the dermatologist is to screen psoriasis patients, establish a suspected diagnosis of these risk factors and, when appropriate, refer the patient to the pertinent specialist for confirmation of the diagnosis and treatment. The dermatologist should also advise the patient on healthy lifestyle habits (diet, exercise, and smoking cessation).

V.1.c.a. Targeted History

Dermatologists should ask their patients whether they have cardiovascular disease and whether their condition is being regularly monitored by the appropriate specialist (cardiologist, neurologist, or internist). Patients should also be asked to provide details of any specific treatment they are receiving for cardiovascular disease because of the potential repercussions this may have on their psoriasis therapy.

V.1.c.b. Frequency of Medical History Update

Patients receiving local treatment for their psoriasis should be screened annually and those on systemic treatment every 6 months.

V.1.c.c. Implications of Psoriasis Treatment on Cardiovascular Disease

- *Methotrexate:* Treatment of psoriasis with methotrexate may induce hyperhomocysteinemia, thereby increasing the risk of vascular disease. However, methotrexate treatment also has a beneficial effect in that it reduces inflammation and may therefore have a vasculoprotective effect. To assess the effect of methotrexate treatment on the incidence of vascular disease in patients with psoriasis and rheumatoid arthritis, Prodanovich et al[56] conducted a retrospective cohort study of veterans in the United States. They found that patients treated with methotrexate had a lower incidence of vascular disease (cardiovascular, cerebrovascular, and arteriosclerosis) than those not prescribed the drug. Moreover, the concomitant use of folic acid with methotrexate also reduces the incidence of vascular disease in patients treated with this drug.
- *Biologic agents:* A number of studies of patients with rheumatoid arthritis have found a lower incidence of cardiovascular events in patients on anti-TNF therapy.[57,58] Other studies have shown that treatment with infliximab improves endothelial function and increases adiponectin levels in patients with rheumatoid arthritis,[59-61] an interesting finding in that high plasma adiponectin concentrations are associated with a lower risk of myocardial infarction.[62,63] While no studies have been found that deal specifically with this hypothesis in patients with psoriasis, given that rheumatoid arthritis and psoriasis share common pathogenic mechanisms, it seems reasonable to postulate that the incidence of cardiovascular events may also be lower in psoriasis patients treated with TNF inhibitors.

However, anti-TNF agents can adversely affect congestive heart failure and are contraindicated in patients with past or current moderate to severe heart failure (New York Heart Association [NYHA] class III or IV, corresponding to dyspnea when resting or on slight exertion). These biologics must also be used with caution in patients with mild heart failure (NYHA class I or II, corresponding to dyspnea on moderate or great exertion).[64] Patients should be closely monitored, and treatment with biologics should be discontinued in patients whose heart failure symptoms worsen or who develop new symptoms.

V.1.c.d. Implications of Cardiovascular Disease Treatment in Psoriasis

The implications of cardiovascular disease for the management of psoriasis are related particularly to the treatment of the risk factors described below.

VI. CARDIOVASCULAR RISK FACTORS IN PSORIASIS

VI.1. Obesity and Psoriasis

VI.1.a. Introduction

Obesity is a chronic multifactorial condition that results from the interaction between the genotype and the environment. It affects a large percentage of the population in developed countries, both sexes, and people of every age and social status. The prevalence of obesity has been increasing and continues to increase alarmingly in our society and in countries with transitional economies, such that the disease is reaching epidemic proportions. Obesity substantially increases the risk not only of diabetes and cardiovascular disease, but also of certain types of cancer[65] and other highly prevalent diseases. As a result, it is now the second leading cause of premature and avoidable death, exceeded only by tobacco use.[66]

A diagnosis of obesity is usually established on the basis of body mass index (BMI), although this index is not a reliable indicator of body fat in athletes and older people. The BMI is, however, the diagnostic method recommended by various medical societies and international health organizations because it is reproducible and easy to use, and it can measure body fat in most of the population. The index is calculated using the following formula: weight in kg/height in m^2. The classification criteria are as follows[67]: *a)* underweight, BMI < 18.5 kg/m^2; *b)* normal weight, BMI 18.5 to 24.9 kg/m^2; *c)* overweight, BMI 25.0 to 29.9 kg/m^2; *d)* obese class I, BMI 30.0 to 34.9 kg/m^2; *e)* obese class II, BMI 35.0 to 39.9 kg/m^2; and *f)* obese class III (morbid obesity), BMI > 40.0. In children and young people, the cut off points for defining overweight and obesity are the age- and sex-specific values of the 85th and 97th percentile, respectively, using the tables published by Cole et al.[68] Obesity is also classified as either abdominal or peripheral, depending on waist circumference. Abdominal obesity is defined as a waist circumference of over 102 cm in men and over 88 cm in women, and is associated with increased cardiovascular risk.

In a Spanish study on diet and cardiovascular risk,[69] the prevalence of obesity in Spain was estimated to be 15.5% (95% CI, 15.2%-15.8%) in the population aged between 25 and 60 years of age, and to be higher in women (17.5%; 95% CI, 17.2%-18.0%) than in men (13.2%; 95% CI, 12.8%-13.7%). The same study estimated the prevalence of overweight to be 39.2% (95% CI, 38.6%-39.7%) and higher among men (46.4%; 95% CI, 45.2%-47.1%) than women (32.9%; 95% CI, 32.4%-33.4%). Overall, it is estimated that some 54.7% of the population between 25 and 64 is overweight.

VI.1.b. Scientific Evidence

We reviewed 23 articles published within the last 10 years that examined the association between obesity and psoriasis (Appendix 3). Of these, 5 studies were carried out in the United Kingdom, 6 in Italy, 3 in the United States, 2 in Israel, 2 in Germany, 1 in Kuwait, 1 in China, 1 in Taiwan, 1 in Sweden, and 1 in the Netherlands. Eleven were large case-control studies based on data from the following automated databases: the General Practice Research Database in the United Kingdom (5 studies); Israel's Clalit Health Services database (2 studies); a German health insurance database (2 studies); a nurses' study in the United States (1 study); and US Medicare data (1 study). The remaining studies analyzed smaller series of patients recruited from dermatology offices or from groups of patients hospitalized due to psoriasis. There were 5 cohort and 8 cross-sectional studies, and the remainder were case-control studies.

In most of these studies, a significant association was observed between psoriasis and obesity, and even between psoriasis and overweight. The risk of being overweight or obese increased with the severity of psoriasis. In many of these studies, risk was adjusted for different variables, most often age and sex. In the studies that analyzed the association without stratifying by the severity of psoriasis, prevalence was between 22% and 37% for overweight and between 11% and 34% for obesity. When the severity of the patient's psoriasis was taken into account, the results were as follows: in mild psoriasis, the prevalence was between 34% and 35% for overweight and between 14% and 17% for obesity; in moderate to severe psoriasis, the prevalence of overweight ranged from 35% to 40% and that of obesity from 20% to 42%. The measures of risk for overweight reported by case-control studies and cross-sectional studies were as follows: in psoriasis in general, the OR ranged from 1.1 (95% CI, 1.04-1.02) to 1.6 (95% CI, 1.0-2.4); in mild or mild to moderate psoriasis, the OR ranged from 1.12 (95% CI, 1.10-1.14) to 1.2 (95% CI, 1.13-1.18); and in severe psoriasis, the OR ranged from 1.10 (95% CI, 1.04-1.24) to 1.3 (95% CI, 1.1-1.4). The OR for obesity ranged from 1.2 (95% CI, 0.9-1.6) to 2.7 (95% CI, 1.4-5.1) in psoriasis in general, from 1.1 (95% CI, 1.08-1.12) to 2.4 (CI 95 %, 1.9-2.9) in mild to moderate psoriasis, and from 1.5 (95% CI, 1.2-2.0) to 5.5 (CI 95 %, from 3.1-9.7) in severe psoriasis. In a cohort study of overweight patients carried out in the United States, researchers reported an HR of 1.4 (95% CI, 1.13-1.73) for overweight, 1.48 (95%, 1.15-1.91) for class I obesity, and 2.69 (95% CI, 2.12-3.40) for class II obesity or higher.

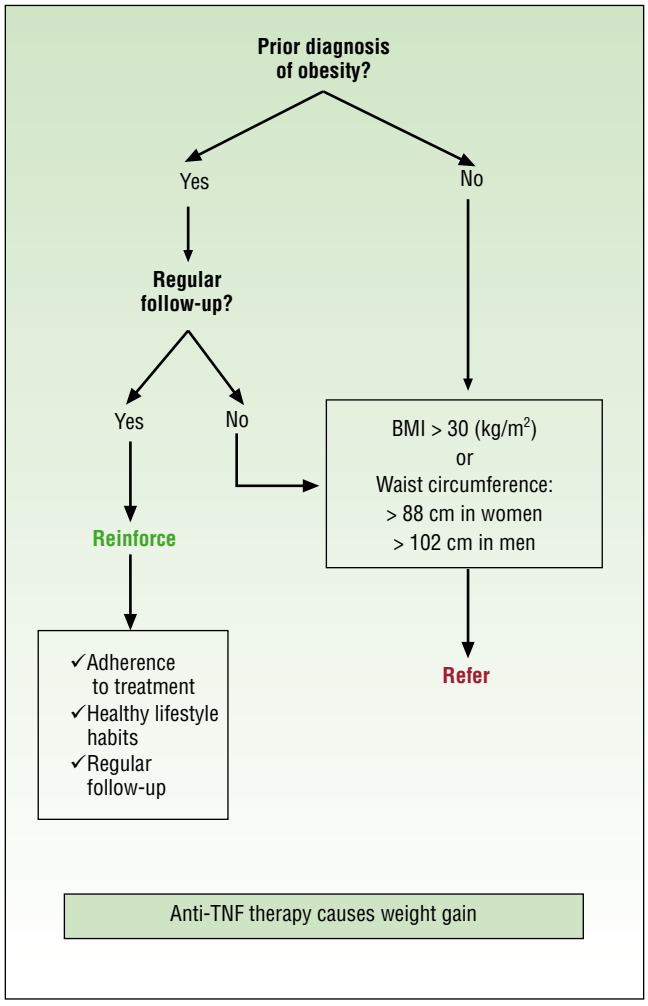

Figure 2. Management of obesity. BMI indicates body mass index; TNF, tumor necrosis factor.

Table 3 How to Measure Waist Circumference

1. Use a traditional measuring tape.
2. With the patient standing, pass the measuring tape around the waist at the middle point between the last rib and the iliac crest (approximately in line with the navel).
3. Ask the patient to breath normally.
4. Carefully take the measurement at the end of expiration.

VI.1.c. Management of Weight Problems in the Dermatology Office

Figure 2 is an algorithm for the clinical management of obesity in the dermatology office.

VI.1.c.a. Targeted History

Not required.

VI.1.c.b. Specific Physical Examination

The following should be recorded: weight (kg), height (in m), BMI (weight/height^2), and waist circumference (see Table 3 for correct measurement procedure).

VI.1.c.c. Specific Additional Tests

None required.

VI.1.c.d. Frequency of Screening

Patients receiving local treatment for their psoriasis should be screened annually and those on systemic treatment every 6 months.

VI.1.c.e. Criteria for the Referral of Patients With Obesity

Obesity (BMI > 30 kg/m^2) or abdominal obesity (waist circumference > 88 cm in women or > 102 cm in men).

VI.1.c.f. Recommended Action in Patients Diagnosed With Obesity

If the patient is being regularly monitored by their primary care physician or other specialist, stress the importance of adherence to the treatment prescribed, including all recommendations on healthy lifestyle habits (diet, exercise, tobacco cessation, and moderation in alcohol consumption), and emphasize the importance of continuing with regular follow-up visits.

Patients who are not being regularly monitored for their obesity should be referred appropriately.

VI.1.c.g. Implications of Psoriasis Treatment in Patients with Obesity

Several studies have indicated that treatment with anti-TNF agents (adalimumab, etanercept, and infliximab) can cause patients to gain weight, thereby increasing their BMI.[70-72] This possibility should be taken into account in the overall treatment strategy used to manage psoriasis.

VI.1.c.h. Implications of Obesity for the Treatment of Psoriasis

None have been described.

VI.2. Diabetes and Psoriasis

VI.2.a. Introduction

Diabetes is a metabolic disorder characterized by hyperglycemia resulting from defects in insulin secretion and/or action. Chronic hyperglycemia is associated with long-term damage, dysfunction, and failure of various organs, in particular the eyes, kidneys, nerves, heart, and blood vessels. Today, we know that many of the complications associated with diabetes can be prevented. Early diagnosis is therefore essential to ensure strict control of blood glucose levels and a high degree of involvement on the part of the patient. Symptoms of marked hyperglycemia include polyuria, polydipsia, weight loss, and occasionally polyphagia. The most serious acute and life-threatening consequences of uncontrolled diabetes are hyperglycemia with ketoacidosis and the nonketotic hyperosmolar syndrome. However, the most common cause of death in patients with diabetes is cardiovascular disease.

The current classification of diabetes distinguishes between 2 major types designated type 1 and type 2.

a) Type 1 diabetes mellitus is the result of the destruction of pancreatic β-cells, usually leading to absolute insulin deficiency. It accounts for only 5% to 10% of all cases of diabetes. Typically diagnosed in childhood or early adulthood (although it can develop at any time of life), type 1 diabetes is an autoimmune disease and patients test positive for several antibodies, including antibodies to glutamic acid decarboxylase, pancreatic islet cells, and insulin. In the early stages, patients usually present the classic symptoms of diabetes, including polyuria, polydipsia, weight loss, and ketonemia. Insulin treatment is necessary from first onset.

b) Type 2 diabetes mellitus, which accounts for 90% to 95% of all cases of diabetes, is characterized by insulin resistance and a relative, rather than absolute, insulin deficiency. It usually develops in adults over 40 years of age, and patients do not always require insulin treatment. The risk of developing this form of diabetes increases with age, weight, and physical inactivity, and it is more common in patients who are obese, hypertensive, or dyslipidemic. It may remain undiagnosed for years because hyperglycemia develops slowly in the early stages. The condition is often not severe enough for the patient to notice any of the classic symptoms of the disease.

Experts have now recognized the existence of an intermediate group of individuals whose blood glucose levels (between 101 mg/dL and 125 mg/dL) do not meet the criteria for diabetes (see VI.2.c.e) but are, nontheless, too high to be considered normal. These patients also have impaired glucose tolerance and impaired fasting glucose. They are said to be prediabetic because there is a relatively high risk that their condition will progress to diabetes or that they will develop cardiovascular disease even without developing diabetes.

The incidence and prevalence of diabetes has been increasing in recent years, making the disease a major health problem worldwide. This increased prevalence can be attributed to several causes: firstly, modification of the criteria used to diagnose diabetes (the threshold for fasting glucose used to define the disease was lowered from 140 mg/dL to 126 mg/dL[73,74]); and secondly, the progressive aging of the population and generalized lifestyle changes that lead to decreased physical activity and dietary habits likely to promote diseases such as obesity.[75] Other factors associated with the development of diabetes include a family history of diabetes, sedentary habits, low socioeconomic status, impaired glucose tolerance, hypertension, and hyperlipidemia.[76]

A study carried out in 2004 estimated that by 2025 the number of persons in the world with diabetes may reach 366 million, most of whom will have type 2.[77] Countries with the fastest growing incidence of diabetes include India, China, Indonesia, Pakistan, and Bangladesh, in addition to developed countries, such as the United States, Italy, and Japan. The impact of diabetes on the health of the population is significant because of its high prevalence. It is associated with a high social and economic burden because numerous microvascular and macrovascular complications develop as the disease progresses. These complications in turn give rise to a high level of comorbidity and very high mortality in this population.

In Spain, the prevalence of diabetes is estimated at around 6.5% in the adult population aged between 30 and 65 years of age, although rates reported in different studies range from 6% to 12%.[78-81] Data from the Spanish National Health Interview Survey show that the prevalence of diabetes (based on the reports of the survey respondents) increased from 4.1% to 5.9% between 1993 and 2003, reaching rates as high as 16.7% in those between 65 and 74 years of age, and 19.3% in those over 75 years.[82]

VI.2.b. Scientific Evidence

We reviewed 25 studies examining the association between diabetes and psoriasis (Appendix 4). Five of these were carried out in the United States, 4 in Israel, 1 in Kuwait, 1 in China, and the remaining 14 in Europe. Sixteen were large case-control studies based on data from automated databases, as follows: 6 in the United Kingdom (the General Practice Research Database); 4 in Israel (3 from the Clalit Health Services database and 1 from the Maccabi Healthcare Services database); 2 in Germany (a health insurance database); 1 from a nurses' study in the United States; 1 from a medical service for veterans in the United States; 1 based on the IMS Health Integrated Claims Database and the MarketScan Commercial Claims and Encounters Database in the United States; and 1 from the National Health and Wellness Survey database in the United States. The remaining studies analyzed smaller series of patients recruited from dermatology offices or from groups of patients hospitalized due to psoriasis. There were 3 cohort studies and 3 cross-sectional studies. The remainder were case-control studies.

The criteria used to identify patients with diabetes varied. In most of the studies, patients were selected on the basis of a code assigned to diabetes in the database. In the others, selection was based on a diagnosis of type 2 diabetes or on medical records showing that the patient was receiving antidiabetic medication or had a fasting blood glucose greater than 6.1 mmol/L.

The prevalence of diabetes reported in these studies varied widely, with rates of between 2.35% and 37.4% in psoriasis in general, and of between 7.5% and 41.9% in severe psoriasis. A significant association was found in 20 of the studies. In the case-control and cross-sectional studies, the measures of risk for diabetes (irrespective of the severity of psoriasis) ranged from an OR of 1.13 (95% CI, 1.08-1.18; adjusted for age, sex, hypertension, hyperlipidemia, tobacco use, and BMI) to an OR of 3.14 (95% CI, 2.68-3.68; unadjusted). In patients with severe psoriasis, the unadjusted OR ranged from 1.49 (95% CI, 1.29-1.73) to 3.77 (95% CI, 2.60-5.47). In the study of a cohort of nurses,[83] the risk of diabetes ranged from an HR of 2.08 (95% CI, 1.60-2.69; adjusted for age) to an HR of 1.63 (95% CI, 1.25-2.12; adjusted for age, tobacco use, BMI, alcohol, and physical activity).

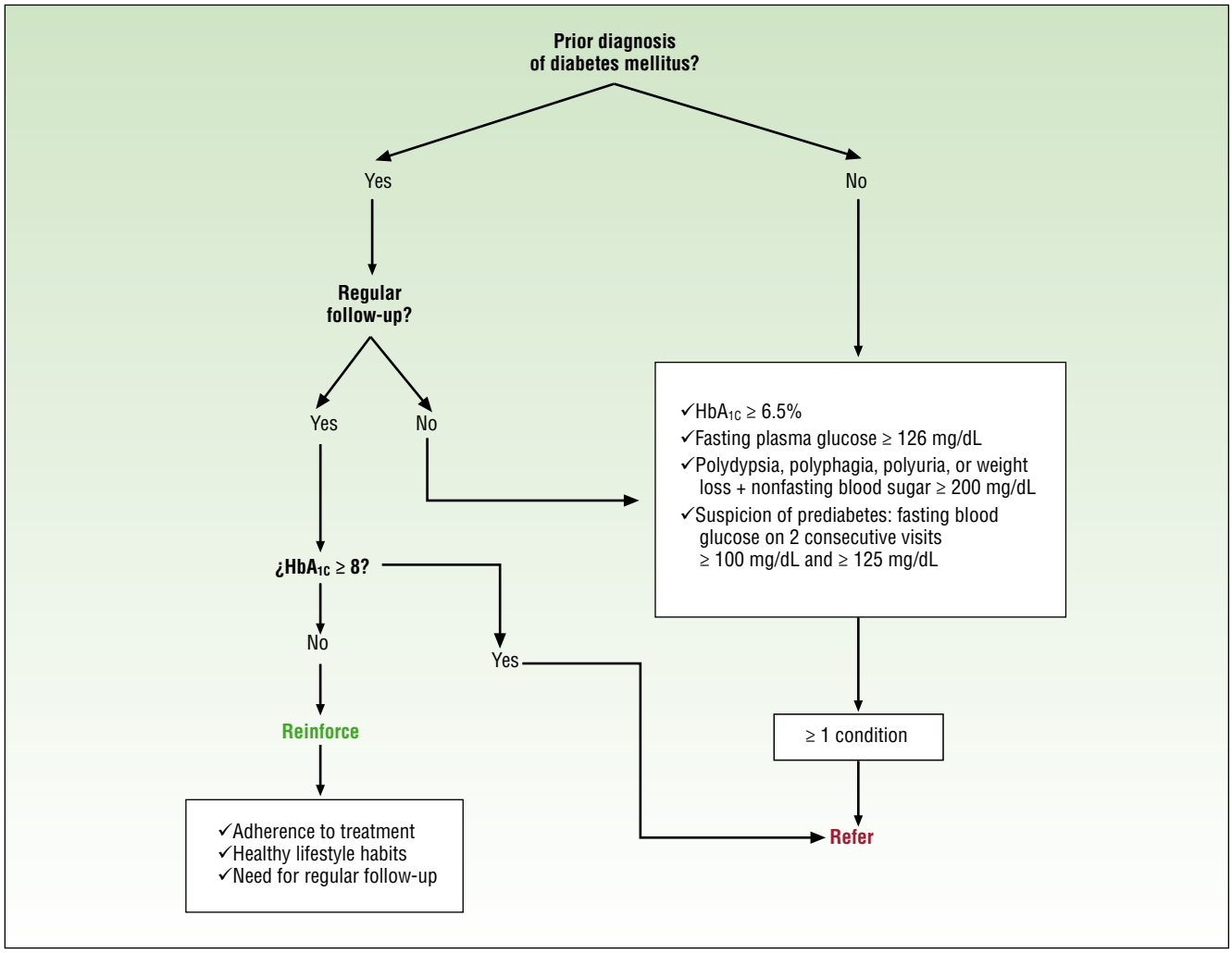

Figure 3. Management of diabetes mellitus.
HbA_{1C} indicates glycated hemoglobin.

VI.2.c. Management of Diabetes Mellitus in the Dermatology Office

Figure 3 is an algorithm for the clinical management of diabetes in the dermatology office.

VI.2.c.a. Targeted History

Family history of diabetes, personal history of diabetes, polydipsia, polyphagia, polyuria, or weight loss, and use of antidiabetic medication.

VI.2.c.b. Specific Physical Examination

Not required.

VI.2.c.c. Specific Additional Tests

Fasting plasma glucose and glycosylated hemoglobin (HbA_{1c}).

VI.2.c.d. Frequency of Screening

Patients receiving local treatment for their psoriasis should be screened annually and those on systemic treatment every 6 months.

VI.2.c.e. Criteria for the Referral of Patients with Suspected Diabetes

The American Diabetes Association defines diabetes as any of the following conditions[84]: *a)* HbA_{1c} ≥ 6.5%; *b)* fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L); or *c)* a random plasma glucose (independent of intake) ≥ 200 mg/dL (11.1 mmol/L) in a patient with classic symptoms of hyperglycemia.

Patients satisfying any of the above criteria should be referred for treatment.

The American Diabetes Association 2011 guidelines also recommend referral of patients considered to be prediabetic, that is, those who, on 2 consecutive occasions, satisfy either of the following criteria: HbA_{1c} between 5.7% and 6.5% or a fasting plasma glucose between 100 mg/dL (6.1 mmol/L) and 125 mg/dL (7.0 mmol/L).

VI.2.c.f. Recommended Action in Patients Diagnosed With Diabetes

In the case of patients who are being monitored by their primary care physician or a specialist, stress the

importance of healthy lifestyle habits (diet, exercise, smoking cessation, and moderate alcohol intake) and adherence to prescribed treatment. Also emphasize the need for the patient to continue with regular follow-up visits.

Refer patients with diabetes to the appropriate clinician if their condition is not currently being managed by a physician or if they are being treated but have an HbA_{1c} greater than 8%.

VI.2.c.g. Implications of Psoriasis Treatment in Diabetes Mellitus

—*Etanercept:* there have been reports of hypoglycemia following start of treatment with etanercept in patients being treated for diabetes, and in some cases a reduction in antidiabetic medication proved necessary (SPC).

—*Adalimumab*: hyperglycemia was a commonly reported adverse event (SPC) in clinical trials with adalimumab.

Physicians should exercise extreme caution when considering the use of biologic agents in patients with a history of chronic or recurrent infections or those who have underlying conditions that may predispose them to infections, such as advanced or poorly controlled diabetes.

VI.2.c.h. Implications of Diabetes Treatment in Psoriasis

There have been reports of patients with diabetes whose psoriasis improved when they received treatment with thiazolidinediones (pioglitazone).[85,86] In a pilot study in India, the effect of pioglitazone on psoriasis was assessed.[87] This was a double-blind, randomized, controlled study in which 70 patients received placebo, 15 mg/d pioglitaxone, or 30 mg/d pioglitazone for 10 weeks. The reductions in Psoriasis Area and Severity Index (PASI) scores were 21.6%, 41.1%, and 47.5% respectively, and the differences were statistically significant. Pioglitaxone has also been assessed in patients with PsA. When 10 patients with active articular disease were treated with 60 mg/d of pioglitazone for 12 weeks, the mean reduction in PASI was 38%.[88]

VI.3. Hypertension and Psoriasis

VI.3.a. Introduction

It is generally accepted that arterial hypertension is a major risk factor for both cardiovascular disease itself and for other diseases associated with a marked increase in cardiovascular risk. This fact, together with the high prevalence of high blood pressure in the population,[89,90] explains why the World Health Organization cites hypertension as the leading cause of death worldwide.[91]

For years, greater importance was placed on diastolic than on systolic blood pressure as a predictor of cardiovascular morbidity and mortality, especially in older patients.[92] However, there is now ample evidence that both systolic and diastolic blood pressure have a continuous relationship with cardiovascular morbidity and mortality,[93] and treatment guidelines for hypertension now recognize the major role of both systolic and diastolic pressure, but particularly systolic in patients over 50 to 55 years of age.[94]

Table 4 Definitions and Classification of Blood Pressure Levels (mm Hg)[a]

Category	Systolic	Diastolic
Optimal	< 120 and	< 80
Normal	120-129 and/or	80-84
High-normal	130-139 and/or	85-89
Grade 1 hypertension	140-159 and/or	90-99
Grade 2 hypertension	160-179 and/or	100-109
Grade 3 hypertension	≥ 180 and/or	≥ 110

[a]2007 Guidelines for the Management of Arterial Hypertension.[94]

In Spain, the prevalence of hypertension in adults is approximately 35% (reaching 40% in middle age and 68% in the population over 60 years of age), and the disease affects some 10 million adults.[95] Awareness of the condition and the level of pharmacological treatment of hypertension in the general population is moderately high in Spain, but control of hypertension—and of high systolic blood pressure in particular—is limited.[95-98]

Adequate control of hypertension is achieved in under 40% of patients receiving treatment and in under 15% of those with increased cardiovascular risk, such as patients with diabetes or kidney disease.[99,100] It is estimated that adequate control could reduce coronary mortality by 20% and death from stroke by 24%.[101]

Table 4 shows the classification of hypertension for use in daily practice established by the 2007 Guidelines for the Management of Arterial Hypertension issued by the European Society of Cardiology and the European Society of Hypertension.[94]

With respect to the quantification of cardiovascular risk, the guidelines specify the following provisos: *a)* when a patient's systolic and diastolic blood pressures fall into different categories, the higher category should apply; *b)* isolated systolic hypertension should be graded with the same categories (1, 2, or 3) indicated for systolic-diastolic hypertension in the table. However, cardiovascular risk will be increased if this is associated with a very low diastolic blood pressure (< 80).

VI.3.b. Scientific Evidence

We reviewed 22 studies examining the association between hypertension and psoriasis (Appendix 5). Four of these were carried out in the United States, 3 in Israel, 1 in Kuwait, 1 in China, and the remaining 13 in Europe (5 in the United Kingdom, 4 in Germany, 3 in Italy, and 1 in the Netherlands). Thirteen were large case-control studies based on data from automated databases, as follows: 4 in the United Kingdom (the General Practice Research Database); 3 in Israel (2 from the Clalit Health Services database and 1 from an insurance company database); 2 in Germany (medical insurance database); 1 from a nurses' study in the United States; 1 from a medical service for veterans in the United States; 1 based on the IMS Health Integrated Claims

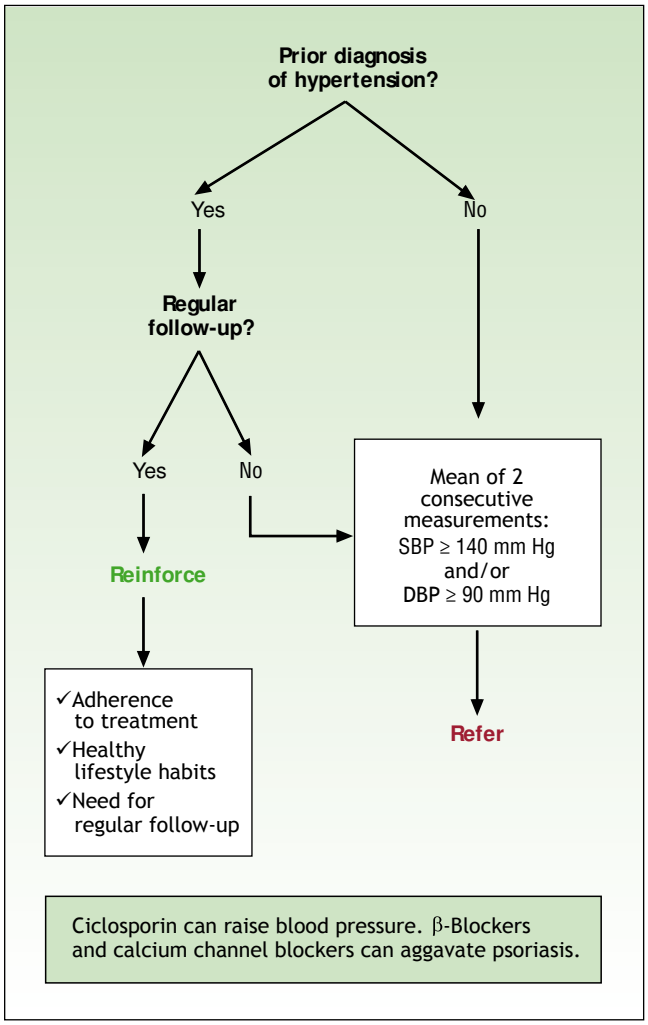

Figure 4. Management of hypertension. DBP indicates diastolic blood pressure; SBP indicates systolic blood pressure.

Database and the MarketScan Commercial Claims and Encounters Database in the United States; and 1 from the National Health and Wellness Survey database in the United States. The remaining studies analyzed smaller series of patients recruited from dermatology offices or from groups of patients hospitalized due to psoriasis.. There were 5 cohort and 3 cross-sectional studies. The remainder were case-control studies.

The definitions of hypertension varied greatly from study to study. Some patients were selected on the basis of a history of hypertension in their medical record. In other cases, the criterion was prior antihypertensive treatment, a specific code used in the database from which the data were drawn, or a blood pressure value of more than 135/85 mm Hg or more than 140/90 mm Hg.

Most authors reported a significant association between hypertension and psoriasis and a correlation between hypertension risk and severity of psoriasis. In some studies, the risk was adjusted for different variables, most often age and sex. In the studies that analyzed the association without taking into account the severity of psoriasis, the prevalence of hypertension ranged from 8.9% to 44.4% (60% in older patients). When severity was taken into account, the prevalence ranged from 15.1% to 32% in patients with mild psoriasis, and from 19% to 40.3% in those with moderate to severe psoriasis. With respect to the risk of hypertension in the population with psoriasis as a whole, the case-control and cross-sectional studies reported an OR ranging from 0.8 (95% CI, 0.5-1.37; adjusted for age and sex) to 1.3 (95% CI, 1.2-1.5; adjusted for age, sex and tobacco use), or 2.2 (95% CI, 2.2-2.3) in the same study without adjusting for other variables. In patients with mild psoriasis, the OR for hypertension ranged from 1.03 (95% CI, 1.01-1.06; adjusted for age, sex, hyperlipidemia, BMI, and tobacco use) to 3.6 (95% CI, 3.02-4.23; unadjusted). In patients with severe psoriasis, the OR reported ranged from 1.0 (95% CI, 0.87-1.14; adjusted for age, sex, hyperlipidemia, BMI, and tobacco use) to 5.17 (95% CI, 3.5-7.6; unadjusted). A cohort study carried out in the United States reported an HR for hypertension of 1.17 (95% CI, 1.06-1.39) adjusted for age, tobacco use, alcohol consumption, BMI, and physical activity.

VI.3.c. Management of Hypertension in the Dermatology Office

Figure 4 is an algorithm for the clinical management of hypertension in the dermatology office.

VI.3.c.a. Targeted History

Personal history of hypertension, current prescription for hypertension medication.

VI.3.c.b. Specific Physical Examination

Blood pressure measurement. Blood pressure should be measured using the method recommended in the 2007 Guidelines for the Management of Arterial Hypertension issued by the European Society of Cardiology and the European Society of Hypertension (Table 5).[94]

VI.3.c.c. Specific Additional Tests

None required.

VI.3.c.d. Frequency of Screening

Blood pressure should be checked annually in patients receiving local treatment for their psoriasis and every 6 months in patients on systemic treatment.

VI.3.c.e. Criteria for the Referral of Patients With Suspected Hypertension

After blood pressure has been measured using the method specified above, patients should be referred if they have a mean systolic blood pressure greater than 140 mm Hg or diastolic blood pressure greater than 90 mm Hg in 2 consecutive measurements.

VI.3.c.f. Recommended Action in Patients Diagnosed With Hypertension

In the case of patients who are being monitored by their primary care physician or by a specialist, stress the importance of healthy lifestyle habits (diet, exercise, smoking cessation, and moderate alcohol intake) and

adherence to prescribed treatment. Also stress the importance of continuing with regular follow-up visits.

Patients who are not being regularly monitored for their hypertension should be referred to the appropriate specialist.

VI.3.c.g. Implications of Psoriasis Treatment in Hypertension

Hypertension is a commonly reported adverse reaction in patients taking ciclosporin, making it essential to monitor blood pressure regularly in this setting and to start appropriate treatment if hypertension should develop. Ciclosporin is contraindicated in patients with uncontrolled hypertension (SPC). A calcium channel blocker, such as amlodipine, may be an appropriate treatment for controlling hypertension caused by ciclosporin.

Hypertension is also a commonly reported adverse reaction in clinical trials of adalimumab (SPC).

VI.3.c.h. Implications of Hypertension Treatment in Psoriasis

There have been reports that β-beta blockers (including atenolol, metoprolol, propranolol, timolol, and oxprenolol) and calcium channel blockers (including nifedipine, amlodipine and felodipine) have aggravated lesions or triggered flares in patients with psoriasis. In some cases, the response recurred when the drug was reintroduced after withdrawal. However, in a population-based case-control study in the United Kingdom, no association was found between use of hypertensive medication and psoriasis risk.[102,103]

VI.4. Dyslipidemia and Psoriasis

VI.4.a. Introduction

Dyslipidemia is an acquired or genetic disorder affecting the synthesis or catabolism of lipoproteins which gives rise to an increase in total plasma cholesterol, triglyceride levels, or both. Typically, it takes the form of increased low density lipoprotein cholesterol (LDL-C) and very-low-density lipoprotein cholesterol and/or a reduction in high-density lipoprotein cholesterol (HDL-C). Increased total cholesterol or LDL-C and low levels of HDL-C are considered modifiable cardiovascular risk factors and causes of cardiovascular disease. These factors are classified as modifiable because medical intervention is possible and are considered causal because there is abundant evidence concerning their role in atherogenesis. However, hypertriglyceridemia is considered a conditional risk factor because its role in the atherogenic process is less clear.[104]

Dyslipidemia, hypertension, and diabetes are considered to be the leading risk factors for cardiovascular disease. Numerous cohort studies, including the pioneer Framingham Heart Study,[105] have demonstrated the association between high total cholesterol and cardiovascular events. This risk is continuous and gradual, and a reduction in total cholesterol correlates with a reduction in risk until the cholesterol value falls to 180 mg/dL or less. Most of this risk is explained by LDL-C. There is also a clear inverse association between the risk for coronary artery disease and HDL-C levels.

Table 5 Method for Measuring Blood Pressure in the Physician's Office[a]

1. Allow the patients to sit for several minutes in a quiet room before beginning blood pressure measurements.
2. Take at least 2 measurements spaced by 1 to 2 minutes, and additional measurements if the first 2 are quite different.
3. Use a standard bladder (12-13 cm long and 35 cm wide) but have a larger and a smaller bladder available for fat and thin arms, respectively. Use the smaller bladder in children.
4. Have the cuff at the heart level, whatever the position of the patient.
5. Measure blood pressure in both arms at first visit to detect possible differences due to peripheral vascular disease. In this instance, take the higher value as the reference one.
6. Measure blood pressure 1 and 5 minutes after assumption of the standing position in elderly subjects, diabetic patients, and in other conditions in which postural hypotension may be frequent or suspected.

[a]2007 Guidelines for the Management of Arterial Hypertension.[94]

Table 6 Diagnostic Criteria for Dyslipidemia[a]

Lipid	Value, mg/dL	Criteria
Total cholesterol	< 200	Desirable
	200-239	Borderline high
	≥ 240	High
LDL-C	< 100	Optimal
	100-129	Normal/slightly high
	130-159	Borderline high
	160-189	High
	≥ 190	Very high
HDL-C	< 40	Low
	≥ 60	High
Triglycerides	< 150	Normal
	150-159	Borderline high
	200-499	High
	≥ 500	Very high

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

[a]Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (ATP III), 2002.[106]

Table 6 shows the diagnostic criteria for dyslipidemia specified by the 2002 report of the Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).[106]

In the EUROASPIRE II study of Europeans over 70 years of age with serious coronary heart disease, 58.8% of

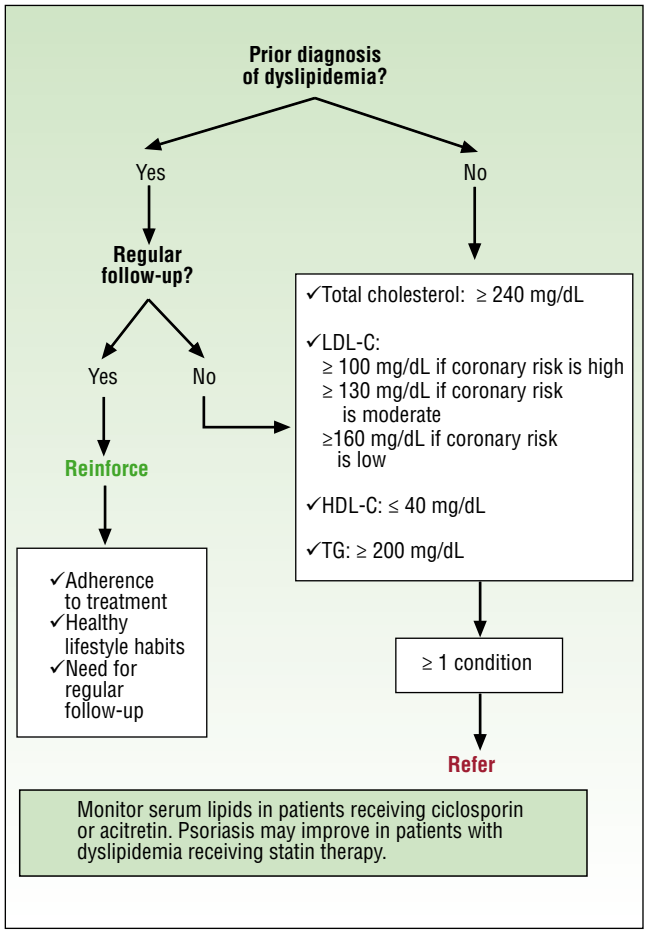

Figure 5. Management of dyslipidemia. HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

those surveyed had a total cholesterol value greater than 5 mmol/L (193 mg /dL); in Spain, this percentage was somewhat lower (53%).[107] The World Health Organization MONICA study, which defined hypercholesterolemia as a total cholesterol level greater than 6.5 mmol/L (251 mg/dL), reported a prevalence in Catalonia of 21% in men and 19% in women.[108] According to a meta-analysis of cardiovascular risk factors in Spain, 23% of the population have a total cholesterol level higher than 250 mg/dL.[109] The HISPALIPID study found a prevalence of dyslipidemia in Spain of 21.4% (95% CI, 20.3%-22.5%) among primary care patients and of 36.4% (95% CI, 34.5%-36.4%) among patients receiving specialist care.[110] In that study, prevalence was observed to rise with age, reaching a peak in the sixth decade of life among men and the seventh among women; a direct relationship was also observed between the prevalence of dyslipidemia and increased BMI.

VI.4.b. Scientific Evidence

We reviewed 19 studies examining the association between dyslipidemia and psoriasis that provided data on prevalence and/or measures of risk (Appendix 6). Five were carried out in the United Kingdom, 4 in Germany, 3 in Italy, 3 in the United States, 2 in Israel, 1 in Kuwait, 1 in China, and 1 in the Netherlands. We also reviewed a further 7 studies in which the results of lipid parameters were presented as continuous variables, making it impossible to estimate prevalence and risk in the comparison between patients with and without psoriasis. The results of those 7 studies are presented in an annex to Appendix 6.

Eleven of the 19 studies were large case-control series taken from automated databases, as follows: 4 from the General Practice Research Database in the United Kingdom; 2 from the Clalit Health Services database in Israel; 2 from a German health insurance database; 1 from a medical service for veterans in the United States; 1 from the IMS Health Integrated Claims Database and the MarketScan Commercial Claims and Encounters Database in the United States; and 1 from the National Health and Wellness Survey database in the United States. The remaining 8 studies analyzed smaller series of patients recruited from dermatology offices or from groups of patients hospitalized due to psoriasis. There were 4 cohort and 2 cross-sectional studies, and the remainder were case-control studies.

The definition of dyslipidemia varied between studies. In most cases patients with dyslipidemia were identified by the code assigned to this disease in the database or the condition was assumed if the patient was receiving lipid-lowering medication; the selection criterion used in other studies was a total cholesterol level exceeding 6.5 mmol/L.

The prevalence of dyslipidemia among patients with psoriasis in these studies varied widely, ranging from 6.4% to 50.9% in psoriasis in general (severity unspecified), from 5.2% to 29.9% in patients with mild psoriasis, and from 6.0% to 29.9% in patients with severe psoriasis. A significant association was found between psoriasis and dyslipidemia in 17 of the studies. With respect to the risk of dyslipidemia in patients with psoriasis of unspecified severity, the case-control and cross-sectional studies reported an OR ranging from 1.1 (95% CI, 0.7-1.7; adjusted for age and sex) to 4.35 (95% CI, 3.73-5.06; unadjusted). In the group of patients with mild psoriasis, the OR ranged from 1.16 (95% CI, 1.12-1.21; adjusted for age, sex, hypertension, tobacco use, and BMI) to 3.38 (95% CI, 2.63-4.34; unadjusted). In patients with severe psoriasis, the OR ranged from 1.04 (95% CI, 0.84-1.28; adjusted for age, sex, hypertension, tobacco use, and BMI) to 5.55 (95% CI, 3.49-8.83; unadjusted). Risk of dyslipidemia was assessed in only 1 of the cohort studies, which reported an HR of 1.17 (95% CI, 1.11-1.23; unadjusted).

VI.4.c. Management of Dyslipidemia in the Dermatology Office

Figure 5 is an algorithm for the clinical management of dyslipidemia in the dermatology office.

VI.4.c.a. Targeted History

Personal or family history of dyslipidemia. Use of lipid-lowering medication.

VI.4.c.b. Specific Physical Examination

Not required.

VI.4.c.c. Specific Additional Tests

Measurement of total cholesterol, LDL-C, HDL-C, and triglycerides in plasma.

VI.4.c.d. Frequency of Screening

Patients receiving local treatment for their psoriasis should be screened annually and those on systemic treatment every 6 months.

VI.4.c.e. Referral Criteria for Patients With Suspected Dyslipidemia

Total cholesterol: ≥ 240 mg/dL. LDL-C: ≥ 100 mg/dL in patients with high coronary risk; ≥ 130 mg/dL in patients with moderate coronary risk; and ≥ 160 mg/dL in patients with low coronary risk (in accordance with the updated National Cholesterol Education Program Adult Treatment Panel III [NCEP ATP III] guidelines[111]). HDL-C: < 40 mg/dL. Triglycerides: ≥ 200 mg/dL.

VI.4.c.f. Recommended Action in Patients Already Diagnosed With Dyslipidemia

In the case of patients who are being monitored by their primary care physician or by a specialist, stress the importance of healthy lifestyle habits (diet, exercise, smoking cessation, and moderate alcohol intake), adherence to prescribed treatment, and regular follow-up visits.

Refer patients with dyslipidemia who are not being regularly monitored to the appropriate clinician.

VI.4.c.g. Implications of Psoriasis Treatment in Dyslipidemia

Based on the results of pivotal controlled clinical trials of adalimumab (involving 4419 patients treated with adalimumab and 2552 patients treated with placebo or an active comparator during the control period), elevated blood lipids can be considered a very common adverse reaction (SPC) for which there is at least a possible causal relationship with adalimumab, although significant differences with placebo have not been reported. Elevated blood lipids are very common in patients treated with ciclosporin, hence the recommendation to determine blood lipid values prior to initiating treatment and following the first month of treatment. Should blood lipids become elevated, the intake of fats with food should be restricted, and, if necessary, the ciclosporin dose reduced (SPC).

Elevated serum triglyceride levels have been reported in patients treated with acitretin, particularly in those with predisposing factors such as a family history of lipid metabolism disturbances, diabetes, obesity, alcohol abuse, and tobacco use. These changes are dose-dependent and can be controlled by dietary measures (including restriction of alcohol use) and/or dose reductions. Serum triglycerides must be monitored before starting treatment, 1 month after the commencement, and then every 3 months during treatment (SPC).

VI.4.c.h. Implications of Dyslipidemia Treatment in Psoriasis

In our review of the literature, we found just 1 study in which statins were specifically used to treat psoriasis. It was a pilot study conducted in Russia in 2007 by Shirinsky and Shirinsky[112] to evaluate the efficacy of simvastatin in plaque psoriasis. Seven patients were treated with simvastatin 40 mg/d for 8 weeks and the authors reported a statistically significant reduction (47.34%) in PASI scores. Two patients achieved a 50% improvement in PASI score while another 2 achieved a 75% improvement. Although this was a small, uncontrolled pilot study in which lipid levels were not measured, the results indicate that statins could be useful in the management of psoriasis. Considering what we know about the mechanisms of psoriasis, it is biologically possible that statins might be of benefit in the treatment of this condition because of their immunomodulatory and anti-inflammatory effects. Statins, for example, downregulate adhesion molecules such as lymphocyte function-associated antigen 1(LFA-1), the antigen targeted by efalizumab, and inhibit the production of inflammatory cytokines such as TNF-α, the target of infliximab, etanercept, and adalimumab. They also inhibit IL-17 production and interfere with the activation and migration of type T_H1 cells, which play a key role in the pathogenesis of psoriasis.[113]

Table 7 International Diabetes Federation Criteria for Metabolic Syndrome (2005)[115]

Abdominal obesity (waist circumference > 94 cm in men and > 80 cm in women) plus 2 or more of the following clinical situations:
— Triglycerides > 150 mg/dL or specific treatment
— HDL-C < 40 mg/dL in men or < 50 mg/dL in women or specific treatment
— BP > 130/85 mm Hg or treatment for hypertension
— Fasting plasma glucose > 100 mg/dL or previously diagnosed type 2 diabetes

Abbreviations: BP, blood pressure; HDL-C, high-density lipoprotein cholesterol.

VI.5. Metabolic Syndrome and Psoriasis

VI.5.a. Introduction

Metabolic syndrome is a cluster of highly prevalent disorders that are all risk factors for cardiovascular disease and type 2 diabetes. The risk factors included in the diagnosis of metabolic syndrome are dyslipidemia, hypertension, insulin resistance, established diabetes, proinflammatory states, and thrombosis.[114] There are various definitions of metabolic syndrome but they all include these essential components. The 2 most widely used definitions, which are very similar, are those used by the International Diabetes Federation[115] (Table 7) and the NCEP ATP III[116] (Table 8).

The components of metabolic syndrome coexist more often than would be expected by chance, and the risk of cardiovascular disease associated with this clustering is greater than that associated with any of the individual components.[117] Metabolic syndrome is important because of its high prevalence (12% in the Spanish active working population according to the MEYSAS register[118]and 22% in

Table 8 National Cholesterol Education Program (ATP III) Criteria for Metabolic Syndrome (2002)[116]

Three or more of the following criteria:

- Abdominal obesity (waist circumference > 102 cm in men and > 88 cm in women)
- Triglycerides > 150 mg/dL or specific treatment
- HDL-C < 40 mg/dL in men or < 50 mg/dL in women or specific treatment
- BP > 130/85 mm Hg or treatment for hypertension
- Fasting glucose > 100 mg/dL

Abbreviations: BP, blood pressure; HDL-C, high-density lipoprotein cholesterol.

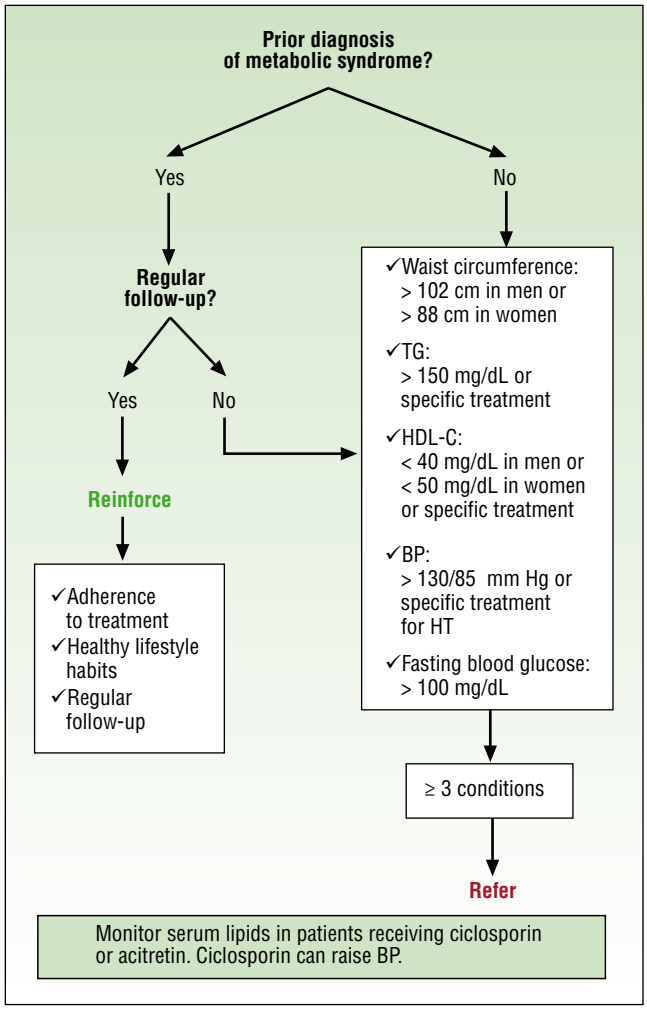

Figure 6. Management of metabolic syndrome. TG indicates triglycerides; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure; HT, hypertension.

the general Spanish population[114]) and its close association with cardiovascular disease. In the United States, the age-adjusted prevalence of cardiovascular disease is 14% in patients with metabolic syndrome and 19% in those with type 2 diabetes.[119]

VI.5.b. Scientific Evidence

Recent studies have detected an increased prevalence of metabolic syndrome in patients with psoriasis, irrespective of the definition used. We reviewed 9 articles examining the association between metabolic syndrome and psoriasis (Appendix 7): 3 relating to Italy, 2 to Germany, 1 to Kuwait, 1 to the United States, 1 to Spain, and 1 to Israel. Two of the studies involved large series of patients selected from automated databases (a health insurance database in Germany and the Clalit Health Services database in Israel). The remaining studies analyzed smaller series of patients recruited from dermatology offices or from groups of patients hospitalized due to psoriasis. In total, there were 6 case-control studies, 2 cross-sectional studies, and 1 cohort study.

These studies show that the presence of metabolic syndrome is associated with psoriasis severity and report an increased frequency of the syndrome in psoriasis patients with more severe disease. While differences in study design and data sources resulted in considerable variations in prevalence, most of the studies found a highly significant association between the risk of metabolic syndrome and psoriasis. In 1 study, the prevalence of metabolic syndrome in patients with mild psoriasis (ie, patients not on systemic treatment) was 16% (OR = 2.6; 95% CI, 2.1%-3.3%), compared to 26% in those with severe psoriasis (ie, on systemic treatment) (OR = 4.9; 95% CI, 3.2%-7.6%). This estimated risk is very similar to that reported for patients with severe psoriasis in Spain (OR = 4.1; 95% CI, 1.6%-10.5%), although the prevalence was higher in the Spanish study (44%). The 2 studies used the same diagnostic criteria. The studies that did not take psoriasis severity into account reported a highly variable prevalence of metabolic syndrome, with rates ranging from 0.18% (prevalence ratio, 2.9) in a cross-sectional study based on German health insurance data to 58.1% (prevalence ratio, 1.7) in a dermatology department in the United States.

VI.5.c. Management of Metabolic Syndrome in the Dermatology Office

Figure 6 is an algorithm for the clinical management of metabolic syndrome in the dermatology office.

VI.5.c.a. Targeted History

Apply the history-taking procedures described for diabetes, hypertension, obesity, and dyslipidemia (see corresponding sections).

VI.5.c.b. Specific Physical Examination

Blood pressure and waist circumference (see section VI.1.c.b. for recommendations on correct waist circumference measurement).

VI.5.c.c. Specific Additional Tests

Triglycerides, HDL-C, and fasting blood glucose.

VI.5.c.d. Frequency of Screening

Patients receiving local treatment for their psoriasis should be screened annually and those on systemic treatment every 6 months.

VI.5.c.e. Referral Criteria for Patients With Suspected Metabolic Syndrome

Patients with suspected metabolic syndrome should be referred to a specialist in accordance with the criteria specified in the 2002 NCEP ATP III guidelines.[116]

VI.5.c.f. Recommended Action in Patients Already Diagnosed With Metabolic Syndrome

In the case of patients who are being monitored by their primary care physician or by a specialist, stress the importance of adherence to the treatment prescribed, including all recommendations on healthy lifestyle habits (diet, exercise, smoking cessation, and moderate alcohol intake), and the importance of continuing with regular follow-up visits.

VI.5.c.g. Implications of Psoriasis Treatment in Metabolic Syndrome

See chapters on obesity, hypertension, dyslipidemia, and diabetes.

VI.5.c.h. Implications of the Treatment of Metabolic Syndrome in Psoriasis

See chapters on obesity, hypertension, dyslipidemia, and diabetes.

VI.6. Other Cardiovascular Risk Factors

The study of cardiovascular risk factors described in the previous chapter should be completed with measurement of creatinine levels and, if possible, estimation of glomerular filtration rate as some of these disorders (eg, diabetes and hypertension) can lead to impaired kidney function.

There is debate on whether hyperuricemia and hyperhomocysteinemia are true cardiovascular risk factors, but in view of the evidence available (see sections VI.6.a. and VI.6.b.) it is not considered necessary for dermatologists to test for these 2 disorders.

VI.6.a. Hyperuricemia

Hyperuricemia is an abnormally high level of uric acid in the blood, that is over 6 mg/dL in women and over 7 mg/dL in men. It is caused by the overproduction and/or the underexcretion of uric acid. Its prevalence in the general population is approximately 7%, but only a small proportion of patients have clinical manifestations (acute or chronic gouty arthritis, chronic nephropathy).[120]

An association has been reported between hyperuricemia and psoriasis.[32] Diseases involving increased cell turnover, such as psoriasis, cause overproduction of uric acid,[120] and certain drugs used to treat psoriasis, including ciclosporin and adalimumab, can also cause elevated levels of uric acid in the blood (SPC).

Hyperuricemia is important because numerous epidemiological studies have found an association between uric acid levels and a wide range of cardiovascular disorders, such as hypertension, metabolic syndrome, coronary artery disease, cerebrovascular disease, vascular dementia, and preeclampsia. Nonetheless, because hyperuricemia is often associated with established cardiovascular risk factors, its role as an independent risk factor is controversial and there is insufficient evidence to recommend the treatment of asymptomatic hyperuricemia.[121]

VI.6.b. Hyperhomocysteinemia

Homocysteine is a sulfur-containing amino acid produced as an intermediate metabolite of methionine. This essential amino acid is a precursor and component of peptides and proteins, and plays an important role in methyl group transfer. Its metabolism is linked to that of several B vitamins, in particular vitamins B_9 (folic acid), B_6, and B_{12}. Elevated blood homocysteine levels are seen in patients with inadequate levels of any of these vitamins. Patients taking methotrexate should also be prescribed folic acid supplements to prevent, among other things, hyperhomocysteinemia. Normal homocysteine levels range between 5 and 15 µmol/L.[122] Hyperhomocysteinemia is defined as mild when levels are between 16 and 30 µmol/L, as moderate when they are between 30 and 100 µmol/L, and as severe when they are over 100 µmol/L.[123]

Several epidemiological studies have shown hyperhomocysteinemia to be associated with an increased risk of coronary, cerebral, peripheral, and aortic atherosclerosis. This risk is independent of other cardiovascular risk factors and increases in homocysteine levels.[124] Hyperhomocysteinemia has also been linked to psoriasis, and its prevalence ranges from 50% to 62.5% in this setting.[125,126] Considering the above, it might seem wise to test homocysteine levels in patients with psoriasis, but according to a recent Cochrane review, there is no evidence to support interventions aimed at reducing homocysteine levels to prevent cardiovascular episodes.[127]

VII. OTHER DISEASES ASSOCIATED WITH PSORIASIS

VII.1. Nonalcoholic Fatty Liver Disease and Psoriasis

VII.1.a. Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disorder in the western world. It is defined as an excessive accumulation (>5%) of triglycerides in the liver cells of patients without a history of excessive alcohol consumption (> 140 g/wk in men and > 70 g/wk in women).[128] Clinically, it is classified according to severity: *a)* simple NAFLD, which consists of fatty infiltration only; *b)* NAFLD with hepatitis (nonalcoholic steatohepatitis [NASH]), in which there is fatty infiltration and lobular inflammation; and *c)* NAFLD with fibrosis or cirrhosis, which may progress to hepatocellular carcinoma.[129]

The prevalence of simple NAFLD in the general population in the United States is estimated at between 20% and 30%,[130,131] contrasting with rates of 2% and 3% for NASH.[132] In obese patients, the prevalence of NAFLD and NASH has been estimated at 91% and 37%, respectively.[133]

Most patients with NAFLD do not manifest liver symptoms.[134] The disorder should generally be suspected in patients with no history of alcohol abuse or hepatitis and slight abnormalities in hepatic transaminases. Typically, these take the form of elevations in both aspartate aminotransferase (AST) and, in particular, of alanine aminotransferase (ALT), with an ALT:AST ratio of > 1 (except

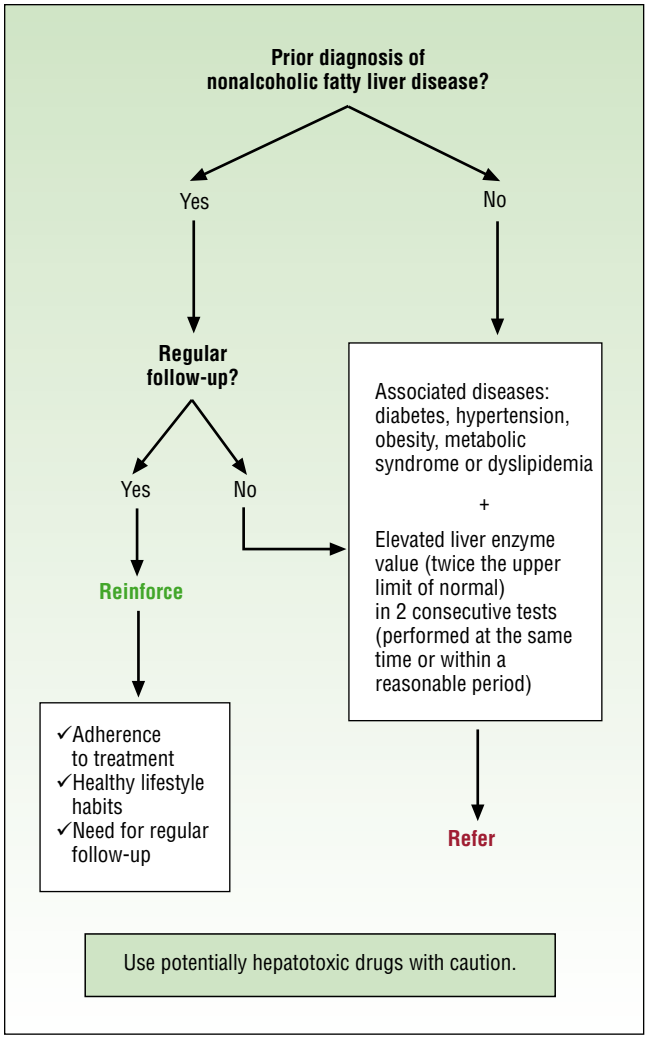

Figure 7. Management of nonalcoholic fatty liver disease

in patients with advanced NAFLD and fibrosis in whom this ratio is inverted). Alkaline phosphatase and gamma-glutamyltransferase (GGT) levels may also be slightly elevated. The levels of all these parameters do not tend to be more than 3 times the upper limit of normal. NAFLD should also be suspected in patients with hepatic steatosis on ultrasound. Ultrasound, however, is not very sensitive in patients with steatosis of less than 30%,[135] nor does it distinguish between simple NAFLD and NASH. Other, rare, signs of NAFLD are nonspecific liver disorder symptoms such as tiredness, poor general health, right upper quadrant pain, and sleep disorders, as well as hepatomegaly and other signs of chronic liver disease.

Computed tomography and MRI can be of diagnostic value in NAFLD, but liver biopsy is the only definitive test for distinguishing NAFLD from NASH. Biopsy can also be used to rule out other causes of liver disease, to estimate the presence and degree of fibrosis, and to establish prognosis. Nevertheless, because there is no effective treatment for NAFLD, in most cases, biopsy does not add any information that might modify treatment. Because the risks outweigh the benefits, it is not recommended as a routine test. Current research is exploring the viability of alternative, noninvasive diagnostic methods.

An accurate diagnosis is important for determining prognosis and assessing the risk of liver damage due to medication. NAFLD progresses to NASH within an average of 7 to 10 years in 30% of cases, while NASH progresses to cirrhosis within 5 years in 13% of patients and within 10 years in 25% of patients.[136] The risk of hepatocellular carcinoma in NAFLD is similar to that observed in patients with cirrhosis due to alcohol or hepatitis C virus infection.[137] The presence of fat deposits in the liver, even in the absence of inflammation, increases the risk of severe hepatotoxicity due to drugs that do not generally carry this risk.[138]

NAFLD has been associated with obesity, diabetes, insulin resistance, hypertension, dyslipidemia, and, in particular, metabolic syndrome. Insulin resistance and metabolic syndrome have been reported in 98% and 80% of patients with NAFLD, respectively,[139] and several studies have suggested that NAFLD is the hepatic expression of metabolic syndrome.[140,141] Indeed, a series of pathogenic mechanisms common to the components of metabolic syndrome, including elevated proinflammatory cytokines (particularly TNF-α and IL-6) and reduced adiponectin levels, have been implicated in NAFLD.[142] These mechanisms have also been implicated in psoriasis, and recent studies have reported a higher prevalence of NAFLD in patients with psoriasis.[143,144]

VII.1.b. Scientific Evidence

We reviewed 2 studies, both conducted in Italy, that analyzed the prevalence of NAFLD in patients with psoriasis[143,144] (Appendix 8). The first, a case-control study, with matching by age, sex, and BMI, found a considerable association between NAFLD and psoriasis, with a prevalence of 47% (OR = 2.7; 95% CI, 1.5%-3.5%).[143] Although the authors did not adjust for the presence of metabolic syndrome, they did match cases and controls by BMI and therefore their findings might indicate that the association between psoriasis and NAFLD is independent of obesity. The second study, a cross-sectional study, detected a high prevalence of NAFLD (59%) in patients with psoriasis.[144]

VII.1.c. Management of NAFLD in the Dermatology Office

Figure 7 is an algorithm for the clinical management of NAFLD in the dermatology office.

VII.1.c.a. Targeted History

Alcohol consumption.

VII.1.c.b. Specific Physical Examination

Not required.

VII.1.c.c. Specific Additional Tests

Because slight changes in liver biochemistry values can be detected in early stages of NAFLD, the following tests should be ordered in patients with suspicious signs or

symptoms: ALT (U/L), AST (U/L), alkaline phosphatase (U/L), and GGT (U/L).

Other tests such as ultrasound, computed tomography, MRI, and liver biopsy are not necessary as these are the responsibility of the specialist.

VII.1.c.d. Frequency of Screening

Patients receiving local treatment for their psoriasis should be screened annually and those on systemic treatment every 6 months.

VII.1.c.e. Referral Criteria for Patients With Suspected NAFLD

NAFLD should be suspected in patients with an associated comorbidity (metabolic syndrome, obesity, diabetes, dyslipidemia, or hypertension) in whom elevated hepatic transaminases are detected in 2 consecutive tests (performed at the same time or within a reasonable period). Levels do not tend to be more than 3 times the upper limit of normal.

Patients in whom elevated hepatic transaminase levels might be explained by other factors (eg, hepatitis, excessive alcohol consumption, use of hepatotoxic drugs, or hemochromatosis) should also be referred to a specialist but not with a clinical suspicion of NAFLD.

VII.1.c.f. Recommended Action in Patients Already Diagnosed With NAFLD

In the case of patients who are being monitored by their primary care physician or by a specialist, stress the importance of adherence to the treatment prescribed, including all recommendations on healthy lifestyle habits (diet, exercise, and smoking and alcohol cessation), and the importance of continuing with regular follow-up visits.

Patients with abnormal biochemical tests who are not being regularly monitored for fat deposits in the liver should be referred to a specialist.

VII.1.c.g. Implications of Psoriasis Treatment in NAFLD

Extra caution should be used when prescribing potentially hepatotoxic drugs to patients with NAFLD or an associated comorbidity (especially metabolic syndrome).

VII.1.c.h. Implications of NAFLD Treatment in Psoriasis

None described.

VII.2. Inflammatory Bowel Disease and Psoriasis

VII.2.a. Introduction

Inflammatory bowel disease (IBD) comprises a group of diseases characterized by chronic inflammation of the gastrointestinal tract. The 2 most common diseases in this group are ulcerative colitis and Crohn disease. IBD mainly affects young people in late adolescence and early adulthood and has a considerable impact on quality of life, family, and work.[145-147]

It also imposes a considerable economic burden on the health care system. Direct healthcare costs—mainly medical and surgical hospitalization—are high[148] but indirect costs (loss of productivity due to absence from work) are even higher.[149,150]

An additional problem is the growing incidence of IBD in industrialized countries in recent years, with an estimated annual rate of 9 new cases per 100 000 population.[151-153]

IBD is characterized by periods of disease activity or recurrence alternating with periods of inactivity or remission. A considerable proportion of patients with IBD have associated systemic manifestations affecting other organs, such as the joints, eyes, and skin. Some patients also develop IBD-related complications, including toxic megacolon, gastrointestinal bleeding, bowel perforation or obstruction, colorectal cancer, and perianal disease.

The aims of treatment are to maximize remission, minimize adverse effects due to medication or surgery, relieve symptoms, resolve complications, and restore quality of life. To achieve these aims, a multidisciplinary approach involving physicians, nurses, dieticians, social workers, and other professionals, is required.[154]

Although the pathogenesis of IBD is not yet fully understood, it is known that genetic and environmental factors such as alterations in luminal bacterial and increased intestinal permeability play an important role in the dysregulation of intestinal immunity, leading to gastrointestinal injury. Genetic analysis has identified risk factors shared by psoriasis and IBD. Several authors have reported polymorphisms in genes encoding the IL-23 receptor associated with psoriasis,[155-158] and similar polymorphisms have been detected in ulcerative colitis and Crohn disease.[159-161]

Ulcerative colitis and Crohn disease have overlapping and very distinct clinical and pathologic features. In ulcerative colitis, for example, the mucosa of the colon becomes inflamed but the small intestine is spared. Ulcerative colitis mainly affects the rectum and the sigmoid colon and can extend proximally and continuously into the rest of the colon. In Crohn disease, however, both the mucosa and the entire bowel wall become inflamed and any part of the gastrointestinal tract can be affected, from the mouth to the anus.

Diagnosis of IBD is complicated and requires a full physical examination and medical history. A number of tests, including blood and fecal tests, endoscopy, biopsy, and imaging studies can help to exclude other causes and confirm a diagnosis. The aim of this guide is not to deal with the definitive diagnosis of IBD but rather to alert the dermatologist to the need to refer patients who present with signs or symptoms indicative of IBD (VII.2.c.a.) to a specialist.

VII.2.b. Scientific Evidence

We reviewed 4 studies that examined the association between psoriasis and ulcerative colitis and Crohn disease. Two of the studies, including 1 in children, were carried out in Germany; the other 2 were carried out in Israel and the United States (Appendices 9 and 10). All 4 studies were based on large series of patients and controls selected from automated databases (a health insurance database in the 2 German studies, the Clalit Health Services database in Israel, and the IMS Health Integrated Claims Database in

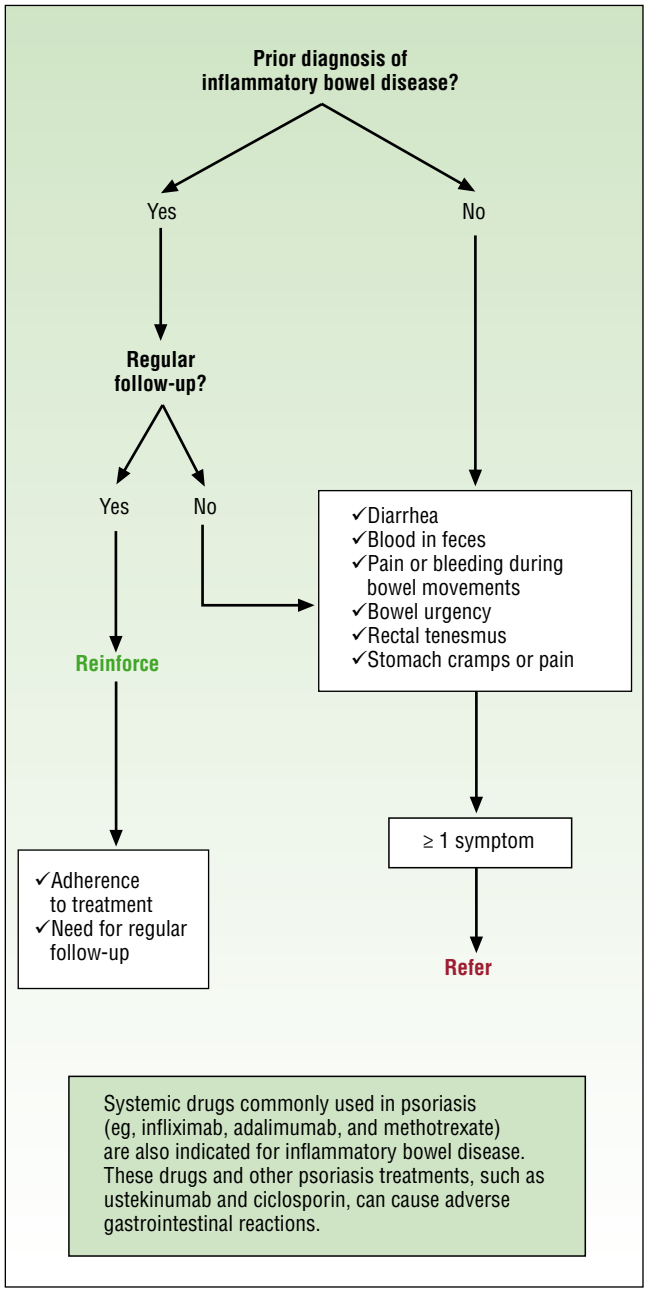

Figure 8. Management of inflammatory bowel disease.

the United States). There were 2 case-control studies and 2 cross-sectional studies.

The 3 studies in adults found a significant association between psoriasis and ulcerative colitis, with increased risk detected in patients with psoriatic arthritis compared to patients with psoriasis alone. No significant association was found for ulcerative colitis in children.

In the case of Crohn disease, in contrast, a significant association was found with psoriasis in both children and adults. As occurred with ulcerative colitis, the risk was higher in patients with psoriatic arthritis than in those with psoriasis alone.

VII.2.c. Management of IBD in the Dermatology Office

Figure 8 is an algorithm for the clinical management of IBD in the dermatology office.

VII.2.c.a. Targeted History

Patients should be questioned about gastrointestinal pain and other symptoms. Possible symptoms are *a)* diarrhea (stools may contain mucus or blood), nocturnal diarrhea, and incontinence; *b)* constipation (this can be a primary symptom of ulcerative colitis involving the rectum [proctitis]); *c)* pain or bleeding during bowel movements; *d)* bowel urgency; *e)* rectal tenesmus; *f)* stomach cramps or pain (typically affecting the lower right quadrant or around the navel in Crohn disease and the lower left quadrant in moderate or severe ulcerative colitis); *g)* nausea and vomiting; and *h)* a range of nonspecific symptoms associated with IBD including fever, loss of appetite, weight loss, fatigue, and night sweats.

VII.2.c.b. Specific Physical Examination

Not required.

VII.2.c.c. Specific Additional Tests

None required.

VII.2.c.d. Frequency of History Taking

Patients receiving local treatment for their psoriasis should be screened annually and those on systemic treatment every 6 months.

VII.2.c.e. Referral Criteria for Patients With Suspected IBD

Patients with symptoms associated with inflammatory injury in the gastrointestinal tract (frequent diarrhea, blood in stools, rectal pain or bleeding, bowel urgency, and stomach pain or cramps) should be referred to a specialist.

VII.2.c.f. Recommended Action in Patients Already Diagnosed With IBD

In the case of patients who are being monitored by their primary care physician or by a specialist, stress the importance of adherence to the treatment prescribed and of continuing with regular follow-up visits.

Refer patients with IBD who are not being regularly monitored to an appropriate clinician.

VII.2.c.g. Implications of Psoriasis Treatment in IBD

Systemic drugs commonly used in psoriasis (eg, infliximab, adalimumab, and methotrexate) are also indicated for certain cases of refractory IBD. Infliximab, for example, is used to treat severe active or fistulizing Crohn disease in adults and children aged over 6 years who do not respond to conventional treatment. It is also used in moderate to severe active ulcerative colitis (SPC). Adalimumab is also indicated for severe active Crohn disease when conventional treatment fails, while methotrexate can be effective in treating active Crohn disease in steroid-dependent patients[162] and in preventing relapse.[163]

It is also important to note that certain psoriasis treatments can cause adverse gastrointestinal effects (described below) that can complicate a diagnosis of IBD.

- Infliximab: abdominal pain, diarrhea, nausea, and dyspepsia (common) (SPC).
- Adalimumab: abdominal pain, nausea, and vomiting (very common). Gastrointestinal hemorrhage, dyspepsia, and gastroesophageal reflux disease (common) (SPC).
- Ustekinumab: diarrhea (common) (SPC).
- Methotrexate: loss of appetite, nausea, vomiting, abdominal pain, inflammation and ulcers in mouth and throat (especially within the first 24-48 hours), stomatitis, and dyspepsia (very common); diarrhea (especially within the first 24-48 hours) (very common). Diarrhea and ulcerative stomatitis are common toxic effects and require discontinuation of therapy because of the risk of ulcerative enteritis and fatal intestinal perforation (SPC).
- Ciclosporin: nausea, vomiting, abdominal pain, and diarrhea (common) (SPC).

VII.2.c.h. Implications of IBD Treatment in Psoriasis

Anti-TNF therapy can cause recurrence of psoriasis or aggravate the condition and one of the forms it can trigger is pustular psoriasis (mainly palmoplantar).

VII.3. Cancer and Psoriasis

VII.3.a. Introduction

There are approximately 35 types of lymphomas, divided into 2 main categories: *1)* Hodgkin lymphoma and *2)* non-Hodgkin lymphoma.

They account for approximately 4.1% of all cancers in Spain and the majority (85.3%) are non-Hodgkin lymphoma. In Spain, the incidence of Hodgkin and non-Hodgkin lymphoma in 2008 was 2.4 and 11.4 cases per 100000 population, respectively; both types of lymphoma are more common in men than in women.[164]

Lymphoma can be difficult to diagnose because it is often asymptomatic and, when there are symptoms, these can be confused with those of common conditions such as flu or other viral infections. The most characteristic sign is the appearance of swollen, painless lymph nodes in cervical, axillary, inguinal, or supraclavicular areas. Other signs and symptoms include splenomegaly, weight loss, fever, night sweats, loss of appetite, fatigue, cough, and dyspnea. A definitive diagnosis is established by biopsy of the affected lymph node or tissue (with a sufficiently large specimen for histologic evaluation), immunohistochemistry, and molecular techniques.[165]

There is an association between psoriasis and the development of lymphoma. The risk of lymphoma in patients with psoriasis may be attributable to either the pathophysiology of psoriasis or its treatment.[166] Pathophysiologic mechanisms include impaired immune response involving increased activity of T cells, antigen-presenting cells (eg, dendritic cells), and T_H1 cells.[167] Increased B-cell activity has also been detected in psoriasis, indicating significant activation of the immune system.[168-170] Since psoriasis is an immune-mediated condition, its pathophysiology may be associated with an increased risk of lymphoma, as has been demonstrated for other T_H1-mediated diseases, such as rheumatoid arthritis.[171,172] Patients with moderate to severe psoriasis tend to take systemic drugs (eg, ciclosporin and methotrexate) that have been associated with the development of lymphoma in psoriasis patients.[173-178]

Finally, patients with psoriasis have an increased risk of non-melanoma skin cancer (NMSC). Approximately 97% of all skin cancers are believed to be NMSCs; these are epithelial tumors, the most common of which are basal cell carcinoma and squamous cell carcinoma.[179] As occurs with lymphoma, several psoriasis treatments, including psoralen-UV-A (PUVA) and ciclosporin, increase the risk of NMSC, and particularly that of squamous cell carcinoma.[166]

VII.3.b. Scientific Evidence

We reviewed 7 studies that analyzed the association between cancer (lymphoma and skin cancer) and psoriasis (Appendix 11). Of these, 2 were carried out in the United Kingdom, 1 in the United States, 2 in Sweden, 1 in Finland, and 1 in Denmark. All 7 were cohort studies. Four analyzed the risk of cancer in hospitalized patients receiving systemic treatment for severe psoriasis, and the other 3 were population-based studies. Of these latter studies, 2 analyzed risk according to psoriasis severity (severe [systemic therapy] vs less severe [nonsystemic therapy]), while 1 analyzed risk in patients aged over 65 years.

Two of the population-based studies analyzed the risk of lymphoma (Hodgkin or non-Hodgkin) in patients with psoriasis. The study conducted in the United Kingdom in general practice patients aged over 65 years found that those with psoriasis had an increased risk of developing lymphoma.[180] The US study concluded that patients with psoriasis had a greater risk of developing a malignancy than those with hypertension, with increased risk observed in those with severe psoriasis (treated with systemic agents) than in those with less severe psoriasis (not treated with systemic agents).[181]

Three studies analyzed the risk of Hodgkin lymphoma in patients with psoriasis. Two of the studies showed an association, with an increased risk of lymphoma seen in patients treated with systemic agents.[182,183] The third study, conducted in Sweden, did not detect a greater risk of Hodgkin lymphoma in patients hospitalized for psoriasis compared with the general population.[184]

The studies conducted in Sweden, Finland, and Denmark analyzed the risk of non-Hodgkin lymphoma in patients hospitalized for psoriasis,[183-186] and all concluded that the risk was slightly higher than in the general population, although the differences were statistically significant in only 2 of the studies.[184,186] The UK study found no differences in the risk of non-Hodgkin lymphoma between patients with and without psoriasis.[180]

Three studies analyzed the risk of cutaneous T-cell lymphoma. One concluded that patients with psoriasis had a greater risk of developing this form of lymphoma than those without, with a higher risk detected in patients who had received systemic therapy.[182] The other 2 studies determined that the risk of mycosis fungoides was much higher in patients with psoriasis than in the general population.[184,186]

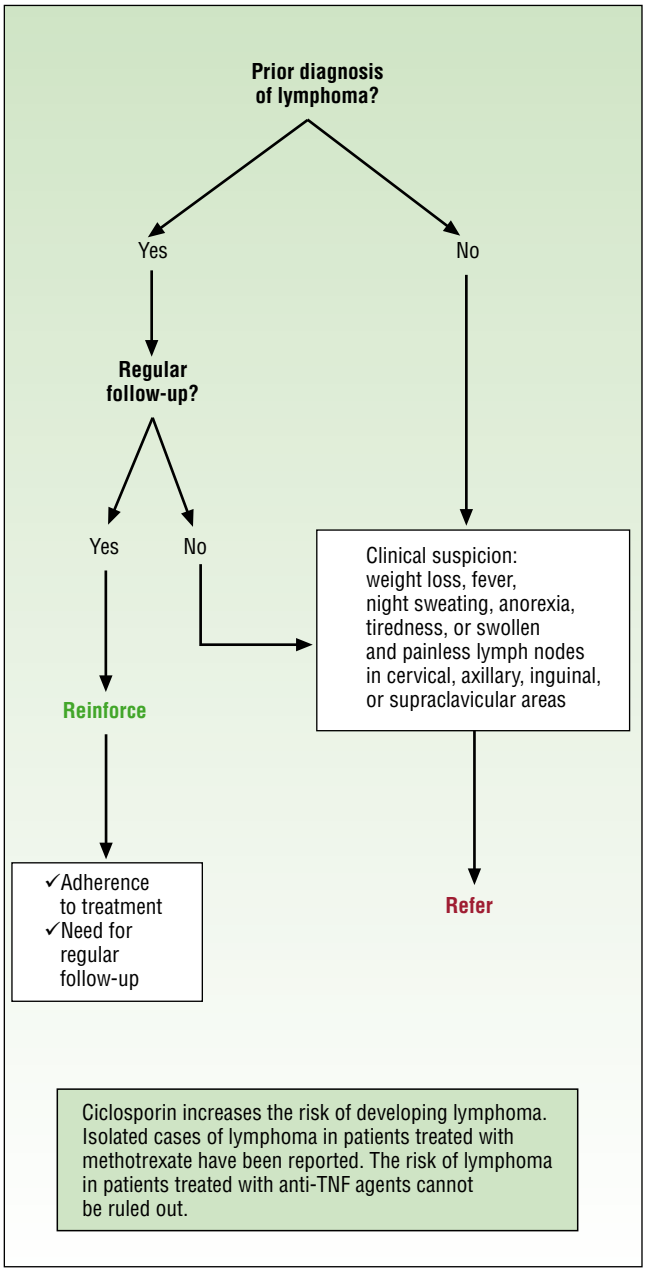

Figure 9. Management of lymphoma. TNF indicates tumor necrosis factor.

All of the 5 studies that analyzed the risk of skin cancer in patients with psoriasis found an association between psoriasis and NMSC.[181,183-186] No such association, however, was found for melanoma.

VII.3.c. Management of Lymphoma in the Dermatology Office

Figure 9 is an algorithm for the clinical management of lymphoma in the dermatology office. Because dermatologists are specialists in skin cancer, this section will focus exclusively on the clinical management of lymphoma, although other types of cancer will be discussed in the section on the implications of psoriasis treatment in cancer (VII.3.c.g).

VII.3.c.a. Targeted History

Because patients with psoriasis have an increased risk of lymphoma, dermatologists should be alert to signs and symptoms, such as swollen lymph nodes, weight loss, fever, night sweats, loss of appetite, tiredness, cough, and dyspnea.

VII.3.c.b. Specific Physical Examination

Confirm the presence of enlarged lymph nodes in patients who report swelling.

VII.3.c.c. Specific Additional Tests

Patients with lymphoma generally have abnormal blood test results and elevated lactate dehydrogenase and β-2-microglobulin levels. These tests, however, are not recommended in the dermatology office as none of the alterations mentioned are specific to lymphoma.

VII.3.c.d. Frequency of Screening

Patients receiving local treatment for their psoriasis should be screened annually and those on systemic treatment every 6 months.

VII.3.c.e. Referral Criteria for Patients With Suspected Lymphoma

Patients with signs or symptoms of lymphoma or with persistent painless swollen lymph nodes should be referred to a specialist.

VII.3.c.f. Recommended Action in Patients Already Diagnosed With Lymphoma

In the case of patients who are being monitored by their primary care physician or by a specialist, stress the importance of adherence to the treatment prescribed and of continuing with regular follow-up visits. Refer patients with lymphoma who are not being monitored regularly.

VII.3.c.g. Implications of Psoriasis for the Treatment of Cancer

Diverse studies have concluded that long-term PUVA therapy increases the risk of squamous cell carcinoma.[187-190] In 1 cohort of patients, PUVA was seen to slightly increase the risk of basal cell carcinoma within 5 years of receiving the first treatment.[189] A later study, performed in the same group, reported that patients treated with PUVA might also be at increased risk of melanoma.[191]

Nonetheless, the combined analysis of 2 cohort studies in which 944 patients were treated with trioxsalen bath PUVA did not show an increased risk of squamous cell carcinoma, suggesting that this treatment option is safer than conventional PUVA.

Patients treated with low doses of methotrexate may develop malignant lymphomas (isolated cases). In such cases, treatment should be interrupted and cytotoxic therapy initiated if the lymphoma shows no signs of spontaneous regression (SPC).

Ciclosporin increases the risk of lymphoma and other malignancies, particularly skin malignancies. Patients with malignant or premalignant skin alterations should only be treated after appropriate treatment of the lesions and only if there is no alternative treatment. A small number of patients with psoriasis treated with ciclosporin have developed lymphoproliferative disturbances which were reversible by immediate discontinuation of therapy. In view of the potential risk of skin malignancy, patients on ciclosporin should be warned to avoid excessive unprotected sun exposure (SPC).

The association between cancer and biologic agents is controversial. In controlled phases of clinical trials, more cases of lymphoma have been observed in patients treated with anti-TNF agents (adalimumab, etanercept, and infliximab) than with placebo. The incidence, however, was low and follow-up was shorter for the placebo group than for the study group. Furthermore, patients with long-term, highly active rheumatoid arthritis have a higher baseline risk of lymphomas, which further complicates the estimation of risk attributable to medication. Based on current knowledge, the risk of lymphoma or other malignancies in patients treated with anti-TNF agents cannot be ruled out. Special caution is required when contemplating starting anti-TNF therapy in patients with a history of neoplasms or continuing it in patients who develop neoplasms.

The SPC of adalimumab lists NMSC as a common undesirable effect but there is no mention of significant differences with patients treated with placebo (SPC). However, the combined analysis of results from several placebo-controlled trials of etanercept showed a higher rate of NMSC in patients treated with etanercept compared to controls. All patients, and in particular patients with a medical history of extensive immunosuppressant therapy or psoriasis patients with a history of PUVA treatment should be examined for the presence of NMSC prior to treatment with anti-TNF agents (adalimumab, etanercept, infliximab). Regular skin examinations should also be performed. (SPC).

Some patients who received ustekinumab in clinical studies developed cutaneous and noncutaneous malignancies. No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving ustekinumab. Thus, caution should be exercised when considering the use of this agent in these patients (SPC).

VII.3.c.h. Implications of Cancer Treatment in Psoriasis

None described.

VII.4. Anxiety/Depression and Psoriasis

VII.4.a. Introduction

In addition to having an impact on physical well-being, psoriasis can adversely affect all aspects of quality of life (work, family, sexual relations, emotional well-being, etc) and have profound psychosocial effects.[192] Indeed, the impact of psoriasis on mental well-being is comparable to that of other chronic diseases such as cancer and diabetes.[193]

A review of psychiatric comorbidity in patients with psoriasis found that psoriasis can adversely affect patient self-image, self-esteem, and emotional stability.[194] Impaired psychosocial functioning is not always proportional to or influenced by disease severity and is rated by patients as one of the worst aspects of their disease. Many patients experience feelings of social rejection and stigmatization due to the visibility of lesions; the impact on quality of life is accordingly highly variable and is linked to both lesion visibility and age of onset.[192] Stigmatization has been shown to be significantly correlated with psychological distress and level of depression.[195]

Many patients with psoriasis have anxiety or depression, or both. Studies in both humans and animals have shown that increased levels of proinflammatory cytokines associated with the pathogenesis of psoriasis, such as TNF-α and IL-1, are associated with depression.[196-198] Furthermore, demoralization caused by treatment failure may contribute to depression and affect treatment adherence.[199]

Many studies have highlighted the need for psychosocial support in patients with psoriasis.[192,200-206] Effective treatment requires a multidimensional approach aimed at achieving physical, social, and emotional well-being.

A preliminary diagnosis of depression or anxiety can be made using a number of diagnostic scales, but this should always be confirmed using structured interviews such as the Structured Clinical Interview for DSM Disorders (SCID) or the Mini International Neuropsychiatric Interview (MINI). Examples of these preliminary assessment scales are the Goldberg Anxiety and Depression Scale (GADS), the Hamilton Depression Rating Scale (HDRS), the Hamilton Anxiety Rating Scale (HARS), the Montgomery-Asberg Depression Rating Scale (MADRS), the Yesavage Short Form Geriatric Depression Scale (GDS), the Zung Self-Rating Depression Scale (ZSDS), the Beck Depression Inventory (BDI), the Tryer Brief Scale for Anxiety (BSA), the Anxiety Screening Questionnaire (ASQ-15), the Patient Health Questionnaire (PHQ-9), the Hospital and Anxiety Depression Scale (HADS), and the Generalized Anxiety Disorder Assessment (GAD-7). A thorough review of these instruments is provided in Bobes et al.[207]

The Goldberg Anxiety and Depression Scale is simple, short, and easy to administer for nonpsychiatric specialists. It was designed to detect anxiety and depression in primary care settings and can also be useful for screening for these diseases in the dermatology office. It can be used to conduct a structured interview, or to assess the prevalence, severity, and course of disease. The Spanish version has been shown to be both valid and reliable in primary care settings, with a sensitivity of 83.1%, a specificity of 81.8%, and a positive predictive value of 95.3%.[208] It is a self-report questionnaire, designed for use in the general population, comprising an anxiety subscale and a depression subscale. The symptoms assessed in the scales refer to the 2 weeks prior to the visit, and all the items are rated in the same way.

VII.4.b. Scientific Evidence

We reviewed 12 studies (1 from the United States, 1 from China, and 10 from Europe) that examined the

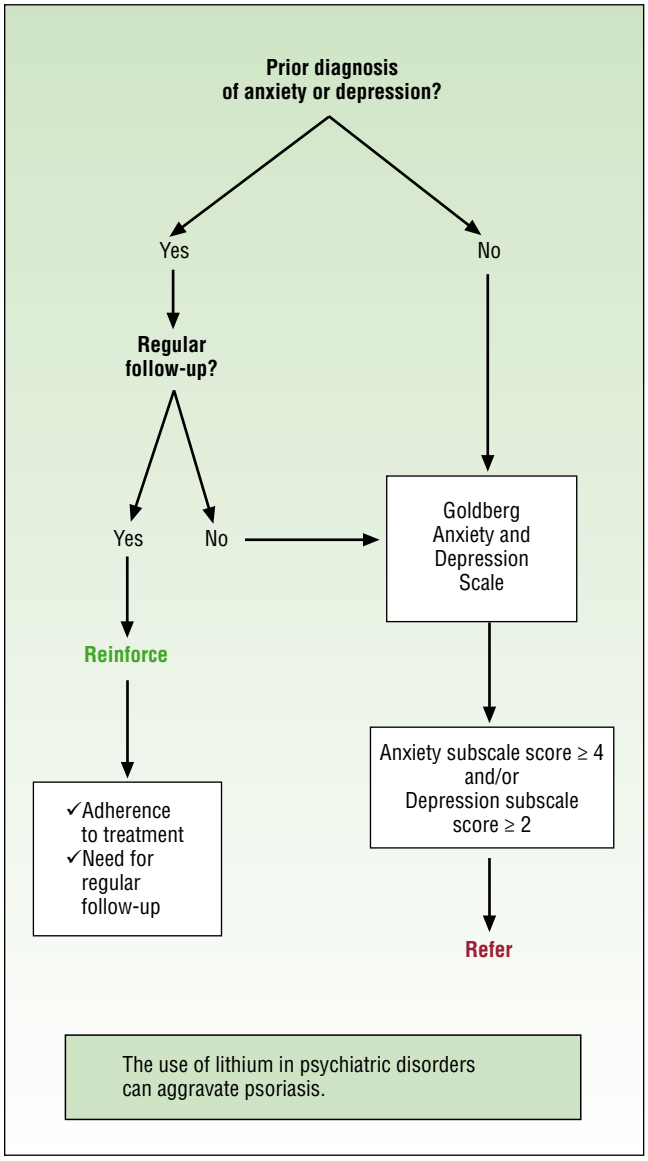

Figure 10. Management of anxiety and depression.

association between psoriasis and depression. There were 7 cross-sectional studies and 5 case-control studies. (One of the case-control studies examined differences in psychopathology between patients with psoriasis and those with prurigo nodularis and was used only to determine the prevalence of depression in psoriasis patients.[209]) Different scales and cutoffs were used to diagnose depression in these studies (Appendix 12).

The prevalence of depression varied enormously, with rates ranging from 9% to 62%. All of the case-control studies reported a significant association between depression and psoriasis. One of the studies, conducted in Turkey with 105 cases and 109 controls, did not analyze prevalence or risk but it did report a significantly higher Beck Depression Inventory score in patients with psoriasis than in those without (14.0 vs 9.3).[210]

Nine of the studies analyzed the association between anxiety and psoriasis. Seven were conducted in Europe (1 in Spain), 1 the United States, and 1 in China. Four were cross-sectional studies and the other 5 were case-control studies. As mentioned previously, the study of differences between patients with psoriasis and those with prurigo nodularis was used only to determine the prevalence of anxiety in psoriasis.[209] Different scales were used but the most common one was the Hospital Anxiety and Depression Scale (Appendix 13).

The prevalence of anxiety found ranged from 11% to 43%. Of the 5 case-control studies, only 1 (the US study) analyzed risk, reporting an OR of 1.57 (95% CI, 1.29-1.92).[211] The case-control study conducted in Turkey with 105 cases and 109 controls reported a Beck Anxiety Inventory score of 14.9 for patients with psoriasis and of 13.2 for those without, but the difference was not significant.[210] In another Turkish study (50 cases and 50 controls), patients with psoriasis had higher mean state and trait anxiety scores as measured on the Spielberger State-Trait Anxiety Scale, but again, the differences were not significant.[212] Interestingly, however, a study conducted in Spain using the same scale with 29 cases and 20 controls reported significantly higher mean state and trait scores in patients with psoriasis.[213]

VII.4.c. Management of Anxiety and Depression in the Dermatology Office

Figure 10 is an algorithm for the clinical management of anxiety and depression in the dermatology office.

VII.4.c.a. Targeted History

Check for the presence of anxiety and/or depression in patients with suspicious symptoms using the Goldberg Anxiety and Depression Scale (Table 9).

VII.4.c.b. Specific Physical Examination

Not required.

VII.4.c.c. Specific Additional Tests

None required.

VII.4.c.d. Frequency of Screening

Patients receiving local treatment for their psoriasis should be screened annually and those on systemic treatment every 6 months.

VII.4.c.e. Referral Criteria for Patients With Suspected Anxiety or Depression

Refer patients to a specialist if they answer yes to 4 or more questions on the anxiety subscale and/or yes to 2 or more questions on the depression subscale.

VII.4.c.f. Recommended Action in Patients Already Diagnosed With Anxiety or Depression

In the case of patients who are being monitored by their primary care physician or by a specialist, stress the importance of adherence to the treatment prescribed and of continuing with regular follow-up visits.

Refer patients with anxiety or depression who are not being monitored regularly.

VII.4.c.g. Implications of Psoriasis Treatment in Anxiety
Pivotal clinical trials involving 4419 patients treated with adalimumab and 2552 patients treated with placebo or an active comparator during the control period found anxiety to be a common adverse reaction to this drug.

VII.4.c.h. Implications of Psoriasis Treatment in Depression
Depression has been reported as an adverse reaction in patients treated with ustekinumab in 3 clinical trials involving 2266 psoriasis patients, including 1970 exposed for at least 6 months, 1285 exposed for at least 1 year, and 373 exposed for at least 18 months (SPC). In the Psoriasis 2 (PHOENIX 2) trial, anxiety and depression (evaluated using the Hospital Anxiety and Depression Scale) decreased significantly in each of the ustekinumab groups compared to the placebo group (SPC).

Based on evidence from pivotal controlled clinical trials involving 4419 patients treated with adalimumab and 2552 patients treated with placebo or an active comparator during the control period, mood changes (including depression) are a common adverse reaction to adalimumab (SPC). Nonetheless, in a double-blind, randomized controlled trial involving 96 patients, there was a greater reduction in depression symptoms (Zung Self-Rating Depression Scale) in patients treated with adalimumab than in those treated with placebo.[200] In a double-blind, randomized, placebo-controlled phase III trial involving 618 patients, there was also a greater reduction in depression symptoms (Beck Depression Inventory) in patients treated with etanercept than in those treated with placebo.[214]

In view of the small proportion of patients with moderate to severe depression in both arms of the etanercept study at baseline, the authors suggested that treatment with this drug might relieve symptoms of depression.[214,215]

Table 9 Goldberg Anxiety and Depression Scale[208]

Anxiety Subscale
1. Have you felt keyed up, high strung or on edge?
2. Have you been worrying a lot?
3. Have you been irritable?
4. Have you had any difficulty relaxing?

(If the patient answers yes to 2 or more of these questions, continue with the test.)

5. Have you been sleeping poorly?
6. Have you had headaches or neck-aches?
7. Have you had any of the following symptoms: trembling, tingling, dizzy spells, sweating, or diarrhea (vegetative symptoms)?
8. Have you been worried about your health?
9. Have you had difficulty falling asleep or staying asleep?

Depression Subscale
1. Have you been lacking in energy?
2. Have you lost interest in things?
3. Have you lost confidence in yourself?
4. Have you felt desperate, without hope?

(If the patient answers yes to any of the above questions, continue with the test.)

5. Have you experienced difficulty concentrating?
6. Have you lost weight (due to loss of appetite)?
7. Have you been waking up too early?
8. Have you felt slowed down?
9. Have you tended to feel worse in the mornings?

In the validated Spanish version the result is considered positive if the patient answers yes to 4 or more questions on the anxiety subscale and/or 2 or more questions on the depression subscale.

VII.4.c.i. Implications of the Treatment of Anxiety and Depression in Psoriasis
The use of lithium as a mood stabilizer in patients with psoriasis may be problematic due to the associated risk of flare-ups.[194,216,217]

VIII. TOBACCO AND ALCOHOL USE AND PSORIASIS

VIII.1. Tobacco Use and Psoriasis

VIII.1.a. Introduction
Tobacco use is a chronic, addictive habit that is very prevalent worldwide. It is associated with numerous diseases and is the leading cause of avoidable disease and premature death in developed countries.

As stated by the World Health Organization, "Tobacco use kills more than 5 million people per year and is responsible for 1 in 10 adult deaths. Among the 5 greatest risk factors for mortality, it is the single most preventable cause of death."[218] The organization also stated that "If current patterns continue, tobacco use will kill more than 8 million people per year by 2030. Up to half of the world's more than 1 billion smokers will die prematurely of a tobacco-related disease."

According to the 2009 European Health Interview Survey,[219] 30% of Europeans aged over 16 years are smokers, with 26% smoking every day and 4% smoking occasionally; there are also more male than female smokers (35% vs 25%). These percentages are very similar to those reported in 2006 by the Spanish national health interview survey,[220] which estimated that 29% of the Spanish population aged over 16 years smoked (26% every day) and that there were more male than female smokers (35% vs 24%). According to the Spanish Drug Observatory, 30% of the Spanish population aged between 16 and 64 years smoke every day.[221] The organization, however, also reported that there has been a considerable decrease in tobacco use in recent years, particularly in men aged between 35 and 64 years and in younger members of the population (15-34 years). This is possibly related to the success of interventions to reduce consumption. Despite the reduction in the number of smokers, however, tobacco use continues to wreak havoc in the Spanish population,

with 54 233 tobacco-attributable deaths every year (49 366 in men and 4867 in women).[222]

The association between tobacco use and increased risk of mortality was clearly demonstrated for numerous diseases years ago. These include cancer (of the lungs, mouth, esophagus, pharynx, larynx, pancreas, cervix, kidneys, and bladder), cardiovascular diseases (ischemic heart disease and stroke), chronic respiratory diseases (chronic obstructive pulmonary disease), digestive diseases (esophagitis, gastritis, gastroduodenal ulcer, IBD), neonatal disease, and premature skin aging. The results of more recent research have focused attention on the immunomodulatory effects of nicotine and consequently its participation in the pathogenesis of immune-mediated diseases such as arteriosclerosis, rheumatoid arthritis, IBD, and psoriasis. The immunopathogenic mechanisms related to tobacco use that might favor the development of psoriasis include T-cell activation and overproduction of inflammation-associated factors such as TNF-α, IL-1B, IL-6, and nuclear factor-κB.[223,224]

VIII.1.b. Scientific Evidence

The literature provides considerable evidence of an association between psoriasis and tobacco use. In most cases, it is believed that tobacco use (via the pathophysiologic mechanisms mentioned in the previous section) favors the development of psoriasis.[3,225-226] However, some studies have suggested that the decision to start smoking or not to quit might be the result of negative lifestyle changes and stress brought on by the appearance of psoriasis.[226,227] The direction of the association between psoriasis and tobacco use, however, cannot be determined on the basis of the studies conducted to date (mostly case-control studies and some cross-sectional studies), but it does seem clear that the correlation is positive. Current smokers have been found to have a higher risk of psoriasis than ex-smokers, with risk increasing with pack-years in both groups.[225]

We reviewed 20 studies that analyzed tobacco use in patients with psoriasis (Appendix 14). Six of the studies were conducted in Italy, 3 in the United Kingdom, 3 in the United States, 3 in China, 2 in Germany, 1 in Sweden, 1 in the Netherlands, and 1 in Spain. Four were large case-control studies based on data from automated databases (the UK General Practice Research Database in 3 studies and the US Nurses' Health Study database in the fourth). The rest of the studies analyzed patients recruited from dermatology offices or hospital wards. Ten were multicenter and 6 were single-center studies. Four had a cohort design, and 1 a cross-sectional design. The rest were case-control studies.

Most of the studies analyzed found a significant association between psoriasis and tobacco use. The prevalence of tobacco use varied, primarily according to the definition of smoker used and the population analyzed. The prevalence of current smokers ranged from 50%[226,228] to 9.9%,[229] but 2 of the studies analyzed specific populations, namely men[226] and veterans.[229] Several studies reported prevalence rates of over 40% for current smokers and of over 60% for current and ex-smokers combined.

The vast majority of studies reported a significantly increased risk of psoriasis in smokers, with 1 study reporting an OR of 4.0 (95% CI, 3.3-4.9) following adjustment for age and sex.[230] Psoriasis was also found to be more severe in patients who had smoked more and for a longer period.[228] Inversely, smoking is more common in patients with severe psoriasis (25.5%) than in those with mild psoriasis (19.1%).[52] In psoriasis patients who smoke, the risk of smoking 25 or more cigarettes a day (OR = 2.4; 95% CI, 1.3-4.3) is higher than that of smoking between 16 and 24 cigarettes a day (OR = 1.8; 95% CI, 1.2-2.7), which is, in turn, higher than that of smoking 15 or fewer cigarettes a day (OR = 1.5; 95% CI, 1.1-2.1).[231] Of the 6 studies that estimated the probability of being an ex-smoker, only 4 found it to be significantly increased in patients with psoriasis.[3,83,231,232]

VIII.1.c. Management of Tobacco Dependence in the Dermatology Office

Figure 11 is an algorithm for the clinical management of tobacco dependence in the dermatology office.

VIII.1.c.a. History and Specific Recommendations

Ask the patient whether they smoke and classify them as: *a)* a current smoker (record how many cigarettes they smoke a day and how many years they have been smoking); *b)* an ex-smoker (record how long it has been since they quit); or *c)* a never-smoker.

Warn current smokers about the harmful effects of smoking in general, and its impact on psoriasis in particular. Ask them whether they are interested in quitting.

If the patient has recently stopped smoking, reinforce the decision by reiterating the harmful effects of smoking in general, and its impact on psoriasis in particular.

VIII.1.c.b. Specific Physical Examination

Not required.

VIII.1.c.c. Specific Additional Tests

None required.

VIII.1.c.d. Frequency of History Taking

Patients receiving local treatment for their psoriasis should be screened annually and those on systemic treatment every 6 months.

VIII.1.c.e. Referral Criteria for Patients Who Smoke

Over 60% of smokers want to stop and have tried to do so in the last year.[233]

Many use self-help books but others do not know where to find effective help. If a patient is interested in quitting, refer them to an appropriate specialist.

VIII.1.c.f. Implications of Psoriasis Treatment in Patients Addicted to Tobacco

None described.

VIII.1.c.g. Implications of the Treatment of Tobacco Dependence in Psoriasis

None described.

VIII.2. Alcohol Consumption and Psoriasis

VIII.2.a. Introduction

According to a report published by the World Health Organization, per capita alcohol consumption in the European Region is the highest in the world and double the global average.[234] The same report identified alcohol as the third most important of 26 risk factors for burden of disease in that area, exceeded only by hypertension and tobacco use. In young generations, it was the leading risk factor.

The 2009 European Health Interview Survey[219] estimated that 41.2% of Europeans aged over 16 years drink alcohol at least twice a month and that 12% do so daily. It also found that more men than women drink, with 55.6% of men drinking more than twice a month and 19.0% drinking every day. The respective figures for women were 27.3% and 5.5%. These percentages are lower than those reported by a Spanish survey carried out in 2006, which found that 55.7% of Spaniards (70.2% of men and 41.8% of women) aged over 16 years had consumed alcohol in the preceding 2 weeks.[220] The Spanish Preventive Activities and Health Promotion Program (PAPPS) defines harmful alcohol use as a weekly intake of over 280 g in men and of over 170 g in women, or the consumption of 50 g in the space of 24 hours, once or twice a month.[235]

It has been known for years that excessive alcohol consumption is associated with a range of skin disorders, including seborrheic dermatitis, rosacea, acne vulgaris, infections, porphyria cutanea tarda, and psoriasis. Lomholt,[236] in 1963, was the first to note an association between alcohol use and psoriasis. Since then, numerous studies have reported a positive association between alcohol consumption and the presence, severity, and extent of psoriasis.[237-239] Furthermore, the association has been reported as independent of hepatic involvement.[238,240] Regarding the pathophysiological role that alcohol may play in psoriasis severity, it is well known that alcohol suppresses the immune system and that patients who consume excessive amounts have a greater predisposition to infection.[241] Given that infections, and streptococcal infections in particular, aggravate psoriasis lesions, one of the harmful effects of alcohol may have on psoriasis could involve an increased susceptibility to infection.[242] Alcohol also causes vasodilation and increased vessel permeability, and favors neutrophilic granulocyte migration and infiltration.[243] Furthermore, chronic exposure to alcohol increases arachidonic acid concentrations and inhibits adenylyl cyclase activity, thereby reducing cyclic adenosine monophosphate levels.[244] All of these pathophysiological effects of alcohol (keratinocyte hyperplasia, infiltration of granulocytes, and abnormal hyperplasia, and expansion of dermal blood vessels) can favor the appearance of typical plaque psoriasis lesions.[245]

Nevertheless, whether excessive alcohol consumption has a role in the pathogenesis of psoriasis or whether it is actually psoriasis that triggers or favors excessive alcohol consumption remains a matter of debate. Several authors have suggested that tobacco use might act as confounder in the association between alcohol and psoriasis. Supporting this hypothesis is the fact that no studies to date have found an increased risk of psoriasis in former drinkers or an association between psoriasis and duration of alcohol consumption.[231]

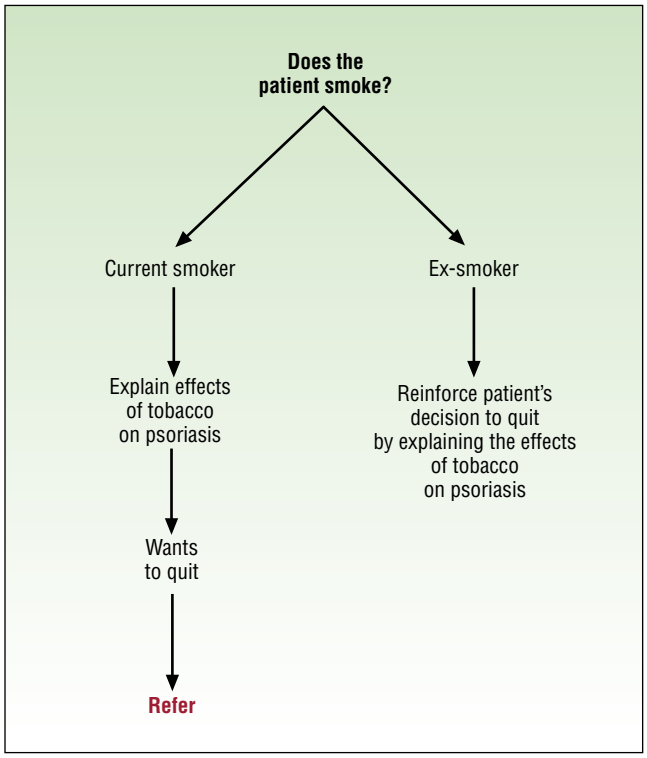

Figure 11. Management of tobacco dependence.

VIII.2.b. Scientific Evidence

We reviewed 9 studies dating back to 1999 that examined the prevalence and/or risk of alcohol consumption in patients with psoriasis (Appendix 15). The findings were inconsistent and the prevalence rates reported for alcohol consumption were highly variable, although it should be noted that consumption habits vary from country to country, and there were also differences in the definition and quantification of alcohol intake. Three of the studies were carried out in Italy[3,228,231] 2 in Germany,[246,247] 2 in the United Kingdom,[4,248] 1 in Sweden,[249] and 1 in China.[226] Two of the studies were cross-sectional[4,228] and the rest were case-control studies. All the studies but 1 (which had just 83 patients[4]) analyzed over 400 psoriasis patients.

Strong associations were found between alcohol consumption and psoriasis when adjustments were not made for tobacco use. In a recent study of psoriasis patients in Germany, Gerdes et al[246] reported that 15.6% of these patients (23% of male patients and 5.7% of female patients) were found to drink excessive amounts of alcohol (defined as > 1 drink a day on a regular basis) (OR = 3.1; 95% CI, 2.5-3.8). The risk of excessive drinking was considerably lower in men (OR = 2.9; 95% CI, 2.3-3.6) than in women

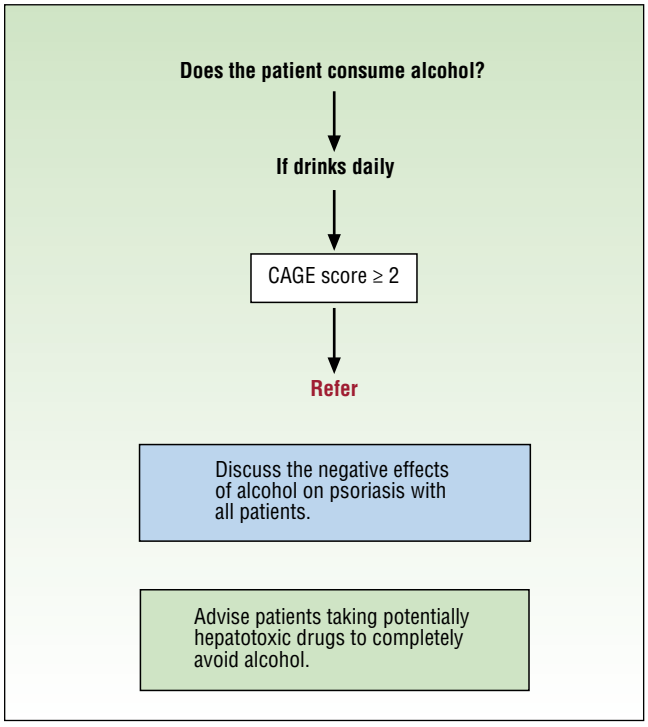

Figure 12. Management of excessive alcohol consumption. CAGE indicates Cut-down, Annoyed, Guilty, Eye-opener questionnaire.

(OR = 5.1; 95% CI, 3.1-8.4). These results are similar to those reported by an earlier German study[247] (OR = 3.6; 95% CI, 1.8-7.1), which adjusted for sex, and to those reported in China. The definition of excessive alcohol consumption in the Chinese study was over 50 mL of spirits or half a liter of beer at least twice a week. This study also reported a higher risk in women than in men (OR = 6.6; 95% CI, 2.4-19.6 vs OR = 4.2; 95% CI, 2.8-6.2). Weaker associations between alcohol consumption and psoriasis were observed in the Swedish and Italian studies, which both adjusted for tobacco use (OR of 1.7 [95% CI, 1.0-3.0] in the Swedish study).[249] It therefore appears that much of the association between alcohol consumption and psoriasis might be due to the higher proportion of smokers among alcohol consumers. Furthermore, the Italian study only found a significant difference for men who consumed more than 2 drinks a day (OR = 1.9; 95% CI, 1.0-3.3). Poikolainen et al[250] described alcohol as a risk factor for psoriasis in men as early as 1990, but later studies, including one by the same group, found that alcohol worsened existing psoriasis.[239,251]

In summary, several of the studies reviewed found a strong association between psoriasis and alcohol consumption, but none of these controlled for tobacco consumption. One of the studies found a significant association only on comparing frequent consumption of alcohol (> 20 drinks a month) with infrequent consumption (< 5 drinks a month). Another study only found a significant association in men who consumed more than 2 drinks a day. These last 2 studies controlled for tobacco use in the multivariate analysis. None of the other studies that adjusted for tobacco use found a significant association between psoriasis and alcohol consumption for any of the subgroups analyzed.

VIII.2.c. Management of Alcohol Consumption in the Dermatology Office

Based on the available evidence, it would seem that alcohol only plays an important role in the development and/or course of psoriasis when consumed in excessive amounts. However, because patients with psoriasis frequently take drugs with known hepatotoxic potential, they should avoid alcohol, at least when taking these drugs. Figure 12 is an algorithm for the clinical management of alcohol consumption in the dermatology office.

According to PAPPS, the 2 most useful tests for screening for alcohol dependence are the MAST (Michigan Alcoholism Screening Test) and the CAGE (Cut-down, Annoyed, Guilty, Eye-opener) questionnaire.[235] The CAGE questionnaire is easier to use. It has 4 yes/no questions, a specificity of 100%, and a positive predictive value of 84%. A score of 2 or 3 indicates a high level of suspicion of alcohol dependence, while a score of 4 is generally pathognomonic (Table 10).

Biomarkers can also be used to identify excessive alcohol consumption but their systematic use in the general population is not justified. They can, however, be of value in patients who are on or about to start systemic treatment with potentially hepatotoxic drugs. AST, GGT, and mean corpuscular volume (MCV) are particularly useful as they are sensitive and accessible markers. GGT levels return to normal after 6 weeks of abstinence, and are therefore particularly useful for follow-up tests. They may, however, also be altered in other liver diseases, in pancreatitis, or following the intake of drugs. One new marker, not yet used on a widespread scale, is carbohydrate-deficient transferrin, whose levels increase in patients consuming over 50 to 80 g of ethanol a day.

VIII.2.c.a. History and Specific Recommendations

Ask the patient about their alcohol consumption habits and record if they: *a)* never drink or drink only occasionally; *b)* drink but not daily; or *c)* drink daily.

If the patient never drinks or drinks only occasionally, reinforce their behavior, and recommend that they avoid alcohol completely when they are taking potentially hepatotoxic drugs.

If the patient drinks, but not every day, mention the negative effects that alcohol can have on psoriasis, and recommend that they cut down. Recommend that they avoid alcohol completely when taking potentially hepatotoxic drugs.

If the patient drinks every day, ask them the CAGE questions (Table 10).

If the score is 0 to 1, mention the negative effects that alcohol can have on psoriasis, and recommend that they cut down. Recommend that they avoid alcohol completely when taking potentially hepatotoxic drugs. If the score is 2 or higher, emphasize the negative effects that alcohol has on psoriasis and suggest referring them to primary care services for a more thorough evaluation, and, if considered necessary, treatment for alcohol

dependence. Only allow patients to continue treatment with potentially hepatotoxic drugs if you are sure their alcohol consumption is under control and if they do the necessary liver tests.

VIII.2.c.b. Specific Physical Examination
Not required.

VIII.2.c.c. Specific Additional Tests
There are no specific tests, but certain blood test results, particularly elevated GGT, AST, and MCV can suggest excessive consumption.

Other tests such as ultrasound and liver biopsy are not necessary as these are the responsibility of the specialist.

VIII.2.c.d. Frequency of Screening
Patients receiving local treatment for their psoriasis should be screened annually and those on systemic treatment every 6 months.

VIII.2.c.e. Referral Criteria for Patients Suspected of Excessive Alcohol Consumption
Patients who score 2 or higher on the CAGE questionnaire should be referred to a specialist, regardless of their blood test results.

VIII.2.c.f. Implications of Psoriasis Treatment in Patients Who Drink Excessively

Patients taking potentially hepatotoxic drugs should not drink alcohol because of its hepatotoxic effect.

VIII.2.c.g. Implications of the Treatment of Excessive Alcohol Consumption in Psoriasis
None described.

IX. ALGORITHM SUMMARIZING THE MANAGEMENT OF COMORBIDITIES IN PSORIASIS

Figure 13 is an algorithm for managing comorbidity in patients with psoriasis. It essentially summarizes the information presented in the previous chapters, showing the steps needed to screen for concomitant diseases (history taking, physical examination, and specific tests), the appropriate referral criteria, and the impact that any concomitant disease might have on the treatment of psoriasis.

Figure 14 contains a list of the comorbidities associated with psoriasis, the basic tests that should be performed by the dermatology office, as well as the Goldberg Anxiety and Depression Scale, and the CAGE alcohol dependence questionnaire.

Funding

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Table 10 CAGE Questionnaire

1. Have you ever felt you **C**ut down on your drinking?
2. Have people **A**nnoyed you by criticizing your drinking?
3. Have you ever felt bad or **G**uilty about your drinking?
4. Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (**E**ye-opener)?

Scoring (1 point for each affirmative answer)
0-1: Social drinker
2: At risk for drinking problems. Sensitivity > 85% and specificity of 90% for the diagnosis of alcohol abuse or dependency
3: Harmful drinking
4: Alcohol dependence

Conflict of Interests

Esteban Daudén has been an advisory board member, received grants and research support, participated in clinical trials, and received speakers' fees from the following pharmaceutical companies: Abbott, Astellas, Biogen, Centocor Ortho Biotech Inc., Galderma, Glaxo, Janssen-Cilag, Leo Pharma, MSD, Pfizer, Novartis, Stiefel, Wyeth Pharmaceuticals, 3M, and Celgene.

Santos Castañeda has received education and research support and consultancy fees and speakers' fees from the following pharmaceutical companies: Abbott, Amgen, Bristol Myers Squibb, MSD, Novartis, and Pfizer.

Carmen Suárez has received education and research support and consultancy and speakers' fees from the following pharmaceutical companies: Bristol Myers Squibb, MSD, Pfizer, Glaxo, Leo Pharma, Novartis, Sanofi, Almirall, Bayer, Boheringer, Esteve, Ferrer, and Janssen-Cilag.

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Lluís Puig has received education and research support and consultancy and speakers' fees from the following pharmaceutical companies: Abbott, Amgen, Celgene, Janssen, MSD, Novartis, and Pfizer.

José Luis Sánchez-Carazo has received grants and speakers' fees from the following pharmaceutical companies: Wyeth, Pfizer, Abbott, MSD, and Novartis.

The other authors declare no conflicts of interest.

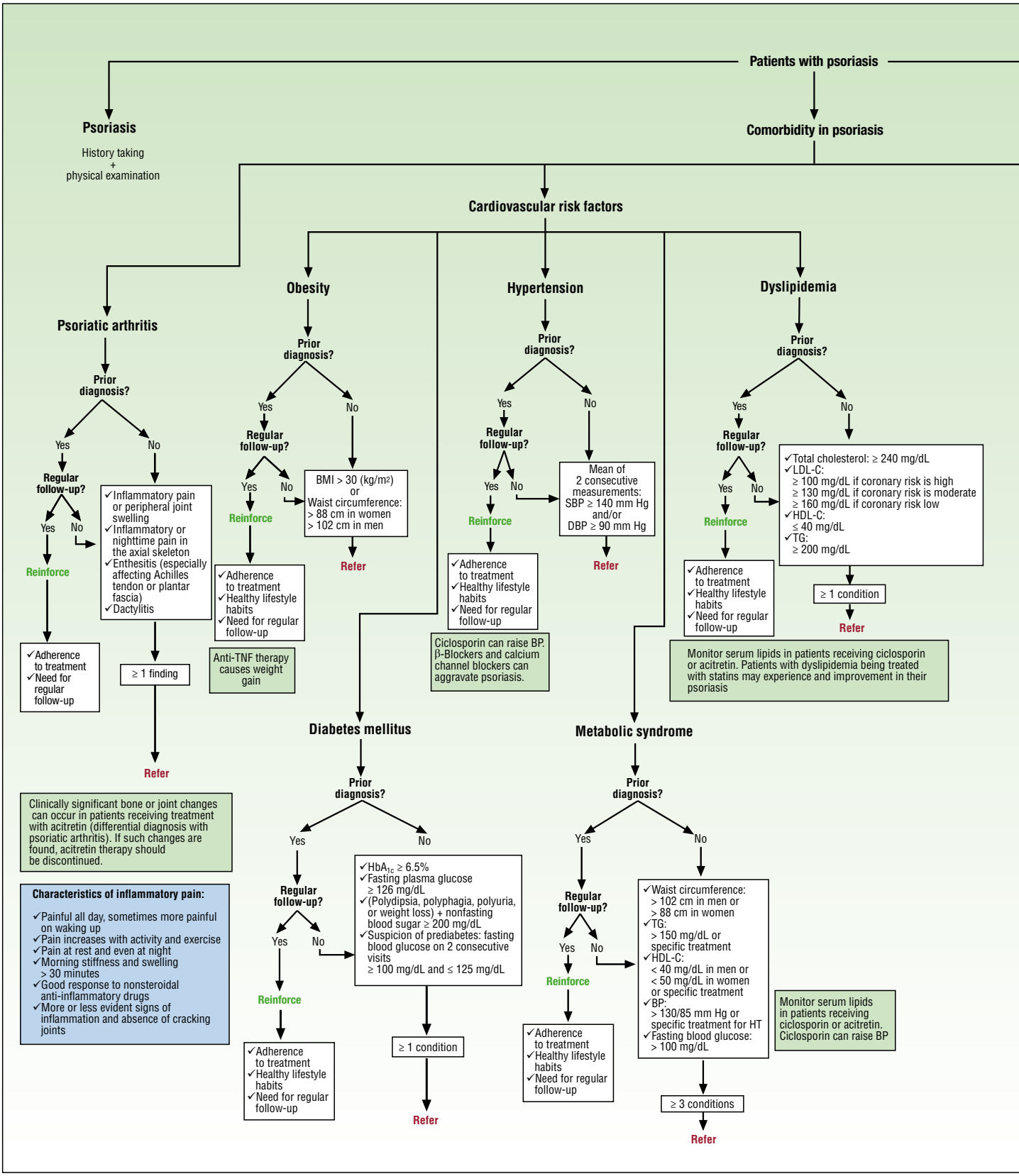
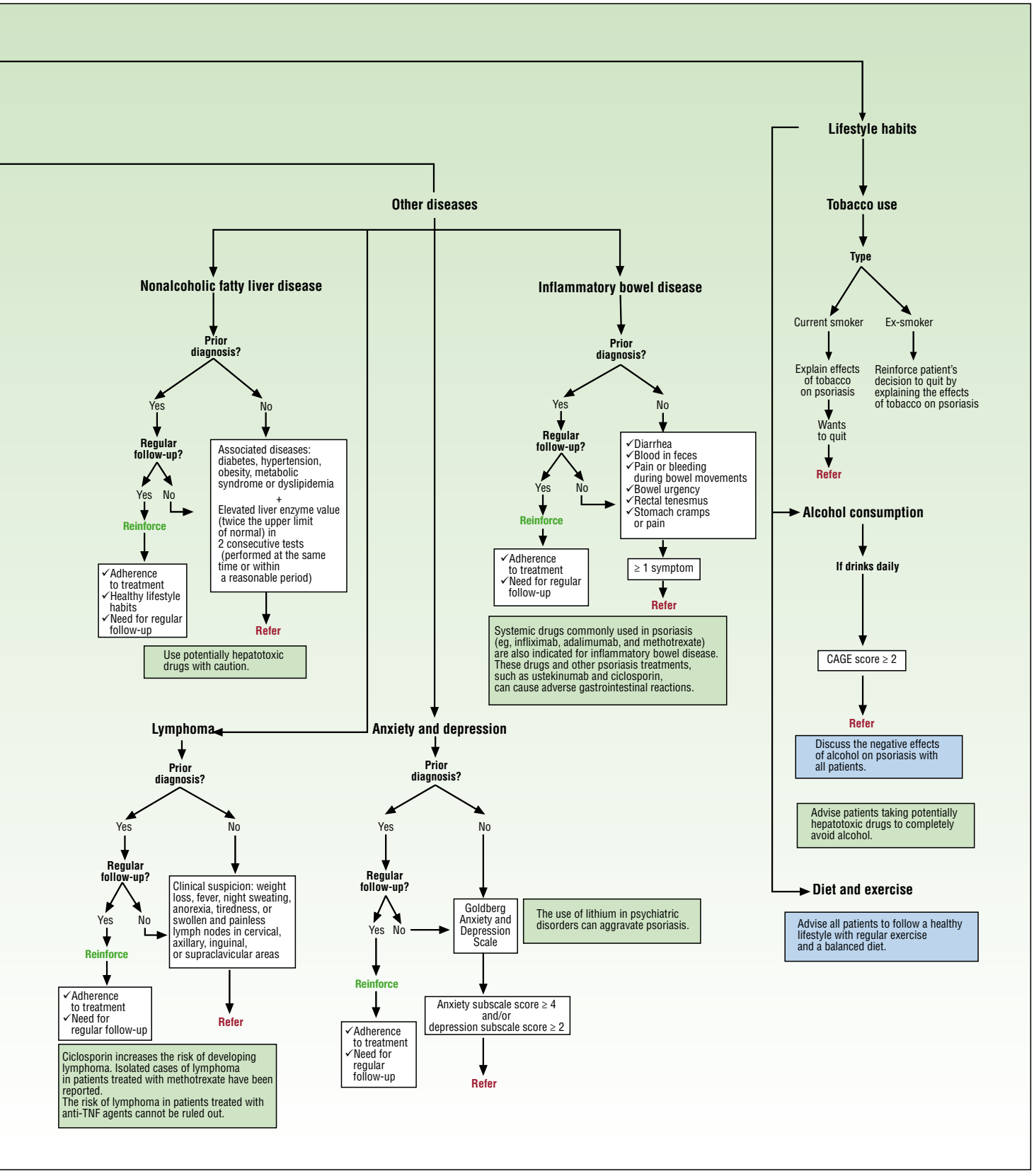


Figure 13. Management of comorbidity in psoriasis. BMI indicates body mass index; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; TG, triglycerides; TNF, tumor necrosis factor.



HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HT, hypertension; LDL-C, low-density lipoprotein cholesterol;

Comorbidities Associated With Psoriasis

- Joint diseases: psoriatic arthritis
- Cardiovascular disease
- Cardiovascular risk factors
  - Obesity (OB)
  - Diabetes mellitus (DM)
  - Hypertension (HT)
  - Dyslipidemia (DLP)
  - Metabolic syndrome (MetSyn)
- Other diseases
  - Nonalcoholic fatty liver disease
  - Inflammatory bowel disease
  - Lymphoma and skin cancer
  - Anxiety and depression

Consumption habits associated with psoriasis:

- Tobacco
- Alcohol

Basic Tests

General assessment and pharmacologic follow-up

Complete blood count
Liver enzymes (ALT, AST, GGT, ALP)
Renal function (creatinine, estimated glomerular filtration rate)

Specific to cardiovascular risk

Weight: _____ kg (OB)
Height: _____ m (OB)
Waist circumference: _____ cm (OB, MetSyn)
Systolic BP: _____ mm Hg (HT, MetSyn)
Diastolic BP: _____ mm Hg (HT, MetSyn)
HbA_{1c}: ___,__ % (DM)
Fasting blood glucose: ____ mg/dL (DM, MetSyn)
Total cholesterol: _____ mg/dL (DLP)
LDL-C _____ mg/dL (DLP)
HDL-C: _____ mg/dL (DLP, MetSyn)
Triglycerides: _____ mg/dL (DLP, MetSyn)

Goldberg Anxiety and Depression

Scale Anxiety Subscale

1. Have you felt keyed up, high strung or on edge?
2. Have you been worrying a lot?
3. Have you been irritable?
4. Have you had any difficulty relaxing?

(If the patient answers yes to 2 or more of these questions, continue with the following questions)

5. Have you been sleeping poorly?
6. Have you had headaches or neck-aches?
7. Have you had any of the following symptoms: trembling,tingling, dizzy spells, sweating, diarrhea? (vegetative symptoms)
8. Have you been worried about your health?
9. Have you had difficulty falling or staying asleep?

Depression subscale

1. Have you been lacking in energy?
2. Have you lost interest in things?
3. Have you lost confidence in yourself?
4. Have your felt desperate, without hope?

(If the patient answers yes to any of the above questions, continue with the test.)

5. Have you experienced difficulty concentrating?
6. Have you lost weight (due to loss of appetite)?
7. Have you been waking up too early?
8. Have you felt slowed down?
9. Have you tended to feel worse in the mornings?

In the validated Spanish version the result is considered positive if the patient answers yes to 4 or more questions on the anxiety subscale and/or to 2 or more questions on the depression subscale

CAGE Questionnaire (suspected alcohol dependence):

1. Have you ever felt you **C**ut down on your drinking?
2. Have people **A**nnoyed you by critizing your drinking?
3. Have you ever felt bad or **G**uilty about your drinking?
4. Have you ever felt the need to have a drink first thing in the morning to steady your nerves or to get rid of a hangover (**E**ye-opener)?

Positive if the patient answers yes to 2 questions on the subscale

Recommended screening intervals for associated comorbidities:
– Every 6 months in patients on systemic treatment
– Every 12 months in patients receiving local treatment

Figure 14. Tools for screening for comorbidity in patients with psoriasis. ALP indicates alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; GGT, gamma-glutamyltransferase; HbA_{1C}, glycosylated hemoglobin; HDL-C, high-density lipoprotein colesterol; LDL-C, low-density lipoprotein colesterol.

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Members of the Spanish Psoriasis Group of the Spanish Academy of Dermatology and Venereology.

APPENDICES 1 a 15

Appendix 1. Prevalence of Psoriatic Arthritis (PsA) in Patients With Psoriasis

Authors, year[ref]	Country	No. of Patients	Prevalence, % (95% CI)	Criteria for PsAs
Christophers et al, 2010[37]	United Kingdom, Italy, France, Spain, Germany	1560	8.1 (6.7-9.5)	Medical history
Al-Mutairi et al, 2010[32]	Kuwait	1790	20.9 (19.0-22.9)	Medical history
Miele et al, 2009[144]	Italy	142	29.6 (21.7-37.4)	CASPAR
Ibrahim et al, 2009[252]	United Kingdom	93	13.8 (7.1-24.1)	CASPAR
Radtke et al, 2009[253]	Germany	2009	19.0 (17.4-20.0)	CASPAR
Reich et al, 2009[254]	Germany	1511	20.6 (18.6-22.7)	Moll and Wright
Wilson et al, 2009[255]	United States	1633	5.9 (4.8-7.2)	CASPAR
Ejaz et al, 2009[34]	Pakistan	100	46.0 (35.7-56.3)	Moll and Wright
Wu et al, 2008[211]	United States	1127	2.0 (1.2-2.9)	Medical history
Jamshidi F, 2008[256]	Iran	320	9.1(5.8-12.4)	Moll and Wright
García-Díez et al, 2008[17]	Spain, Portugal	3320	12.8 (11.6-13.9)	Medical history
Sommer et al, 2006[247]	Germany	581	16.9 (13.8-19.9)	Medical history
Gisondi P, 2005[257]	Italy	936	7.6 (5.8-9.3)	ESSG
Herron et al, 2005[230]	United States	557	26.2 (22.5-30.0)	Medical history
Pavlica et al, 2005[258]	Yugoslavia	1976	9.3 (8.0-10.6)	EX, BR, and blood workup
Gelfand et al, 2005[259]	United States	601	11.8 (9.1-14.5)	Medical history
Alenius et al, 2002[35]	Sweden	202	48.0 (41.1-54.9)	PAQ + EX and BR
Ferrándiz et al, 2002[36]	Spain	1774	9.4 (8.0-10.8)	Medical history
Zachariae et al, 2002[260]	Scandinavian countries	6497	30.0 (28.9-31.1)	Medical history
Shbeeb et al, 2000[261]	United States	1056	6.6 (5.0-8.2)	Inflammatory arthritis
Salvarani et al, 1995[262]	Italy	205	23.9 (18.0-29.7) 21.0 (15.4-26.6)	ESSG Moll and Wright
Barisic-Drusko et al, 1994[263]	Croatia	533	7.2 (5.1-9.5)	Moll and Wright
Falk and Vandbakk, 1993[264]	Lapland, Norway	40	15.0 (3.9-26.1)	Questionnaire
Zanolli and Wikle, 1992[265]	United States	459	17.0 (13.6-20.4)	Questionnaire
Biondi et al, 1989[266]	Italy	647	21.3 (18.2-24.5)	Moll and Wright
Stern, 1985[267]	United States	1285	20.7 (18.5-22.9)	Questionnaire

Abbreviations: BR, Bone radiograph; CASPAR, Classification criteria for psoriatic arthritis; ESSG, European Spondylarthropathy Study Group; EX, physical examination; PAQ, Canadian Psoriasis and Arthritis Questionnaire.

Appendix 2 Risk of Cardiovascular Disease in Patients With Psoriasis

Authors, year[ref]	Country	Population	Design	Matching Variables	With Psoriasis, No.	Without Psoriasis, No.	Prev, %	Results (95% CI)	Adjustment Variables	Disease
Wakkee et al, 2010[268]	Germany	Pharmo Record Linkage System Database	CH	Age and sex	15 820	27 577		HR = 1.10 (0.99-1.23) HR = 1.05 (0.95-1.17)	 Age, sex, treatment (HT, DM, HPL), no. of hospital admissions for noncardiac causes	IHD
Metha et al, 2010[232]	United Kingdom	General Practice Research Database. Severe: on systemic treatment.	CH	Doctor and date of observation	3603[a]	14 330		HR = 1.42 (1.14-1.76) HR = 1.57 (1.26-1.96) HR = 1.57 (1.26-1.96)	 Age and sex Age, sex, DM, HT, HPL, tobacco	CV mortality
Xiao et al, 2009[52]	China	Patients with mild psoriasis (not on systemic treatment) or severe psoriasis (on systemic treatment) from the medical records of 5 hospitals. Random controls from 1 of the hospitals.	CC		1619 1473[a]	1521 1521	6.00 8.01	OR = 2.11 (1.45-3 047) OR = 1.72 (1.29-2.30) OR = 2.32 (1.65-3.28) OR = 2.01 (1.45-2.79)	Age and sex Age, sex, obesity, DM, HT, HPL, tobacco Age and sex Age, sex, obesity, DM, HT, HPL, tobacco	
Prodanovich et al, 2009[229]	United States	Patients from a veterans hospital	CC		3236	2500		OR = 2.18 (1.59-3.01) OR = 1.78 (1.51-2.11) OR = 1.70 (1.33-2.17) OR = 1.98 (1.38-2.82)	Age, sex, DM, HT, HPL tobacco	ATH IHD CVD PVD
Driessen RJB, 2009[269]	Netherlands	Dermatology patients	CC		107[a]	396	3.7	OR = 1.59 (0.46-5.49) OR = 1.59 (0.46-5.49)		MI CVD
Brauchli YB, 2009[270]	United Kingdom	General Practice Research Database	CH		31 568	32 071		IDR = 1.07 (0.89-1.29) IDR = 0.92 (0.77-1.09) IDR = 0.98 (0.81-1.19)		MI CeInf TIA
Gelfand et al, 2009[55]	United Kingdom	General Practice Research Database. Mild: not on systemic treatment. Severe: on systemic treatment.	CH	Doctor and date of observation	129 143 3603[a]	496 666 14 330		HR = 0.91 (0.86-0.95) HR = 1.07 (1.02-1.12) HR = 1.06 (1.01-1.11) HR = 1.38 (1.05-1.80) HR = 1.44 (1.10-1.88) HR = 1.43 (1.10-1.87)	 Age and sex Age, sex, DM, HT, HLP, tobacco, history of TIA or CeINF Age and sex Age, sex, DM, HT, HLP, tobacco, history of TIA or CeINF	CeInf
Kaye et al, 2008[53]	United Kingdom	General Practice Research Database	CH	Age, sex, date of start of follow-up	44 164	219 784		HR = 1.21 (1.10-1.42) HR = 1.20 (1.12-1.29) HR = 1.28 (1.10-1.48) HR = 1.29 (1.13-1.47) HR = 1.12 (1.00-1.25)		MI Angina ATH PVD CeInf
Kimball et al, 2008[50]	United States	IMS Health Integrated Claims Database	CC	Age, sex, region, and duration of MIC	25 556	101 507	7.8 0.9 2.7 1.2 3.1	OR = 1.18 (1.12-1.25) OR = 1.07 (0.92-1.23) OR = 1.25 (1.15-1.37) OR = 1.33 (1.16-1.51) OR = 1.18 (1.09-1.28)		IHD MI PVD ATH CVD
		MarketScan Commercial Claims and Encounters Database	CC	Age, sex, region, and duration of MIC	20 614	82 456	4.6 1.6 4.9 2.4 6.5	OR = 1.19 (1.11-1.29) OR = 1.22 (1.08-1.39) OR = 1.26 (1.17-1.35) OR = 1.27 (1.15-1.41) OR = 1.13 (1.06-1.20)		IHD MI PVD ATH CVD

Shapiro et al, 2007[271]	Israel	Maccabi Healthcare Services database	CC		46 095	1 579 037		OR = 1.28 (1.04-1.59)	Age	ATH
Ludwig et al, 2007[6]	Germany	Patients with plaque psoriasis diagnosed > 10 years earlier. Controls: radiology department database.	CC	Age, sex, CVRFs (tobacco, DM, HT, BMI, HPL , CRP)	32	32	59.4	OR = 3.74 (1.31-10.62)		Coronary artery calcification
Sommer et al, 2006[247]	Germany	Hospitalized patients. Controls: patients with surgically treated melanomas.	CC		581	1044	5.5	OR = 1.77 (1.07-2.93)	Age and sex	Coronary heart disease
Gelfand et al, 2006[54]	United Kingdom	General Practice Research Database. Mild: not on systemic treatment. Severe: on systemic treatment.	CH	Doctor and date of observation	127 139 3837[a]	556 995 556 995		HR = 1.11 (1.07-1.17) HR = 1.54 (1.24-1.91)[b] HR = 1.43 (1.18-1.72) HR = 7.08 (3.06-16.36)[b]	Age, DM, history of MI, HPL, sex, and tobacco Age, DM, history of MI, HPL, HT, sex, and tobacco	MI
Pearce et al, 2005[51]	United States	Patients from a dermatology practice	CS		753		14.3	O/Ex = 1.27[c]		Heart disease (congestive heart failure, coronary artery disease, cardiomyopathy, etc).
Mallbris et al, 2004[272]	Sweden	Inpatient cohort: Swedish Inpatient Registry. Outpatient cohort: Swedish Psoriasis Association.	CH		8991 19 757			SMR = 1.52 (1.44-1.60) SMR = 0.94 (0.89-0.99)	Age and sex	Mortality

Abbreviations: ATH, artherosclerosis; BMI: body mass index; CC, case-control; CeINF, cerebral infarction; CH, cohort; CRP, C-reactive protein; CS, cross-sectional; CV, cardiovascular; CVD, cerebrovascular disease; CVRF, cardiovascular risk factors; DM, diabetes mellitus; IHD, ischemic heart disease; HPL, hyperlipidemia; HR, hazard ratio; HT, hypertension; IDR: incidence density ratio; MI, myocardial infarction; MIC, medical insurance coverage; OR, odds ratio; PR: prevalence ratio; Prev: prevalence; PVD: peripheral vascular disease; SMR: standardized mortality rate; TIA, transient ischemic attack.

[a]Severe psoriasis.

[b]Values not directly interpretable as there was an age × psoriasis interaction term.

[c]Observed/expected according to the National Health Interview Survey.

Appendix 3. Risk of Overweight and Obesity in Patients With Psoriasis

Authors, year[ref]	Country	Population	Design	Matching Variables	With Psoriasis, No.	Without Psoriasis, No.	Prev, %	Results (95% CI)	Adjustment Variables	Criteria
Metha et al, 2010[232]	United Kingdom	General Practice Research Database. Severe: on systemic treatment	CH	Doctor and date of observation	3603[b]	14 330	35.4 22.5	OR = 1.29 (1.17-1.43) OR = 1.78 (1.58-2.00)		BMI 25-29.9 BMI ≥ 30
Al-Mutairi et al, 2010[32]	Kuwait	Dermatology patients in 2 hospitals. Controls: patients in the same hospitals	CC	Age, sex, area of residence	1661[a] 129[b]	1835 1835	32.5 41.0	OR = 2.36 (1.93-2.87) OR = 3.42 (2.30-5.10)		
Augustin et al, 2010[273]	Germany	Medical insurance organization	CS		33 981	1 310 090	17.8	PR = 1.72 (1.68-1.76)		
Augustin et al, 2010[274]	Germany	Medical insurance organization. Juvenile Psoriasis	CS		2549	331 758	8.4	PR = 1.7 (1.49-1.93)		
Bardazzi et al, 2010[275]	Italy	Dermatology patients with severe psoriasis (treated with biologic agents)	CS		33[b]		40.0 42.0			BMI 25-29 BMI ≥ 30
Huang et al, 2010[276]	Taiwan	Patients with chronic psoriasis from a hospital	CS		399[b]			OR = 2.70 (1.42-5.11)	Age, sex, tobacco, and disease duration	BMI > 30
Miele et al, 2009[144]	Italy	Dermatology patients from a hospital	CH		142		21.8			BMI ≥ 30
Wolk et al, 2009[249]	Sweden	Cases: patients from the Stockholm area whose psoriasis had developed in the preceding 12 months. Controls: Swedish Population Registry.	CC	Age, sex, and zip code	369	369	37 15	OR = 1.6 (1.0-2.4) OR = 2.0 (1.1-3.6)	Age, sex, zip code, weight gain, alcohol, tobacco	BMI 25-29.9 BMI ≥ 30
Xiao et al, 2009[52]	China	Patients with mild psoriasis (not on systemic treatment) or severe psoriasis (on systemic treatment) from the medical records of 5 hospitals. Random controls from 1 of the hospitals.	CC		1619[a] 1473[b]	1 521 1 521	14.02 20.10	OR = 1.41 (1.08-1.85) OR = 1.51 (1.15-1.98)	Age and sex	BMI > 30
Driessen et al, 2009[269]	Netherlands	Dermatology patients	CC		107[b]	396		OR = 5.49 (3.09-9.74)		
Kaye et al, 2008[53]	United Kingdom	General Practice Research Database	CH	Age, sex, date of Ps	44 164	219 784		HR = 1.18 (1.14-1.23)		
Cohen et al, 2008[277]	Israel	Clalit Health Services Database	CC		16 850	48 677	8.4	OR = 2.4 (2.3-2.6) OR = 1.7 (1.5-1.9)	Age, sex, and tobacco	
Naldi et al, 2008[278]	Italy	Dermatology patients from 20 hospitals	CC	Age	560	690	12.9 28.0	OR = 1.7 (1.1-2.6) OR = 1.6 (1.1-2.2)	Age, sex, tobacco, alcohol, marital status	BMI ≥ 30 BMI 26-29
Huerta et al, 2007[248]	United Kingdom	General Practice Research Database	CC	Age, sex, date	3994	10 000	22.33 11.32	OR = 1.11 (1.0-1.24) OR = 1.33 (1.16-1.52)	Age, sex, year, tobacco, and GP visits	BMI 25-29 BMI ≥ 30

Cohen et al, 2007[279]	Israel	Clalit Health Services Database. Controls: patients who had undergone hernioplasty or appendectomy.	CC		340	6643	29.4	OR = 1.4 (1.1-1.7) OR = 1.3 (1.0-1.7)	Age and sex	
Gisondi et al, 2007[280]	Italy	Dermatology patients from 3 hospitals	CC		338	334		OR = 1.19 (0.91-1.55)		BMI > 30
Setty et al, 2007[281]	United States	Women from 15 US states	CH		892	78 626		HR = 1.4 (1.13-1.73) HR = 1.48 (1.15-1.91) HR = 2.69 (2.12-3.40)	Age, tobacco, alcohol Age, tobacco, alcohol Age, tobacco, alcohol	BMI 25-29.9 BMI 30-34.9 BMI ≥ 35
Gelfand et al, 2006[54]	United Kingdom	General Practice Research Database. Mild: not on systemic treatment. Severe: on systemic treatment.	CH	Doctor and date of observation	129 143[a] 3603[b]	496 666 14 330	33.8 16.6 35.4 22.5	OR = 1.16 (1.13-1.18) OR = 1.10 (1.08-1.12) OR = 1.13 (1.04-1.24) OR = 1.51 (1.36-1.68)		BMI 25-29 BMI >30 BMI 25-29 BMI >30
Neimann et al, 2006[282]	United Kingdom	General Practice Research Database	CC	Doctor and date of observation	127 706[a] 3854[b] 127 706[a] 3854[b]	465 252 14 065 465 252 14 065	15.75 20.66 34.98 37.68	OR = 1.29 (1.26-1.32) OR = 1.27 (1.24-1.31) OR = 1.84 (1.60-2.11) OR = 1.79 (1.55-2.05) OR = 1.12 (1.10-1.14) OR = 1.12 (1.10-1.14) OR = 1.28 (1.15-1.43) OR = 1.27 (1.14-1.42)	Age, sex, person-years Age, sex, person-years, HT, HPL, tobacco Age, sex, person-years Age, sex, person-years, HT, HPL, tobacco Age, sex, person-years Age, sex, person-years, HT, HPL, tobacco Age, sex, person-years Age, sex, person-years, HT, HPL , tobacco	BMI > 30 BMI > 30 BMI 25-30 BMI 25-30
McGowan et al, 2005[283]	United States	MEPS 2000 MCBS 1992-2000	CS CS		69 331	15 872 44 708	27.8 37.0 20.8 6.9	OR = 1.21 (0.69-2.09) OR = 1.18 (0.71-1.96) OR = 1.26 (0.96-1.66) OR = 1.16 (0.92-1.46)		BMI > 30 BMI 25.0-29.9 BMI > 30 BMI 25.0-29.9
Herron et al, 2005[230]	United States	Patients from a hospital dermatology department. Compared with population-based data.	CS		557	4 080	34.5	OR = 2.39 (1.98-2.90)	Age, sex	BMI >30
Naldi et al, 2005[3]	Italy	Dermatology patients from 20 hospitals	CC	Age	560	690	12.9 28.0	OR = 1.9 (1.2-2.8) OR = 1.6 (1.1-2.1)	Age, sex, tobacco, alcohol, education, marital status, hospitalization	BMI ≥ 30 BMI 26-29
Marino et al, 2004[284]	Italy	Dermatology outpatients from Tor Vergata University in Rome	CS		406		35.7 16.5			BMI > 25-29 BMI ≥ 30

Abbreviations: BMI, body mass index; CC, case-control; CH, cohort; CS, cross-sectional; DM, diabetes mellitus; HPL, hyperlipidemia; HR, hazard ratio; HT, hypertension; BMI, body mass index; MCBS, Medicare Current Beneficiary Survey; MEPS, Medical Expenditure Panel Survey; OR, odds ratio; PR, prevalence ratio; Prev, prevalence; Ps, psoriasis.

[a]Mild to moderate psoriasis (no systemic treatment).

[b]Severe psoriasis (systemic treatment).

Appendix 4. Risk of Diabetes Mellitus in Patients With Psoriasis

Authors, year[ref]	Country	Population	Design	Matching Variables	With Psoriasis, No.	Without Psoriasis, No.	Prev, %	Results (95% CI)	Adjustment Variables	Criteria
Metha et al, 2010[232]	United Kingdom	General Practice Research Database. Severe: on systemic treatment.	CH	Doctor and date of observation	3.603[b]	1433	7.5	OR = 1.49 (1.29-1.73)		Code
Al-Mutairi et al, 2010[32]	Kuwait	Dermatology patients in 2 hospitals. Controls: hospitalized patients.	CC	Age, sex, and area of residence	1661 129[b]	1835 1835	37.4 41.9	OR = 3.14 (2.68-3.68) OR = 3.77 (2.60-5.47)		DM II
Augustin et al, 2010[273]	Germany	Medical insurance organization	CS		33 981	1 310 090	12.12	PR = 2.02 (1.96-2.08)		Code
Augustin et al, 2010[274]	Germany	Medical insurance organization. Juvenile psoriasis.	CS CH	CH	2549	331 758	0.86	PR = 2.01 (1.32-3.04)		Code
Miele et al, 2009[144]	Italy	Hospitalized dermatology patients			142		19.7			DM II
Qureshi et al, 2009[83]	United States	Nurses' Health Study	CH		1813	76 248		HR = 2.08 (1.60-2.69) HR = 1.63 (1.25-2.12)	Age Age, tobacco, BMI, alcohol, physical activity	Patient report
Xiao et al, 2009[52]	China	Patients with psoriasis from 5 hospitals. Random controls from 1 of the hospitals.	CC		1619[a] 1473[b]	1521 1521	10.01 16.97	OR = 1.45 (1.11-1.91) OR = 1.69 (1.32-2.17)	Age and sex Age and sex	Medical history
Prodanovich et al, 2009[229]	United States	Patients from a veterans hospital	CC		3236	2500	27.3	OR = 3.79 (3.24-4.44)		Code
Driessen et al, 20092[269]	Netherlands	Dermatology patients	CC		107[b]	396	13.1	OR = 1.91 (0.91-4.04)		Cases: code. Controls: patient report
Brauchli et al, 2008[285]	United Kingdom	General Practice Research Database	CH		32 593	32 856		IDR = 1.36 (1.20-1.53)		Code
Gerdes et al, 2008[286]	Germany	Hospitalized patients Controls: National Health Survey	CC		1131[b]	7099	9.2	OR = 2.70 (1.97-3.68) OR = 2.27 (1.64-3.13)	 Age and sex	DM II
Kaye et al, 2008[53]	United Kingdom	General Practice Research Database	CH	Age, sex, date of start of follow-up monitoring.	44 164	219 784		HR = 1.33 (1.25-1.42)		Code
Kimball et al, 2008[50]	United States	IMS Health Integrated Claims Database MarketScan Commercial Claims and Encounters Database	CC CC	Age, sex, region, and duration of MIC Age, sex, region, and duration of MIC	25 556 20 614	101 507 82 456	10.2 13.3	OR = 1.27 (1.21-1.33) OR = 1.20 (1.14-1.25)		Code Code
Wu et al, 2008[211]	United States	National Health and Wellness Survey	CC	Age, sex, region, and race	1127	1127		OR = 1.42 (1.10-1.84)		Patient report

Cohen et al, 2008[287]	Israel	Clalit Health Services Database	CS		16 851	74 987	13.8	OR = 2.83 (2.68-2.99) OR = 1.58 (1.49-1.68) OR = 1.23 (1.10-1.37)[c]	 Age and sex Age, sex obesity	Code
Cohen et al, 2008[277]	Israel	Clalit Health Services Database	CC		16 850	48 677	13.8	OR = 2.0 (1.9-2.1) OR = 1.2 (1.0-1.3)	 Age, sex, tobacco	Code
Naldi et al, 2008[278]	Italy	Dermatology patients from 20 hospitals	CC	Age	560	690	3.8	OR = 1.1 (0.6-2.0)	Age and sex	Patient report
Huerta et al, 2007[248]	United Kingdom	General Practice Research Database	CC	Age, sex, date	3994	10 000	2.35	OR = 0.96 (0.75-1.22) OR = 0.74 (0.58-0.95)	 Age, sex, year, tobacco, visits to GP, BMI	Code
Cohen et al, 2007[279]	Israel	Clalit Health Services Database. Controls: hernioplasty or appendectomy.	CC		340	6 643	27.9	OR = 1.6 (1.2-2.0)	Age and sex	Code
Gisondi et al, 2007[280]	Italy	Dermatology patients from 3 hospitals	CC		338	334	19.2	OR = 0.90 (0.62-1.31)		Fasting plasma glucose > 6.1 mmol/L
Shapiro et al, 2007[271]	Israel	Maccabi Healthcare Services database	CC		46 095	1 579 037		OR = 1.27 (1.10-1.48)	Age	Code
Gelfand et al, 2006[54]	United Kingdom	General Practice Research Database	CC	Doctor and date of observation	129 143[a] 3603[b]	496 666 14 330	4.5 7.5	OR = 1.01 (0.98-0.95) OR = 1.49 (1.29-1.73)		Code
Sommer et al, 2006[247]	Germany	Hospitalized patients Controls: localized stage I melanoma	CC		581	1044	11.7	OR = 2.48 (1.70-3.61)	Age and sex	DM II
Neimann et al, 2006[282]	United Kingdom	General Practice Research Database	CC	Doctor and date of observation	127 706[a] 38 54[b]	465 252 14 065	7.1 4.4	OR = 1.27 (1.23-1.31) OR = 1.13 (1.08-1.18) OR = 1.86 (1.58-2.19) OR = 1.62 (1.30-2.01)	Age, sex, person-years Age, sex, person-years, HT, HPL, tobacco, BMI Age, sex, person-years Age, sex, person-years, HT, HPL, tobacco, BMI	Code
Pearce et al, 2005[51]	United States	Patients treated in a specialized clinic	CS		753		14.3	O/Ex[d] = 2.35		DM I and II

Abbreviations: CC, case-control; CH, cohort; CS, cross-sectional; DM I, type 1 diabetes mellitus; DM II, type 2 diabetes mellitus; HPL, hyperlipidemia; HR, hazard ratio; HT, hypertension; IDR, incidence density ratio; MIC, medical insurance cover; OR, odds ratio; Prev, prevalence; PR, prevalence ratio.

[a]Mild psoriasis.

[b]Severe psoriasis.

[c]No. = 9228.

[d]Observed/expected according to the National Health Interview Survey.

Appendix 5. Risk of Hypertension in Patients With Psoriasis

Authors, year[ref]	Country	Population	Design	Matching Variables	With Psoriasis, No.	Without Psoriasis, No.	Prev, %	Results (95% CI)	Adjustment Variables	Criteria
Metha et al, 2010[232]	United Kingdom	General Practice Research Database. Severe: on systemic treatment.	CH	Doctor and date of observation	3603[a]	14 330	23.8	OR = 1.16 (1.06-1.26)		
Al-Mutairi et al, 2010[32]	Kuwait	Dermatology patients from 2 hospitals. Controls: hospitalized patients.	CC	Age, sex, area of residence	1661[a]	1835	32	OR = 3.6 (3.02-4.23)		
					129[b]	1 835	40.3	OR = 5.17 (3.53-7.55)		
Augustin et al, 2010[273]	Germany	Medical insurance organization	CS		33 981	1 310 090	35.6	PR = 1.73 (1.71-1.76)		
Augustin et al, 2010[274]	Germany	Medical insurance organization. Juvenile psoriasis.	CS		2549	331 758	1.65	PR = 1.89 (1.47-2.67)		
Cohen et al, 2010[288]	Israel	Healthcare company database	CC	Age and sex	12 502	24 285	38.8	OR = 1.37 (1.29-1.46)	Age, sex, tobacco, obesity, DM, NSAIDs, COX-2 inhibitors	
Miele et al, 2009[144]	Italy		CH		142		38.0			BP ≥ 130/85
Xiao et al, 2009[52]	China	Patients with psoriasis from 5 hospitals. Random controls from 1 of the hospitals.	CC		1619[a]	1521	15.1	OR = 1.39 (1.04-1.85)	Age and sex	
					1473[b]	1521	19.0	OR = 1.41 (1.06-1.88)		
Prodanovich et al, 2009[229]	United States	Patients from a veterans hospital	CC		3236	2500	60.1	OR = 5.57 (4.94-6.28)		
Qureshi et al, 2009[83]	United States	Nurses' Health Study	CH		1813	76 248	21.3	HR = 1.32 (1.19-1.45)	Age	BP ≥ 140/90
								HR = 1.17 (1.06-1.30)	Age, tobacco, BMI, alcohol, physical activity	
Driessen et al, 2009[269]	Netherlands	Dermatology patients	CC		107[b]	396		OR = 1.93 (1.16-3.23)		
Gerdes et al, 2008[286]	Germany	Hospitalized patients.[b] Controls: National Health Survey.	CC		1131	7099	25.3	OR = 2.10 (1.81-2.44)		
								OR = 1.93 (1.63-2.28)	Age and sex	
Kaye et al, 2008[53]	United Kingdom	General Practice Research Database	CH	Age, sex, date of DM	44 164	219 784		HR = 1.09 (1.05-1.14)		
Kimball et al, 2008[50]	United States	IMS Health Integrated Claims Database	CC	Age, sex, region, duration of MIC	25 556	101 507	29.3	OR = 1.18 (1.14-1.22)		
		MarketScan Commercial Claims and Encounters Database	CC	Age, sex, region, duration of MIC	20 614	82 456	35.5	OR = 1.14 (1.10-1.17)		
Wu et al, 2008[211]	United States	National Health and Wellness Survey	CC	Age, sex, region, race	1127	1127		OR = 1.49 (1.23-1.80)		
Cohen et al, 2008[277]	Israel	Clalit Health Services Database	CC		16 850	48 677	27.5	OR = 2.2 (2.2-2.3)		
								OR = 1.3 (1.2-1.5)	Age, sex, tobacco	
Naldi et al, 2008[278]	Italy	Dermatology patients from 20 hospitals	CC	Age	560	690	8.9	OR = 0.8 (0.5-1.37)	Age and sex	

Cohen et al, 2007[279]	Israel	Clalit Health Services Database. Controls: patients who had undergone hernioplasty or appendectomy.	CC		340	6643	44.4	OR = 1.4 (1.1-1.7) OR = 1.3 (1.0-1.7)	Age and sex	
Gisondi et al, 2007[280]	Italy	Dermatology patients from 3 hospitals	CC		338	334	40.8	OR = 1.06 (0.8-1.5)		BP ≥ 135/85
Gelfand et al, 2006[54]	United Kingdom	General Practice Research Database. Mild (not on systemic treatment). Severe (on systemic treatment).	CH	Doctor and date of observation	129 143[a] 3603[b]	496 666 14 330	17.7 23.8	OR = 0.99 (0.98-1.01) OR = 1.16 (1.06-1.26)		
Sommer et al, 2006[247]	Germany	Hospitalized patients. Controls: patients with surgically treated localized stage I melanoma.	CC		581	1044	21.9	OR = 3.27 (2.41-4.43)	Age and sex	
Neimann et al, 2006[282]	United Kingdom	General Practice Research Database. Mild (not on systemic treatment). Severe (on systemic treatment).	CC	Doctor and date of observation	127.06[a] 3854[b]	465 252 14 065	14.66 19.95	OR = 1.16 (1.14-1.18) OR = 1.03 (1.01-1.06) OR = 1.25 (1.13-1.39) OR = 1.00 (0.87-1.14)	Age, sex, person-years Age, sex, person-years, HT, HPL, tobacco, and BMI Age, sex, person-years Age, sex, person-years, HT, HPL, tobacco, and BMI	
Pearce et al, 2005[51]	United States	Patients from a dermatology clinic	CS		753			O/Ex[c] = 1.41		

Abbreviations: BP, blood pressure; CC, case-control; CH, cohort; CS, cross-sectional; COX, cyclooxigenase; DM, diabetes mellitus; HPL, hyperlipidemia; HR, hazard ratio; HT, hypertension; MIC, medical insurance coverage; OR, odds ratio; Prev, prevalence; PR, prevalence ratio.

[a]Mild psoriasis.

[b]Severe psoriasis.

[c]Observed/expected according to the Health Interview Survey

Appendix 6. Risk of Dyslipidemia in Patients With Psoriasis

Authors, year[ref]	Country	Population	Design	Matching Variables	With Psoriasis, No.	Without Psoriasis, No.	Prev, %	Results (95% CI)	Adjustment Variables	Criteria
Metha et al, 2010[232]	United Kingdom	General Practice Research Database	CH	Doctor and date of observation	3603[b]	14 330	6.9	OR = 1.19 (1.03-1.38)		
Al-Mutairi et al, 2010[32]	Kuwait	Dermatology patients from 2 hospitals. Controls: hospitalized patients.	CC	Age, sex, and area of residence	1661[a] 129[b]	1835 1835	14.1 22.5	OR = 3.38 (2.63-4.34) OR = 5.55 (3.49-8.83)		
Augustin et al, 2010[273]	Germany	Medical insurance organization	CS		33 981	1 310 090	29.9	PR = 1.75 (1.72-1.78)		
Augustin et al, 2010[274]	Germany	Medical insurance organization	CS		2549	331 758	2.1	PR = 2.15 (1.65-2.8)		
Miele et al, 2009[144]	Italy	Hospitalized dermatology patients	CH		142		45.0			
Xiao J, 2009[52]	China	Patients with psoriasis from the medical records of 5 Chinese hospitals. Random controls from 1 of the hospitals.	CC		1619[a] 1473[b]	1521 1521	23.9 29.9	OR = 1.37 (1.06-1.78) OR = 1.43 (1.11-1.84)		
Prodanovich et al, 2009[229]	United States	Patients from a veterans hospital	CC		3236	2500	31.6	OR = 4.35 (3.73-5.06)		
Driessen et al, 2009[269]	Netherlands	Dermatology patients	CC		107[b]	396	20.6	OR = 1.17 (0.66-2.09)		
Gerdes et al, 2008[286]	Germany	Hospitalized patients. Controls: National Health Survey.	CC		1131	7099	7.7	OR = 1.86 (1.46-2.39) OR = 1.55 (1.20-2.00)	 Age and sex	
Kaye et al, 2008[53]	United Kingdom	General Practice Research Database	CH	Age, sex, date of psoriasis	44 164	219 784		HR = 1.17 (1.11-1.23)		
Kimball et al, 2008[50]	United States	IMS Health Integrated Claims Database of MIC	CC	Age, sex, region, duration of disease	25 556	101 507	31.6	OR = 1.26 (1.22-1.30)		
		MarketScan Commercial Claims and Encounters Database of MIC	CC	Age, sex, region, duration of disease	20 614	82 456	31.2	OR = 1.19 (1.15-1.22)		
Wu et al, 2008[211]	United States	National Health and Wellness Survey	CC	Age, sex, region, race	1127	1127		OR = 1.35 (1.11-1.63)		
Cohen et al, 2008[277]	Israel	Clalit Health Services Database	CC		16 850	48 677		OR = 1.0 (1.0-1.3) OR = 0.9 (0.8-1.0)	Age, sex, tobacco Age, sex, tobacco	Elevated TG and low HDL-C
Naldi et al, 2008[278]	Italy	Dermatology patients from 20 hospitals	CC	Age	560	690	6.4	OR = 1.1 (0.7-1.70)	Age and sex	
Cohen et al, 2007[279]	Israel	Clalit Health Services Database. Controls: hernioplasty or appendectomy.	CC		340	6643	50.9	OR = 1.3 (1.1-1.6) OR = 1.2 (1.0-1.6)	 Age and sex	

Gisondi et al, 2007[280]	Italy	Dermatology patients from 3 hospitals	CC		338	334	37.8	OR = 2.0 (1.4-2.8) OR = 0.8 (0.5-1.2)		TG > 1.7 mmol/L HDL-C < 1 mmol/L (M); HDL-C < 1.3 mmol/L (W)
Sommer et al, 2006[247]	Germany	Hospitalized patients. Controls: localized stage I melanoma.	CC		581	1044	5.2	OR = 2.09 (1.23-3.54)	Age and sex	
Neimann et al, 2006[282]	United Kingdom	General Practice Research Database	CC	Doctor and date of observation	127 706[a]	465 252	4.7	OR = 1.28 (1.24-1.33) OR = 1.16 (1.12-1.21)	Age, sex, person-years Age, sex, person-years, HT, HPL, tobacco, BMI	
					3854[b]	14 065	6.0	OR = 1.31 (1.11-1.56) OR = 1.04 (0.84-1.28)	Age, sex, person-years Age, sex, person-years, HT, HPL, tobacco, BMI	
Gelfand et al, [4] 2006[5]	United Kingdom	General Practice Research Database	CH	Doctor and date of observation	129 143[a] 3603[b]	496 666 14 330	5.2 6.9	OR = 1.15 (1.12-1.18) OR = 1.19 (1.03-1.39)		

Abbreviations: CC, case-control; CH, cohort; CS: cross-sectional; HDL-C, high-density lipoprotein cholesterol; HPL, hyperlipidemia; HR, hazard ratio; HT, hypertension; M: men; MIC: medical insurance coverage; OR: odds ratio; PR, prevalence ratio; Prev, prevalence; Ps, psoriasis; TG, triglycerides; W: women.
[a]Mild psoriasis.
[b]Severe psoriasis.

Annex to Appendix 6. Studies on the Association Between Dyslipidemia and Psoriasis With No Data on Prevalence or Risk[a]

Authors, year[ref]	Country	Design	With Psoriasis, No.	Without Psoriasis, No.	Association With Psoriasis
Bajaj et al, 2009[289]	Pakistan	CC	79	79	In TC, TG, and LDL-C
Akhyani et al, 2007[290]	Iran	CC	50	50	In TG and LDL-C
Tekin et al, 2007[291]	Turkey	CC	84	40	In all lipid profile parameters
Farshchian et al, 2006[292]	Iran	CC	30	30	None
Reynoso et al, 2003[293]	Mexico	CC	50	50	In HDL-C
Piskin et al, 2003[294]	Turkey	CC	100	100	In TC and LDL-C
Vanizor et al, 2003[126]	Turkey	CC	35	35	In all lipid profile parameters

Abbreviations: CC, case-control; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.
[a]Dependent variables are shown as continuous variables.

Appendix 7. Risk of Metabolic Syndrome in Patients With Psoriasis

Authors, year[ref]	Country	Population	Design	Matching Variables	With Psoriasis, No.	Without Psoriasis, No.	Prev, %	Results (95% CI)	Adjustment Variables	Criteria
Al-Mutairi et al, 2010[32]	Kuwait	Dermatology patients from 2 hospitals. Controls: hospitalized patients.	CC	Age, sex, area of residence	1661[a] 129[b]	1835 1835	16.0 26.3	OR = 2.6 (2.09-3.28) OR = 4.9 (3.2-7.6)		NCEP (ATP III)
Augustin et al, 2010[273]	Germany	Medical insurance organization	CS		33 981	1 310 090	0.18	PR = 2.9 (2.21-3.71)	HT + Ob + DLP + DM ICD-10	
Raydchauri et al, 2010[295]	United States	Dermatology patients and population-based data from the NHANES III	CS		105		58.1	PR = 1.65		
Miele et al, 2009[144]	Italy	Hospitalized dermatology patients	CH		142		48.5			NCEP (ATP III)
Gisondi et al, 2009[143]	Italy	Hospitalized dermatology patients. Controls: healthy hospital personnel.	CC	Age, sex, BMI	130	260	28	OR = 1.08 (0.67-1.73)		NCEP (ATP III)
Arias et al, 2009[296]	Spain	Patients with severe psoriasis (PASI > 10 and BSA > 10%) treated in a dermatology department	CC	Age and sex	50	50	44.2	OR = 4.12 (1.6-10.5)		NCEP (ATP III)
Cohen et al, 2008[277]	Israel	Clalit Health Services Database	CC		16 850	48 677	8.4	OR = 1.3 (1.1-1.4)	Age, sex, tobacco	Ob + 2 of the following: elevated TG, low HDL-C, HT, DM
Gisondi et al, 2007[280]	Italy	Dermatology patients from 3 hospitals	CC		338	334	30.1	OR = 1.65 (1.16-2.35)	Age and sex	NCEP (ATP III)
Sommer et al, 2006[247]	Germany	Hospitalized patients. Controls: patients who underwent surgery for stage I melanoma.	CC		581	1044	4.3	OR = 5.92 (2.78-12.8)	Age and sex	WHO

Abbreviations: BSA, body surface area; CC, case-control; CH, cohort; CS, cross-sectional; DM, diabetes mellitus; DLP, dyslipidemias; HDL-C high-density lipoprotein cholesterol; HPL, hyperlipidemia; HT, hypertension; ICD, International of Diseases; LDL-C, low-density lipoprotein cholesterol; Ob, obesity; OR, odds ratio; NCEP (ATP III), National Cholesterol Education Program Adult Treatment Panel III guidelines; PASI, Psoriasis Area and severity. index; PR, prevalence ratio; Prev, prevalence; WHO, World Health Organization.

[a]Mild to moderate psoriasis.

[b]Severe psoriasis.

Appendix 8. Risk for Nonalcoholic Fatty Liver Disease (NAFLD) in Patients With Psoriasis

Authors, year[ref]	Country	Population	Design	Matching Variables	With. Psoriasis, No.	With Psoriasis, No.	Prev, %	Results (95% CI)	Criteria
Gisondi et al, 2009[143]	Italy	Dermatology patients from a hospital. Controls: apparently healthy hospital staff.	CC	Age, sex, BMI	130	260	47	OR = 2.26 (1.46-3.51)	NAFLD diagnosed by ultrasonography after excluding other secondary causes of chronic liver disease
Miele et al, 2009[144]	Italy	Dermatology patients from a hospital	CS		142		59.2		Medical history, laboratory results, and ultrasound findings

Abbreviations: BMI, body mass index; CC, case-control; CS, cross-sectional; OR, odds ratio; Prev, prevalence.

Appendix 9. Risk of Ulcerative Colitis in Patients W ith Psoriasis

Authors, year[ref]	Country	Population	Design	Matching Variables	With Psoriasis, No.	Without Psoriasis, No.	Prev, %	Results (95% CI)	Adjustment Variables
Augustin et al, 2010[273]	Germany	Medical insurance organization	CS		33 981	1 310 090	1.09	PR =1.91 (1.72-2.11)	
Augustin et al, 2010[274]	Germany	Medical insurance organization. Juvenile Psoriasis	CS		2549	331 758	0.12	PR =1.13 (0.38-3.33)	
Cohen et al, 2009[297]	Israel	Clalit Health Services Database	CC	Age and sex	12 502	24 285	0.48	OR = 1.64 (1.15-2.33)	Age, sex, socioeconomic status
Makredes et al, 2009[298]	United States	IMS Health Integrated Claims Database	CC	Age, sex, region, and duration of MIC	22 490[a] 3066[b]	89 960 12 264		PR = 1.3 (1.1-1.6) PR = 2.0 (1.3-3.1)	

Abbreviations: CC, case-control; CS, cross-sectional; MIC, medical insurance coverage; OR, odds ratio; Prev, prevalence; PR, prevalence ratio.
[a]Only psoriasis.
[b]Psoriatic psoriasis.

Appendix 10. Risk of Crohn disease in Patients With Psoriasis

Authors, year[ref]	Country	Population	Design	Matching Variables	With Psoriasis, No.	Without Psoriasis, No.	Prev, %	Results (95% CI)	Adjustment Variables
Augustin et al, 2010[273]	Germany	Medical insurance organization	CS		33 981	1 310 090	0.92	PR = 2.06 (1.84-2.31)	
Augustin et al, 2010[274]	Germany	Medical insurance organization. Juvenile psoriasis.	CS		2549	331 758	0.51	PR = 3.69 (2.15-6.35)	
Cohen et al, 2009[297]	Israel	Clalit Health Services Database	CC	Age and sex	12 502	24 285	0.51	OR = 2.49 (1.71-3.62)	Age, sex, socioeconomic status
Makredes et al, 2009[298]	United States	IMS Health Integrated Claims Database	CC	Age, sex, region, and duration of MIC	22 490[a] 3066[b]	89 960 12 264		PR = 1.6 (1.4-2.0) PR = 2.1 (1.3-3.3)	

Abbreviations: CC, case-control; CS, cross-sectional; MIC, medical insurance coverage; OR, odds ratio; PR, prevalence ratio; Prev, prevalence.
[a]Only psoriasis.
[b]Psoriatic arthritis.

Appendix 11. Risk of Cancer in Patients With Psoriasis

Authors, year[ref]	Country	Population	Design	Matching Variables	With Psoriasis, No.	Without Psoriasis, No.	Results (95% CI)	Adjustment Variables	Cancer
Ji et al, 2009[185]	Sweden	Swedish Hospital Discharge Register. Patients hospitalized for psoriasis.	CH		15 858		SIR = 0.95 (0-66-1.32)	Age, sex, socioeconomic status, area of residence	Melanoma
							SIR =2.08 (1.67-2.55)		SCC
							SIR =1.31 (1.01-1.69)		NHL
Gelfand et al, 2006[182]	United Kingdom	General Practice Research Database	CH	Doctor and date of observation	149 203[a]	765 950	HR = 1.34 (1.16-1.54)	Age and sex	Lymphoma
					3994[b]	765 950	HR = 1.59 (0.88-2.89)		
					14 9203[a]	765 950	HR = 1.15 (0.97-1.37)		NHL
					3994[b]	765 950	HR = 0.73 (0.28-1.96)		
					149 203[a]	765 950	HR = 1.42 (1.00-2.02)		HL
					3994[b]	765 950	HR = 3.18 (1.01-9.97)		
					149 203[a]	765 950	HR = 4.10 (2.70-6.23)		Cutaneous T-cell lymphoma
					3994[b]	765 950	HR = 10.75 (3.89-29.76)		
Gelfand et al, 2003[180]	United Kingdom	General Practice Research Database. Over 65 years of age.	CH		2 718	105 203	HR = 2.95 (1.83-4.76)		Lymphoma
							HR = 2.94 (1.82-4.74)	Age and sex	
Boffetta et al, 2001[184]	Sweden	Swedish Hospital Discharge Register. Patients hospitalized for psoriasis.	CH		9 773		SIR = 0.32 (0.10-1.32-0.74)		Melanoma
							SIR = 2.46 (1.82-1.32-3.27)		SCC
							SIR = 0.36 (0.01-1.32-2.02)		HL
							SIR = 1.42 (0.89-1.32-2.15)		NHL
							SIR = 19.3 (6.22-1.32-45.01)		MF
Margolis et al, 2001[181]	United States	US Medicaid Database	CH		1101[b]	234 304[c]	IDR = 7.80 (4.42-12.81)		Lymphoma
							IDR = 7.95 (4.94-12.79)	Age, sex, state of origin	
							IDR = 3.19 (2.04-4.77)		NMSC
							IDR = 4.15 (2.52-6.84)	Age, sex, state of origin	
					16 519[a]	234 304[c]	IDR = 2.18 (1.66-2.84)		Lymphoma
							IDR = 2.11 (1.63-2.74)	Age, sex, state of origin	
							IDR = 1.86 (1.61-2.16)		NMSC
							IDR = 2.35 (1.96-2.82)	Age, sex, state of origin	
Hannusksela-Svahn et al, 2000[183]	Finland	Finnish Hospital Discharge Register. Hospitalized patients.	CH		5687		SIR = 0.8 (0.3-1.32-1.6)	Age, sex, calendar year	Melanoma
							SIR = 3.2 (2.3-1.32-4.4)		NMSC
							SIR = 2.2 (1.4-1.32-3.4)		NHL
							SIR = 3.3 (1.4-1.32-6.4)		HL
Frentz and Olsen, 1999[186]	Denmark	Patients diagnosed with psoriasis in a hospital setting between 1977 and 1987	CH		6905		SIR = 1.3 (0.8-1.32-2.1)	Sex, age group (5 years), calendar year	Melanoma
							SIR = 2.46 (2.13-1.32-2.83)		NMSC
							SIR = 1.4 (0.8-1.32-2.2)		NHL
							SIR = 15.1 (4.1-1.32-38)		MF

Abbreviations: CH, cohort; HL, Hodgkin lymphoma; HR, hazard ratio; IDR, incidence density ratio; MF, mycosis fungoides; NHL, Non-Hodgkin lymphoma; NMSC, nonmelanoma skin cancer; SCC, squamous cell carcicoma; SIR, standardized incidence ratio.

[a]Less severe psoriasis (no systemic treatment)

[b]Severe psoriasis (no systemic treatment).

[c]Patients with hypertension.

Appendix 12. Risk of Depression in Patients With Psoriasis

Authors, year[ref]	Country	Population	Design	Matching Variables	With Psoriasis, No.	Without Psoriasis, No.	Prev, %	Results (95% CI)	Criteria
Kirby et al, 2008[4]	United Kingdom	Dermatology patients from a hospital	CS		83		21.7		HADS ≥ 11
Wu et al, 2008[211]	United States	National Health and Wellness Survey. Controls: patients without psoriasis.	CC	Age, sex, region, race	1127	1127		OR = 1.60 (1.30-1.98)	NS
Zachariae et al, 2008[299]	Denmark	Dermatology patients from a hospital	CS		40		30.0		BDI-13 ≥ 9
Schmitt and Ford, 2007[300]	Germany	Patients recruited via the Internet	CS		265		48.7 31.7		CES-D > 16 CES-D ≥ 22
Esposito et al, 2006[301]	Italy	Patients sent a questionnaire	CS		2391		62		CES-D > 23
Schneider et al, 2006[209]	Germany	Dermatology patients with prurigo nodularis. Controls: patients with psoriasis.	CC		91		21		HADS ≥ 9
Yang et al, 2005[302]	China	Patients attending the National Skin Center	CS		93		9.7		HADS ≥ 11
Akay et al, 2002[303]	Turkey	Dermatology patients from a hospital. Controls: individuals with no chronic or acute disease.	CC		50	40	32 26	OR = 3.48 (1.22-9.90) OR = 19.81 (2.41-162.90)	BDI 14-24 BDI ≥ 25
Richards et al, 2001[206]	United Kingdom	Patients treated in a specialized clinic	CS		115		10		HADS ≥ 11
Devrimci-Ozguven et al, 2000[212]	Turkey	Dermatology patients from a hospital. Controls: patients without skin disease.	CC		50	50	28 48	OR = 5.06 (1.76-14.56) OR = 38.99 (8.02-189.51)	BDI 10-17 BDI ≥ 18
Scharloo et al, 2000[304]	Netherlands	Dermatology patients from a hospital	CS		69		20 9		HADS 8-10 HADS > 10

Abbreviations: BDI, Beck Depression Inventory; BDI-13, short 13-item version of the BDI scale; CC, case-control; CES-D, Center for Epidemiological Studies-Depression Scale; CS, cross-sectional; HADS, Hospital Anxiety and Depression Scale; NS, not specified; OR, odds ratio; Prev, prevalence.

Appendix 13. Risk of Anxiety in Patients With Psoriasis

Authors, year[ref]	Country	Population	Design	Matching Variables	With Psoriasis, No.	Without Psoriasis, No.	Prev, %	Results (95% CI)	Criteria
Kirby et al, 2008[4]	United Kingdom	Dermatology patients from a hospital	CS		83		42.2		HADS ≥ 11
Wu et al, 2008[211]	United States	National Health and Wellness Survey. Controls: patients without psoriasis.	CC	Age, sex, region, race	1127	1127		OR = 1.57 (1.29-1.92)	NS
Schneider et al, 2006[209]	Germany	Dermatology patients with prurigo nodularis. Controls: patients with psoriasis.	CC		91		11		HADS ≥ 11
Yang et al, 2005[302]	China	Patients attending the National Skin Center	CS		93		34		HADS ≥ 11
Richards et al, 2001[206]	United Kingdom	Patients treated in a specialized clinic	CS		115		43		HADS ≥ 11
Scharloo et al, 2000[304]	Netherlands	Dermatology patients from a hospital	CS		69		25 16		HADS 8-10 HADS > 10

Abbreviations: CC, case-control; CS, cross-sectional; HADS, Hospital Anxiety and Depression Scale; NS, not specified; OR, odds ratio; Prev, prevalence.

Appendix 14. Tobacco Use in Patients With Psoriasis

Authors, year[ref]	Country	Population	Design	Matching Variables	With psoriasai, No.	Without psoriasis, No.	Prev, %	Results (95% CI)	Adjustment Variables	Criteria
Gerdes et al, 2010[246]	Germany	Patients hospitalized for treatment in 9 dermatology clinics. Controls: National Health Survey (BGS98).	CC		1097	6963	43.3	OR = 2.08 (1.81-2.39)		Smoker
Metha et al, 2010[232]	United Kingdom	General Practice Research Database. Severe: on systemic treatment.	CH	Doctor and date of observation	3603[b]	14 330	6.7 24.3	OR = 1.34 (1.15-1.56) OR = 1.18 (1.08-1.29)		Smoker Ex-smoker
Miele et al, 2009[144]	Italy	Dermatology patients from a hospital	CH		142		38.7			Smoker
Jin et al, 2009[305]	China	Dermatology patients from a hospital	CC	Age, sex, race	178	178	47.1	OR = 2.31 (1.32-3.80) OR = 2.07 (1.12-3.82)	Age, sex, education, occupation, marital status, BMI, WHR	> 360 cig/y
Wolk et al, 2009[249]	Sweden	Cases: Stockholm-area patients who developed psoriasis within the preceding 12 months. Controls: Swedish Population Registry.	CC	Age, sex, and zip code	289	289	37 15	OR = 1.6 (1.0-1.4) OR = 0.9 (0.5-1.4)	Age, sex, zip code, BMI, weight gain, alcohol	Smoker Ex-smoker
Xiao et al, 2009[52]	China	Patient medical records of 5 hospitals. Random controls from 1 of the hospitals.	CC		1619[a] 1473[b]	1521 521	19.08 25.53	OR = 1.35 (1.01-1.80) OR = 1.57 (1.20-2.05)	Age and sex	Smoker
Prodanovich et al, 2009[229]	United States	Patients from a veterans hospital	CC		3236	2500	9.9	OR = 3.42 (2.65-4.40)		Smoker
Arias et al, 2009[296]	Spain	Patients with severe psoriasis (PASI > 10 and BSA > 10%) who attended a dermatology department	CC	Age and sex	50	50	36.8	OR = 1.78 (0.69-4.66)		> 5 cig/d (current)
Driessen et al, 2009[269]	Netherlands	Dermatology patients	CC		107[a]	396	46.7	OR = 1.73 (1.08-2.75)		Smoker
Qureshi et al, 2009[83]	United States	Nurses' Health Study	CH		1813	76 248	26	OR = 1.39 (1.25-1.56) OR = 18 (1.93-1.70)		Smoker Ex-smoker
Naldi et al, 2008[278]	Italy	Dermatology patients from 20 hospitals	CC	Age	560	690	63.7	OR = 1.8 (1.3-2.7)	Age, sex, alcohol, marital status, family history of psoriasis, and BMI	Ex-smoker
Favato, 2008[306]	Italy	Patients in the PSOCARE study. Reference: adult Italian population.	CH		2368 2042		41.0 38.7	SIR =1.85 (0-1.32-66) SIR =1.74 (0-1.32-66)	Age	Smoker
Huerta et al, 2007[248]	United Kingdom	General Practice Research Database	CC	Age, sex, date	3994	10 000	25.36	OR = 1.37 (1.25-1.50) OR = 1.45 (1.31-1.59)	Age, sex, year, tobacco, GP visits, BMI	Smoker
Neimann et al, 2006[282]	United Kingdom	General Practice Research Database	CC	Doctor and date of observation	127 706[a] 3854[b]	465 252 14 065	28.00 30.05	OR = 1.40 (1.38-1.43) OR = 1.31 (1.29-1.34) OR = 1.31 (1.20-1.44) OR = 1.31 (1.17-1.47)	Age, sex, person-years Age, sex, person-years, HT, HPL, tobacco Age, sex, person-years Age, sex, person-years, HT, HPL, tobacco, and BMI	Smoker

Sommer et al, 2006[247]	Germany	Hospitalized patients. Controls: patients with surgically treated stage I localized melanoma.	CC		581	1044	45.4	OR = 2.96 (2.27-3.84)	Age and sex	Smoker
Fortes et al, 2005[228]	Italy	Hospitalized patients with psoriasis	CC		818		50 15			Smoker Ex-smoker
Herron et al, 2005[230]	United States	Patients from a hospital dermatology department. Compared with population-based data.	CS		557	4080	36.8	OR = 4.02 (3.31-4.88)	Age and sex	Smoker
Naldi et al, 2005[3]	Italy	Dermatology patients from 20 hospitals	CC	Age	560	690	18.4 43.2	OR = 1.9 (1.3-2.7) OR = 1.7 (1.1-3.0)	Age, sex, tobacco, alcohol, education, marital status, hospitalization, BMI,	Ex-smoker Smoker
Zhang et al, 2002[226]	China	Dermatology patients from 4 hospitals. Controls: resident in the same geographic region.	CC		440 349	433 356	48.9 2.6	OR = 2.33 (1.74-3.11)[M] OR = 1.86 (0.56-6.43)[W]		> 360 cig/y
Naldi et al, 1999[231]	Italy	Dermatology patients from 20 hospitals. Cases: patients with psoriasis duration of < 2 y.	CC	Age	404	616	18.5 23.5 13.9 5.9	OR = 1.9 (1.3-2.7) OR = 1.8 (1.2-2.6) OR = 1.5 (1.1-2.1) OR = 1.4 (1.0-2.0) OR = 1.8 (1.2-2.7) OR = 1.7 (1.1-2.7) OR = 2.4 (1.3-4.3) OR = 2.1 (1.1-3.9)	 Age, sex, tobacco, occupation, marital status, family history, BMI Age, sex, tobacco, occupation, marital status, family history, BMI Age, sex, tobacco, occupation, marital status, family history, BMI	Ex-smoker ≤ 15 cig/d 16-24 cig/d ≥ 25 cig/d

Abbreviations: BMI, body mass index; CC, case-control; CS, cross-sectional; CH, cohort; cig, cigarettes; HPL, hyperlipidemia; HT, hypertension; M, men; OR, odds ratio; Prev, prevalence; ; SIR, standardized incidence ratio; W, women; WHR, waist/hip ratio.

[a]Mild psoriasis (no systemic treatment)

[b]Severe psoriasis (systemic treatment).

Appendix 15. Alcohol Consumption in Patients With Psoriasis

Authors, year[ref]	Country	Population	Design	Matching Variables	With Psoriasis, No.	Without Psoriasis, No.	Prev, %	Results (95% CI)	Adjustment Variables	Criteria
Gerdes et al, 2010[246]	Germany	Cases: patients hospitalized for treatment in 9 clinics. Controls: National Health Survey (BGS98).	CC		1081 615 466	6942 3372 3570	15.6 23 5.7	OR = 3.10 (2.53-3.80) OR = 2.86 (2.29-3.56)[M] OR = 5.12 (3.12-8.39)[W]		> 1 drink/d
Wolk et al, 2009[249]	Sweden	Cases: patients in the Stockholm area who developed psoriasis within the preceding 12 months. Controls: Swedish Population Registry.	CC	Age, sex, zip code	354	354	39 34	OR = 1.5 (0.9-2.6) OR = 1.7 (1.0-3.0)	Age, sex, zip code, BMI, weight gain, tobacco	5-19 drinks/mo vs < 5 drinks/mo ≥ 20 drinks/mo versus < 5 drinks/mo
Kirby et al, 2008[4]	United Kingdom	Dermatology patients	CS		83		30.1 16.9			Problems with alcohol: CAGE scale (Health Screening Survey) Problems with alcohol: MAST
Huerta et al, 2007[248]	United Kingdom	General Practice Research Database	CC	Age, sex, date	3994	10 000	30.52 7.81	OR = 0.91 (0.82-1.00) OR = 0.96 (0.87-1.06) OR = 1.07 (0.92-1.24) OR = 1.06 (0.90-1.25)	 Age, sex, year, tobacco, GP visits, BMI Age, sex, year, tobacco, GP visits, BMI	1-20 g/wk > 20 g/wk
Sommer et al, 2006[247]	Germany	Hospitalized patients. Controls: patients with surgically treated melanoma.	CC		581	1044	42.3 12.9 4.1	OR = 2.78 (2.14-3.62) OR = 3.33 (2.20-5.05) OR = 3.61 (1.85-7.07)	Age and sex Age and sex Sex	1-3 drinks/wk 4 drinks/wk - 1 drink/d > 1 drink/d
Fortes et al, 2005[228]	Italy	Hospitalized patients with psoriasis	CS		818		19 22 14			Less than daily 1-2 drinks/d > 2 drinks/d
Naldi et al, 2005[3]	Italy	Dermatology patients from 20 hospitals	CC	Age	560	690	2.7 33.6 30.7 12.3	OR = 0.7 (0.3-1.6) OR = 0.9 (0.7-1.3) OR = 1.2 (0.9-1.8) OR = 1.4 (0.8-2.2)	Age, sex, tobacco, education, marital status, hospitalization, BMI	Ex-drinker < 2 drinks/d 2-4 drinks/d ≥ 5 drinks/d
Zhang et al, 2002[226]	China	Dermatology patients from 4 hospitals. Controls: residents of the same geographical area.	CC		440 349	433 356	29.8 8.6	OR = 4.17 (2.79-6.23)[Y] OR = 6.60 (2.40-19.62)[M]		≥ 2 times/wkeek ≥ 50mL of spirits or 500 mL of beer
Naldi et al, 1999[231]	Italy	Dermatology patients from 20 hospitals. Cases: patients with psoriasis duration of < 2 y.	CC	Age	404	616	3.0 24.0 31.4 18.3	OR = 1.1 (0.5-2.4) OR = 0.8 (0.4-1.7) OR = 0.9 (0.6-1.3) OR = 0.8 (0.6-1.2) OR = 1.3 (0.9-1.8) OR = 1.2 (0.8-1.7) OR = 1.7 (1.0-3.0) OR = 1.5 (0.9-2.4)	 Age, sex, tobacco, occupation, marital status, family history, BMI Age, sex, tobacco, occupation, marital status, family history, BMI Age, sex, tobacco, occupation, marital status, family history, BMI Age, sex, tobacco, occupation, marital status, family history, BMI	Ex-drinker ≤ 1 drink/d 2-4 drinks/d ≥ 5 drinks/d

Abbreviations: CAGE, Cut-down, Annoyed, Guilty, Eyeopener quetionnaire; BMI, body mass index; CC, case-control; CH, cohort; CS, cross-sectional; MAST, Michigan Alcoholism Screening Test; M, men; OR, odds ratio; Prev, prevalence; ; W, women.

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