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Psoriasis more than skin deep: New insights in the presence of comorbidities and search for a better care.

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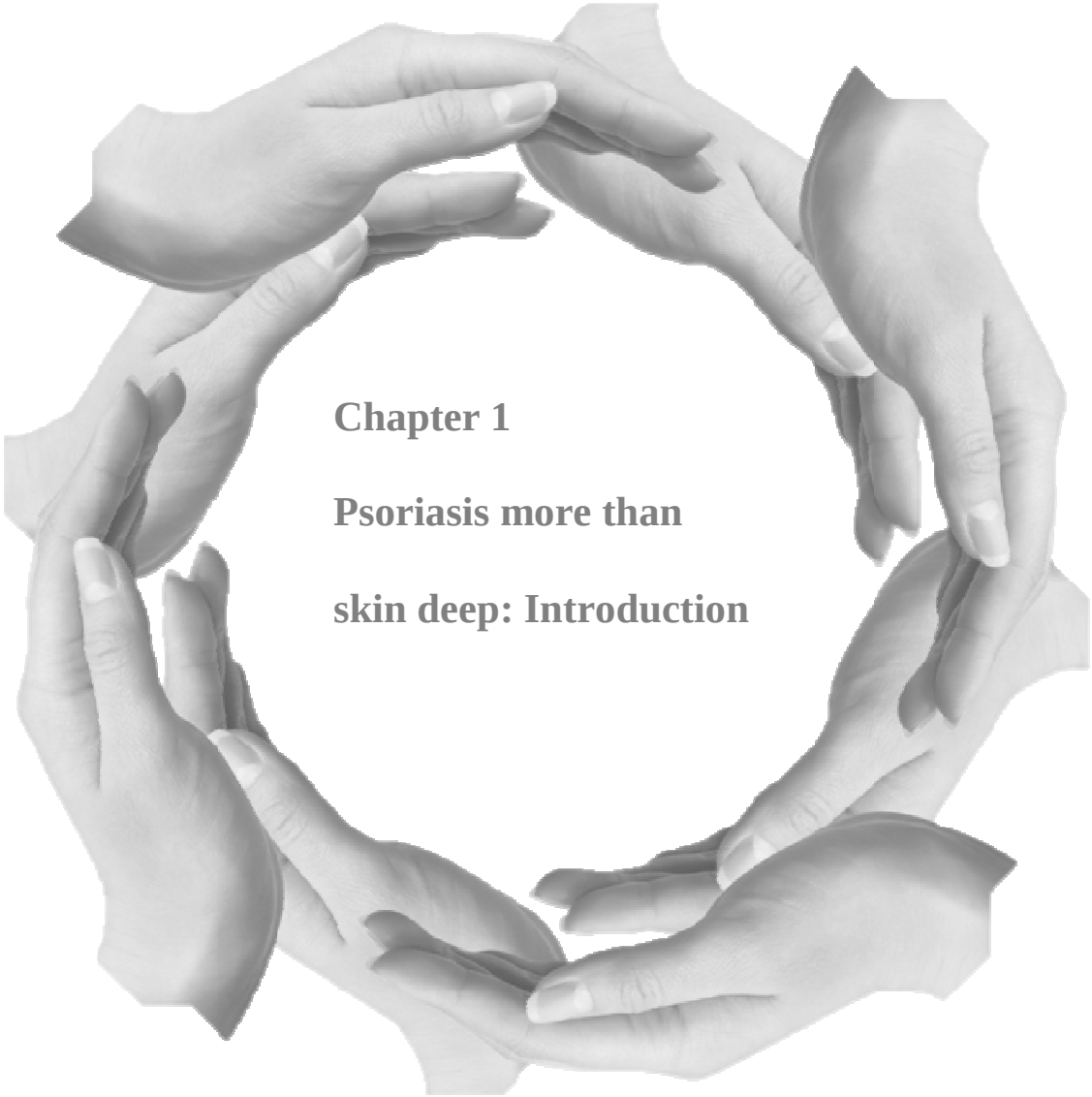
List of abbreviations

95%CI	95% confidence interval
AD	Atopic dermatitis
Anti-TNF	Anti-tumor necrosis factor
AS	Ankylosing spondylitis
AUDIT	Alcohol use disorders identification test
BCG	Bacille Calmette Guérin
BDI	Beck depression inventory
BMI	Body mass index
BSA	Body surface area
CASPAR	Classification criteria for psoriasis arthritis
CD	Crohn's disease
CD4+ Tcells	T helper lymphocytes which express the surface protein CD4
CD8+ Tcells	T cytotoxic lymphocytes which express the surface protein CD8
CDKAL-1	CDK5 regulatory subunit associated protein 1-like 1 gene
CeD	Celiac disease
CI	confidence interval
CLCI	Cumulative life course impairment
COPD	Chronic obstructive pulmonary disease
CPII/C2C	Ratio of C-propeptide of type II collagen to collagen fragment neoepitopes
CRP	C-reactive protein
CsA	Ciclosporin
DEFB4	Defensin, beta 4 gene
DLQI	Dermatology life quality index
DMARD	Disease-modifying anti-rheumatic drug
EASI	Eczema are and severity index
EEWGHP	European expert working group for healthcare in psoriasis
EQ-5D	EuroQol-5D
fMRI	Functional magnetic resonance imaging
GJB2	Gap junction protein, beta 2 gene
GRAPPA	Group for research and assessment of psoriasis and psoriatic arthritis
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus

HLA-Cw6	Human leucocyte antigen-Cw6
HRQOL	Health-related quality of life
hs-CRP	High-sensitivity c-reactive protein
IA	Intra-articular
IDF	International diabetes foundation
IL	Interleukin
IMID	Immune-mediated inflammatory disorders
IQR	Interquartile range
LCE3	Late cornified envelope
LDL	Low-density lipoprotein
LEF	Leflunomide
MMP-3	Matrix metalloproteinase 3
MS	Multiple sclerosis
MTX	Methotrexate
NAFLD	Non-alcoholic fatty liver disease
NAPSI	Nail psoriasis severity index
NFκB	Nuclear factor-κB
NS	Non-significant
NSAID	Non-steroidal anti-inflammatory drugs
NYHA	New York heart association functional classification
OPG	Osteoprotegerin
OR	Odds ratio
OSAS	Obstructive sleep apnea syndrome
PASE	Psoriatic arthritis screening and evaluation
PASI	Psoriasis area and severity index
PASW	Predictive analytics software
PDI	Psoriasis disability index
PEST	Psoriasis epidemiology screening tool
PGA	Physician's global assessment
PIIINP	Procollagen III
PLSI	Psoriasis life stress index
PsA	Psoriatic arthritis
PsO	Psoriasis of the skin
PT	Physiotherapy

PUVA	Psoralen-ultraviolet light A
QoLIAD	Quality of life index for atopic dermatitis
RA	Rheumatoid arthritis
RCT	Randomized controlled trial
RR	Relative ratio
SCORAD	Scoring atopic dermatitis
SD	Standard deviation
SF-36	Short Form-36
SLE	Systemic lupus erythematosus
SNP	Single nucleotide polymorphism
SPI	Salford psoriasis index
SPSS	Statistical package for the social sciences
SSZ	Sulfasalazine
T1D	Type 1 diabetes
Th	T-helper lymphocytes
TNFAIP3	Tumor necrosis factor, alpha-induced protein 3 gene
TNF-α	Tumor necrosis factor-alfa
TNIP1	TNFAIP3-interacting protein 1 gene
ToPAS	Toronto psoriasis arthritis screen
UC	Ulcerative colitis
US	United States
UV	Ultraviolet
UVB	Ultraviolet light B
VO2max	Maximal oxygen consumption
WHO	World health organisation



Chapter 1

Psoriasis more than skin deep: Introduction

Chapter 1: Psoriasis more than skin deep: Introduction

1.1 Introduction on psoriasis

Psoriasis is a common chronic inflammatory disease affecting approximately 2% of the population in Europe and the United States and is less prevalent elsewhere.[7,8] Several different clinical phenotypes of psoriasis exists. They can be observed in the same person, either simultaneously or over time. Plaque psoriasis is the most common phenotype. It is characterised by sharply demarcated, erythematous plaques covered by silvery white scales, that preferentially occur on the scalp, buttocks and extensor sites of the knees and elbows. Other phenotypes are guttate, inverse, seborrhoeic, localized and generalized pustular and erythrodermic psoriasis. The course of the disease is characterised by flares and remissions and psoriasis comes in many different degrees of severity.[9]

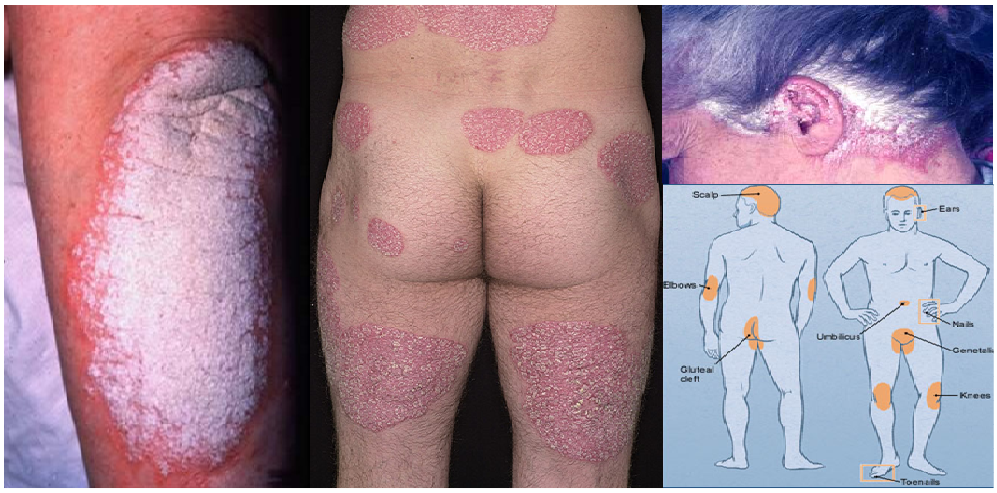


Figure 1 – Plaque psoriasis and predilection places.

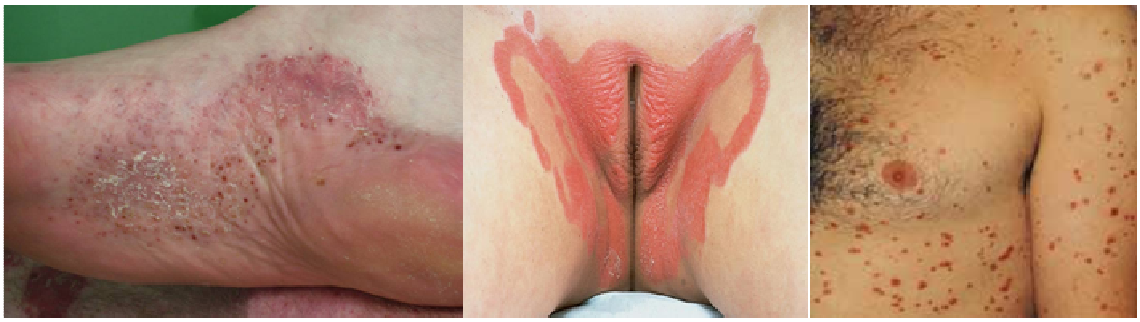


Figure 2 – Other phenotypes of psoriasis: localized pustular (a), inverse (b) and guttate psoriasis (c).

Disease onset is most frequently observed in the early twenties. It has been proposed that two types of psoriasis can be recognized (type I and type II), with type I psoriasis, characterized

by onset age ≤ 40 years, being more likely to be familial, severe, and strongly associated with HLA-Cw6.[10,11]

The evolution of a psoriatic lesion is based on a complex interplay between environmental and genetic factors. After disease initiation, a cascade of events leads to activation of dendritic cells and the generation of T cells that emigrate to the skin. Cross-talk between epithelial cells and immune cells shapes and maintains the inflammatory milieu wherein key cytokines interferon-γ, and TNF-α play an important role.[5]

Population studies clearly indicate that the incidence of psoriasis is greater among first-degree and second-degree relatives of patients than among the general population. That a genetic component may account for this finding is supported by studies of disease concordance among twins that show a risk of psoriasis that is two to three times as high among monozygotic twins as among dizygotic twins.[12]

Recent genome-wide association studies have started to identify specific genetic components of both the immune system and the epidermis that affect disease risk. Genetic risk factors such as different alleles of IL12B and IL23R affect pathways mediated by IL-12 and IL-23 which are crucial for the development of the immune cell subsets that drive the epidermal component of this skin disease.[13] Other factors including TNFAIP3 and TNIP1 affect pathways mediated by NFkB such as immunity and inflammation, cell proliferation and apoptosis. These could affect both immune cells and keratinocytes, and thereby contribute to alterations in epidermal proliferation.[14] By contrast, separate psoriasis genetic risk factors, such as deletions of late cornified envelope (LCE3) genes of the epidermal differentiation complex, are likely to have a direct effect on skin barrier formation.[15]

For many patients, the symptoms of psoriasis improve in summer and worsen in winter, reflecting the well-established notion that the course of the disease is influenced by environmental factors. Physical trauma may trigger psoriatic lesions at sites of injury (Koebner's phenomenon). Also, life style factors such as smoking, alcohol use, obesity and stress can trigger psoriasis onset or have an influence on course of the disease.[16-18]

Several treatment options for psoriasis exist. In basic terms, treatment for generalised psoriasis follows a 1-2-3 approach, starting with topical therapies, followed by light therapy (UVB/PUVA) and conventional systemic medications (methotrexate, acitretin or cyclosporine) or biologics (infliximab, etanercept, adalimumab or ustekinumab). Following

factors are considered in the treatment decision process: type, severity and localisation of psoriasis; age and medical history of patient; patient preferences and impact on health-related quality of life.[19]

After this brief introduction about the general aspects of psoriasis, we look closer at the different comorbidities in psoriasis, the impact on health-related quality of life and the lifestyle factors which have a negative influence on psoriasis and its comorbidities.

1.2 Comorbidities in psoriasis

Epidemiological studies indicate that psoriasis patients have a high risk of developing comorbidities. First of all, psoriatic arthritis is observed. This can be a mild but often debilitating disease with joint damage. Secondly, people with more severe presentations of psoriasis appear to have an increased frequency cardiovascular disease, abdominal obesity, dyslipidemia, hypertension and glucose intolerance or diabetes. A large, population based study found that life expectancy was about four years shorter in patients with severe psoriasis than in healthy controls mainly caused by their increased cardiovascular risk.[20] Thirdly, psychological and psychiatric comorbidities are common in psoriasis having a high impact on quality of life of psoriasis patients. Lastly, other psoriasis-related comorbidities such other immune-mediated inflammatory disorders, malignancies, infections, non-alcoholic fatty liver disease, obstructive sleep apnea syndrome and chronic obstructive pulmonary disease will be discussed in this chapter.

1.2.1 Psoriasis arthritis

Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis marked by stiffness, pain, swelling, and tenderness of the joints, as well as adjacent tendons.[21] PsA occurs in about 1% up to 39% of patients with psoriasis, depending on the population studied. The majority of the patients (approximately 70%) develop psoriasis before articular involvement; in contrast arthritis precedes the onset of psoriasis by more than 1 year in approximately 15% of cases, and in another 15% the two conditions occur together within a 12 months period.[22-24] PsA usually arises between 7 to 10 years after the onset of psoriasis.[25] The onset age of PsA is in the range of 30–55 years with an equal sex distribution.[26]

A strong genetic component for PsA has been suggested by several studies.[27] Common established susceptibility factors for psoriasis and PsA include an HLA-C risk allele[28,29] as well as variants in or near IL23R and IL12B[13,30], whereas a frequent deletion within the

epidermal differentiation complex contributes to skin involvement but not to joint involvement.[15,31]

PsA is classified according to criteria established by Moll and Wright or the ClASsification Criteria for Psoriatic ARthritis (CASPAR). In 1973, Moll and Wright defined PsA in patients seronegative for rheumatoid factor with positive history of psoriasis, current skin or nail psoriasis and inflammatory joints or axial disease. Based on the predominant clinical feature, five subsets were identified including distal interphalangeal arthritis, asymmetrical oligoarthritis, symmetrical polyarthritis, spondylitis and arthritis mutilans.[32] More recent, the CASPAR criteria for psoriatic arthritis require the presence of established inflammatory articular disease with at least 3 points from the following features: current psoriasis, a personal history of psoriasis, a family history of psoriasis, past or present dactylitis, juxta-articular new bone formation, rheumatoid factor negativity, and psoriatic nail dystrophy. Current psoriasis was assigned a score of 2, while all other features were assigned a score of 1.[1] (Table 1) Unfortunately, there are no validated serologic tests available to aid in the diagnosis of psoriatic arthritis.[33]

Table 1: The CASPAR criteria (ClASsification criteria for Psoriatic ARthritis)*[1]
To meet the CASPAR criteria, a patient must have inflammatory articular disease (joint, spine, or entheseal) with ≥3 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 personal history of psoriasis is defined as a history of psoriasis that may be obtained from a patient, 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. Typical 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, according to 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 appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot.
* The CASPAR criteria have specificity of 98.7% and sensitivity of 91.4%. ** Current psoriasis is assigned a score of 2; all other features are assigned a score of 1.

The gravity of PsA is highly variable and can range from a mild arthritis to debilitating polyarticular disease with joint damage and loss of functionality.[33] Three clinical patterns have been identified: oligoarticular (≤4 involved joints) or polyarticular (≥5 involved joints) peripheral disease and axial disease with or without associated peripheral arthritis.[34] Also, distal interphalangeal arthritis and arthritis mutilans may occur.[35] Asymmetric oligoarthritis is the most common pattern at onset.[36] Axial disease has been approximate between 5% and 36% of patients.[37,38] It is characterized by an irregular involvement of the axial skeleton with a preference for the cervical spine.[39] Recurrent episodes of enthesitis and dactylitis represent a characteristic of PsA.[1] Associated with psoriasis and PsA, the nails can be involved in up to 50% of cases. There is a broad spectrum of nail dystrophies, ranging from the common pitting and loosening of the nail plate to the less common discoloration and splinter hemorrhages seen in the nail bed.[40] The nails and joints are associated with inflammation at points of tendon insertion (enthesitis), so it is now valued that both of these sites also share a common microanatomical basis.[41]

Patients with psoriasis should be screened for the presence of PsA, because early detection and aggressive treatment appear to prevent joint damage. Three large validation studies recently identified three patient questionnaires as being highly sensitive and specific tools to diagnose PsA.[42] These questionnaires are the Toronto psoriasis arthritis screen (ToPAS)[43], the psoriatic arthritis screening and evaluation (PASE) tool[44], and the psoriasis epidemiology screening tool (PEST).[45] The ToPAS questionnaire has been developed to screen for PsA in unselected patients, and the PASE and PEST questionnaires are proposed to identify PsA among patients with psoriasis.[46] If indicated, these patients should be referred to a rheumatologist for affirmation of diagnosis and initiation of treatment.[25]

Recently the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) developed treatment recommendations based on a literature review and consensus between rheumatologists and dermatologists (Table 2).[2]

Table 2: Treatment guidelines for psoriatic arthritis categorised by disease characteristics and distinct organ involvement.[2]

GRAPPA treatment guidelines for psoriatic arthritis				
Peripheral arthitis	**Skin and nail disease**	**Axial disease**	**Dactylitis**	**Enthesitis**
Initiate therapy	Initiate therapy	Initiate therapy	Initiate therapy	Initiate therapy
NSAID IA steroids DMARD (MTX, CsA, SSZ, LEF) BIOLOGICS (anti-TNF)	Topicals PUVA/UVB Systemics (MTX, CsA) Biologics (anti-TNF, etc)	NSAID PT Biologics (anti-TNF)	NSAID Steroid injection Biologics (anti-TNF)	NSAID PT Biologics (anti-TNF)

Anti-TNF: anti-tumour necrosis factor; CsA: ciclosporin A; DMARD: disease-modifying anti-rheumatic drug; IA: intra-articular; LEF: leflunomide; MTX: methotrexate; NSAID: non-steroidal anti-inflammatory drug; PT: physiotherapy; PUVA: psoralen–ultraviolet light A; SSZ: sulfasalazine; UVB: ultraviolet light B.

1.2.2 Cardiovascular and metabolic disease

Increasing epidemiological evidence suggests independent associations between psoriasis and metabolic and cardiovascular disease. Metabolic syndrome is a cluster of risk factors, which include abdominal obesity, dyslipidemia, hypertension and glucose intolerance, and is a strong predictor of cardiovascular diseases and diabetes type 2.[47] Psoriasis patients have an increased prevalence of metabolic syndrome and its individual components compared to control patients.[48] This association increases with increasing disease severity.[49] In Table 3, we show an overview of numerous studies that reported associations between psoriasis, metabolic syndrome and cardiovascular disease since 2006.

Table 3: Overview of studies that reported associations between psoriasis and metabolic disease from 2006 till 2012.

Year	Author	Patients	Psoriasis is associated with increased risk of …
2006	Neimann[50]	131 560 pso	diabetes [OR 1.13], hypertension [OR 1.03], hyperlipemia [OR 1.16]
		479 317 co	obesity [OR 1.27] and smoking [OR 1.31]
	Sommer[51]	581 pso	diabetes [OR 2.48], hypertension [OR 3.27], hyperlipidemia [OR 2.09]
		1044 co	metabolic syndrome [OR 5.29]
	Mallbris[52]	200 pso	elevated total cholesterol, HDL and apolipoproteine A1
		285 co	
	Gelfand[53]	130 976 pso	myocardial infarct [OR 1.06/1.43]
		556 995 co	
2007	Cohen[54]	340 pso	diabetes [OR 1.5], hypertension [OR 1.3], dyslipidemia [OR 1.2]
		6643 co	obesity [OR 1.3], ischemic heart disease [OR 1.4]
	Shapiro[55]	46 095 pso	diabetes [OR 1.27] and atherosclerosis [OR 1.28]
		1 579 037 co	
	Gisondi[48]	338 pso	metabolic syndrome [OR 1.65]
		334 co	
	Ludwig[56]	32 pso	coronary arterial calcification [OR 2.11]
		32 co	
2008	Cohen[57]	16 851 pso	diabetes [OR 1.2], hypertension [OR 1.3], obesity [OR 1.7]
		48 681 co	metabolic syndrome [OR 1.3], cardiovascular disease [OR 1.1]
	Dreiher[58]	10669 pso	dyslipidemia [OR 1.48]
		22996 co	
2009	Qureshi[59]	1813 pso	diabetes [RR 1.63] and hypertension [RR 1.17]
		76 248 co	
2010	Schmitt[60]	3147 pso	diabetes [OR 1.21], hypertension [OR 1.34]
		3147 co	dyslipidemia [OR 1.29], obesity [OR 1.63]
	Cohen[61]	12 502 pso	hypertension [OR 1.37]
		24 285 co	
2011	Love[62]	71 pso	metabolic syndrome [OR 2.16]
		2385 co	
	Langan[49]	4065 pso	metabolic syndrome [OR 1.41]; varying in a dose-response manner
		40 650 co	from mild OR [1.22] to severe psoriasis OR [1.98]
	Armesto[63]	661 pso	hypertension [OR 1.44]
		661 co	
2012	Li[64]	3074 pso	diabetes among individuals younger than 60 years [RR 1.26]
		159 621 co	

OR: Odds ratio; RR: Relative risk; pso: psoriasis patients; co: control patients.

In contrary with the results of these studies, Wakkee et al found in their cohort study that psoriasis is not a clinically relevant risk factor for ischemic heart disease hospitalizations on the population level. The authors warned for confounding factors such as an increased healthcare consumption in psoriasis patients compared to controls which may bias the study results of the previous studies.[65]

Identifying the causality of this association remains a challenge. First of all, other major factors that can contribute to this unfavorable cardiovascular risk profile include cigarette smoking, alcohol consumption, physical inactivity and psychological stress, all having a higher prevalence among patients with psoriasis.[66] Secondly, medications commonly used to treat psoriasis may have an influence on cardiovascular risk in psoriasis. For instance, the incidence of hypertension increases with cumulative cyclosporine dose and prolonged therapy. Moreover, Gisondi et al described an association between cyclosporine use and new-onset diabetes. In addition, acitretin and cyclosporine use are associated with lipid abnormalities. Furthermore, Prodanovich et al have shown that methotrexate reduces cardiovascular risk in rheumatoid arthritis and psoriasis but more recently, a study from Chen et al did not confirm this.[67,68] Thirdly, a possible link between psoriasis and metabolic diseases may be their pro-inflammatory state. Th-1 and Th-17 inflammatory cytokines are elevated in the skin and blood of patients with psoriasis. These inflammatory mediators may have pleiotropic effect on insulin signalling, lipid metabolism and adipogenesis.[69] Also, adipokines like leptin and adiponectin originating from adipose tissue, could play a pathogenetic role in the association between psoriasis and metabolic disease. Leptin is upregulated and adiponectin downregulated in both psoriasis and obesity.[70] Further research on this topic will be needed to prove this hypothesis. At last, a genetic basis for the association between metabolic comorbidities and psoriasis is suggested. Overlapping of susceptibility loci (CDKAL-1) has been demonstrated in psoriasis and diabetes type 2.[71]

Physicians treating moderate to severe psoriasis should screen for cardiovascular risk factors. A clinical consensus and recommendations for screening are discussed in Kimball et al. Their council was based on the recommendations of the American Heart Association to screen for cardiovascular risk factors from as early as age 20. By age 40, repeat this at least once every 2 years and to advise lifestyle modifications such as diet, smoking cessation, moderating alcohol intake and exercising 3 times a week for 30 minutes, as first line intervention.[25]

We can conclude that an optimal treatment for psoriasis includes clinical improvement but also takes into account cardiovascular risk. In this context, there is evidence that statins given for its lipid-lowering effects also induce a clinical improvement in psoriasis due to is immunomodulatory and anti-inflammatory effects.[72] An important question for the future is whether biologics will influence cardiovascular and metabolic comorbidities in psoriasis. Until now, there is no clear answer on this subject.[73]

1.2.3 Psychiatric and psychological comorbidity

Psoriasis is associated with a major psychological and psychiatric burden. Decreased quality of life[74], stigmatization[75,76], poor self-esteem, stress[77] and sexual dysfunction[78] are psychological implications of psoriasis. In addition, psoriasis patients are at increased risk for the development of depression, anxiety and suicidality.[79,80]

Psychological stress including actual experiences of discrimination by others and anticipation of the potential for stigmatization can be a long-lasting burden in patients with psoriasis. Psoriasis patients partly avoid situations potentially creating a feeling of stigmatization (e.g. going swinning).[76]

Kleyn et al studied whether the social impact of psoriasis is associated with altered cognitive processing of disgust using functional magnetic resonance imaging (fMRI) in psoriasis patient (n=13) compared to control patients (n=13). They found significantly reduced response in the insula cortex of psoriasis patients compared with controls when observing disgusted faces. One possible explanation for this is that psoriasis patients develop a coping mechanism to protect them from stressful emotional responses by blocking the processing of disgusted facial expressions encountered in others.[81]

Besides, psoriasis patients are more prone to depression than the general population.[79] Prevalence estimates of depression in psoriasis range between 10%[75] to 62%.[82] These wide ranges are likely related to different depression scoring methods. Lower educational level, younger age and the presence of itch were associated with more reported depressive symptoms.[82,83] Links between psoriasis and depression are not only psychopathological but also biological. A study by Himmerich et al suggested that the activation of the TNF-α pathway may contribute to the development of depression.[84] Also, the risk of suicidal ideation is increased in psoriasis patients. Estimates of suicidal ideation in patients with psoriasis ranged from 2.5 to 9.7%.[85]

Richards et al found that perceptions of stigmatisation and depression were the most important variables in predicting psoriasis-related disability. It would appear that the impact of psoriasis on quality of life is not simply reducible to chronicity, severity or location of disease activity.[75]

Additional to this, psoriasis is associated with an augmented alcohol intake. A study by Kirby et al found that 17% up to 30% of psoriasis patients have difficulties with alcohol. Alcohol misuse may increase psoriasis severity and is associated with anxiety and depression in patients with psoriasis.[86] Poikolainen et al found that alcohol intake increases the mortality among patients with psoriasis.[87] Furthermore, excessive alcohol intake can have implications for the cardiovascular comorbidities[88] and treatment in psoriasis.[89]

Dermatologist are well placed to identify alcohol misuse early in psoriasis patients. McAleer et al recommends the Alcohol Use Disorders Identification Test (AUDIT) questionnaire to identify alcohol misuse in patients with moderate to severe psoriasis.[90] If identified, referral for appropriate intervention to prevent potential complications from alcohol misuse is recommended.

Management of the psoriasis patient includes treatment of somatic manifestations but also tackle his or her psychological problems and psychiatric comorbidities. Therefore, multidisciplinary approach, including family physician, dermatologist, psychiatrist and psychologist next to psychosocial interventions are essential. In this context, Fortune et al described a cognitive-behavioural symptom management programme delivered in group format that improved the clinical severity of psoriasis and psychological disability.[91]

1.2.4 Other comorbidities

Immune-mediated inflammatory disorders (IMID)

Psoriasis is considered as an IMID. Associations with other IMIDs are described at higher risk: Crohn's disease, ulcerative colitis, ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis, atopic dermatitis, multiple sclerosis, systemic lupus erythematosus, type 1 diabetes and celiac disease.[92] This is supported by genetic data showing shared genes (Table 4) and immunologic data demonstrate common inflammatory mediators (e.g. TNF-α, IL-17, IL-23) thereby explaining the related efficacy of biologics.[93]

Table 4 : Genes shared by immune-mediated inflammatory disorders (IMIDs)

Gene	Chromo -some	PsO	PsA	CD	UC	MS	AD	RA	SLE	AS	T1D	CeD
IL12B	5q	x	x	x		x	x					
IL23R	1p	x	x	x	x					X		X
CDKAL1	6p	x		x								
PTPN22	18p	x	x					x	x		x	
IL2/IL21	4q	x	x	x	x	x		x	x		x	x

PsO, psoriasis; PsA, psoriatic arthritis; CD, crohn's disease, UC, ulcerative colitis; MS, multiple sclerosis; AD, atopic dermatitis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; AS, ankylosing spondylitis; T1D, type 1 diabetes; CeD, celiac disease. x, documented disease association.[5,6]

Patients with one or more IMIDs carry a higher chronic disease burden which implies a greater healthcare utilization.[92] Further research on the common pathogenesis of these IMIDs may have diagnostic and therapeutic implications.

Malignancies

Various studies have suggested that psoriasis is associated with malignancies such as skin cancer, lymphoproliferative disorders[94] or solid carcinoma.[95]

The increased risk of non-melanoma skin cancer in psoriasis, squamous cell carcinoma, and to a lesser extent basal cell carcinoma, has been reported in several studies.[94,95] Also, melanoma are more prevalent in psoriasis patients.[96] Anti-psoriatic treatments such as long-term psoralen and ultraviolet A and cyclosporine contribute to this increased risk.[96-99]

Besides, psoriasis is associated with an increased risk of lymphoma, especially cutaneous T-cell lymphoma. This association can be related to the chronic lymphoproliferative nature of psoriasis or may be caused by anti-psoriatic treatments such as cyclosporine and methotrexate.[99]

Also, lifestyle factors such as alcohol use and smoking which are more prevalent in psoriasis can have a negative influence on development of carcinoma like oral cavity, esophagus, liver, pancreas, lung, kidney and breast cancer.[95,100]

Infections

Data on the risk of both cutaneous and systemic infection in patients with psoriasis are limited. A large epidemiologic study revealed that patients with psoriasis have an increased resistance to cutaneous infections compared with controls and atopic dermatitis patients.[101] This finding has been related to an increased expression of antimicrobial peptides in psoriatic skin.[102]

On the other hand, several studies have shown an association between streptococcal throat infections and the exacerbation of guttata psoriasis or chronic plaque psoriasis.[103,104] Also, viral infections such as human immunodeficiency virus and hepatitis C can trigger or exacerbate psoriasis.[105,106]

Immunosuppressive anti-psoriatic therapies such as methotrexate, cyclosporine and biologics also increase the risk of systemic infections.[107] Particular attention is required for tuberculosis and appropriate vaccination should be given to psoriasis patients under immunosuppressive therapy.[108]

Non-Alcoholic Fatty Liver Disease (NAFLD)

NAFLD including a spectrum of conditions going from simple steatosis to steatohepatitis and cirrhosis, is now regarded as the hepatic manifestation of metabolic syndrome. Two studies showed an increased prevalence of NAFLD in psoriasis patients (38% and 47%) compared to control patients (28% and 28%).[109,110] Also, psoriasis patients with NAFLD are more likely to have metabolic syndrome and a more severe degree of skin disease than those with psoriasis alone. Because of this comorbidity extra caution should be made when starting up hepatotoxic medication such as methotrexate in the psoriasis population.[109,110]

Obstructive Sleep Apnea Syndrome (OSAS)

Although data are limited with regard to the relationship between psoriasis and OSAS, common comorbidities (e.g. obesity) and similarities in inflammatory mediators give rise to a possible relationship between the two diseases. A preliminary study of 25 psoriasis patients and 19 patients with chronic bronchitis demonstrated a greater prevalence of OSAS in those with psoriasis than in the control group.[111] Furthermore, a small study by Karaca et al studied the sleep quality of 33 psoriasis patients by means of polysomnography, of which 18 psoriasis patients (54,5%) were diagnosed with OSAS.[112] Physicians treating patients with psoriasis need to incorporate this comorbidity into their assessment of disease, especially in obese patients.

Chronic Obstructive Pulmonary Disease (COPD)

A large case-control study by Dreiher et al showed an significantly increased prevalence of COPD in psoriasis patients (5,7%; n=12 502) compared to control patients (3.6%; n= 24 287) ($p < 0.001$). Several mechanisms for the association between psoriasis and COPD can be suggested. Firstly, psoriasis and COPD have a common risk factor i.e. cigarette smoking. Secondly, the chronic inflammatory state in both COPD and psoriasis can be the link between both diseases. Also, similar to patients with psoriasis, patients with COPD often have one or more components of the metabolic syndrome. Further prospective studies are needed to establish this association.[113]

1.3 Health-related quality of life in psoriasis

The impact of psoriasis on patient health-related quality of life (HRQOL) is major and has been well documented in the scientific literature.[74,114,115] Measuring HRQOL provides a complementary assessment of the patient's overall wellbeing because it defines the total impact of an illness and its therapy based on patient's own perception.[115] Different dimensions of HRQOL play a role in psoriasis. Firstly, the physical impact of psoriasis is profound. Disease severity in psoriasis is classically measured by Psoriasis Area and Severity Index (PASI), body surface area (BSA) or Physician's Global Assessment (PGA) judged by a physician. However, this clinical severity measurement does not always correlate with patient's reported degree of disability. For example, patients with psoriasis of only the hands would be rated as mild based on the percentage of BSA involved, but the functional impairment would be great. In contrast, physical impact in HRQOL questionnaires is based on patient's own perception and this has a strong correlation with the psychosocial impact of the disease. In addition, physical symptoms such as pruritus and scaling have a great impact on HRQOL.[114,116] Secondly, the psychological burden in psoriasis, caused by lifelong distress of coping with psoriasis everyday, is tremendously. Feelings of embarrassment, helplessness, frustration and anger can lead to a depression. As a consequence, alcohol abuse, cigarette smoking, the use of tranquilizers, sleeping pills and antidepressants are seen more frequently in psoriasis patients.[116] Thirdly, social stigmatisation and rejection common seen in psoriasis leads to avoidance behaviour. Sequential, social and occupational difficulties may occur, further decreasing their overall HRQOL.[115-117]

HRQOL in psoriasis is most commonly assessed by means of self-report questionnaires. These can be divided into generic, dermatology-specific and psoriasis-specific quality of life questionnaires. Dermatology-specific questionnaires are preferable to generic ones because

they assess relevant dermatology-specific aspects of HRQOL and they are more sensitive to small changes in effects in patients with mild to moderate psoriasis. Examples of commonly used generic HRQOL questionnaires are Short Form-36 (SF-36) and EuroQol-5D (EQ-5D).[118] Dermatology life quality index (DLQI) and Skindex-29 are most frequently used dermatology-specific QOL questionnaires. In Table 5 the clinically important cutt-off scores for DLQI and Skindex-29 are given.[3,4]

Tabel 5: Clinically important cutt-off values for Skindex-29 and Dermatology life quality index (DLQI)[3,4]

Skindex-29	**Scores**	**Effect on patient's quality of life**	**DLQI Scores**	**Effect on patient's quality of life**
Symptoms	0-10	Mild	0-1	no
	11-25	Moderate	2-5	small
	≥ 26	severe to very severe	6-10	Moderate
Emotions	0-24	Mild	11-20	very large
	25-49	Moderate	21-30	extremely large
	≥ 50	severe to very severe		
Functioning	0-10	Mild		
	11-32	Moderate		
	≥ 33	severe to very severe		

For future research Skindex-17 is a promising questionnaire.[119] Psoriasis-specific QOL questionnaires such as Psoriasis Disability Index (PDI), Psoriasis Life Stress Index (PLSI) and Salford Psoriasis Index (SPI) meet a great acceptance by patients but they prohibit comparisons with any other disease.[118] All these questionnaires measure one point-in-time. Meanwhile, the Cumulatieve Life Course Impairment (CLCI) gives an overall effect of psoriasis over a patient's life course, considering the associated clinical and psychological implications that result in an altered or impaired life potential.[117]

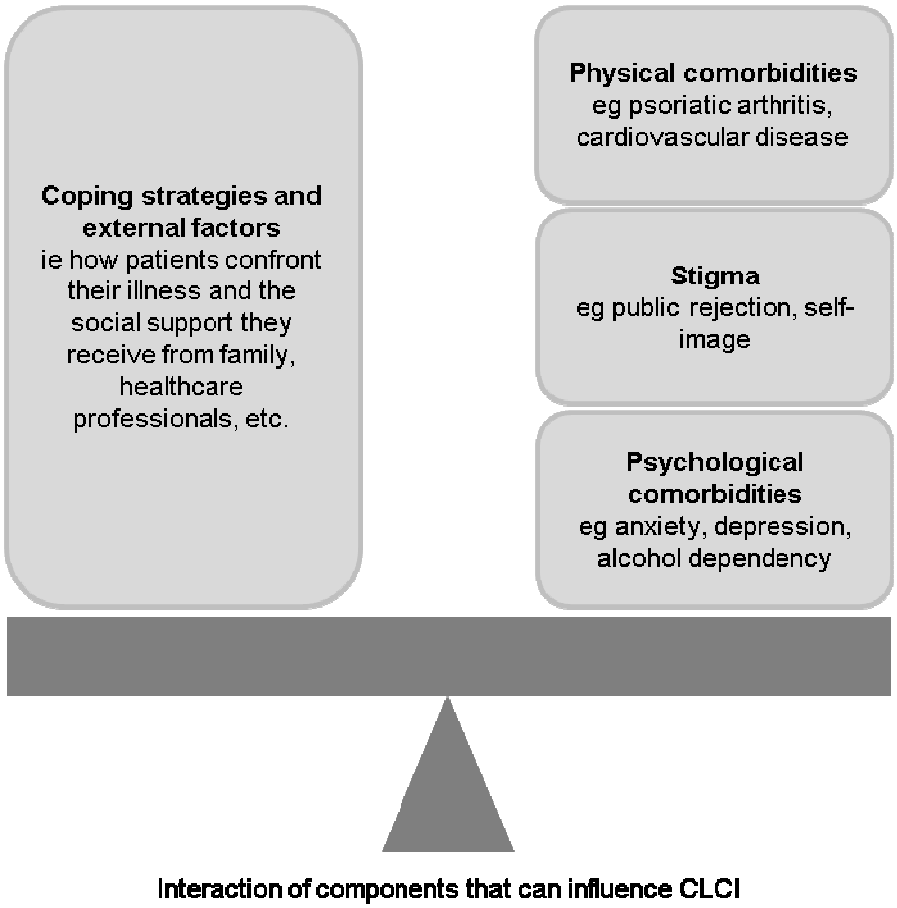


Figure 3 – Cumulative life course impairment (CLCI) occurs from an interaction between the burden of stigmatisation, physical and psychological co-morbidities; and coping strategies and external factors. Important impairment may occur in patients with ineffective coping strategies and little social support, even if they have a limited burden. This impairment may be lower in patients with effective coping strategies and strong social support networks, even if the burden is high. (Figure adapted from Kimball 2010)[117]

1.4 Lifestyle factors in psoriasis

1.4.1 Stress

Increasing evidence shows that psychological stress can influence the course of psoriasis. Verhoeven et al showed that daily stressors affected the course of psoriasis severity and itch at moments when patients experienced a high level of daily stressors.[120] In addition, they have shown a relationship between differences in individual stress reactivity and changes in disease outcome in patients with psoriasis. Patients with high levels of worrying and scratching seem most vulnerable to the influence of daily stressors, particularly at moments of high stress.[121]

Furthermore, patients with persistently high levels of stressors seem to have lowered cortisol levels and may be particularly vulnerable to the influence of stressors on their psoriasis.[122]

A 'brain–skin connection' with local neuro-immuno-endocrine circuitry underlies the pathogenesis of psoriasis, triggered or aggravated by stress.[123] Acute psychosocial stress is associated with an altered hypothalamus-pituitary-adrenal response[124] and changes of immune functions in psoriasis which may be one potential explanation of how stress may trigger psoriatic eruption.[125,126]

In addition, up to 60% of patients believe that the onset of their psoriasis was a result of psychological stress. The disease itself can cause psychological stress, creating a vicious cycle.[127] Therefore, stress management can be important for psoriasis patients vulnerable to the influence of stressors on their skin disease. Different methods of stress management exist such as cognitive behavioural stress management[91], mindfulness-based stress reduction[128,129] or physical activity.[130] Also, biological changes can be seen with these methods of stress management. For example, in a randomised, controlled trial Davidson et al found changes in brain and immune function after 8-weeks mindfulness meditation in 41 healthy persons.[131] Additional research on this topic is needed.

1.4.2 Obesity

An association between obesity and psoriasis is well established. Not only is obesity associated with a higher incidence of psoriasis[17,18] and greater severity[18,132], but it also affects response to treatment.[133] A randomised trial comparing cyclosporine to cyclosporine plus weight loss in obese patients with moderate-to-severe psoriasis demonstrated contributory effects of weight loss on treatment response.[134] Also, complete remission after gastric bypass surgery has been reported in cases.[135,136]

Several mechanisms explaining the association between psoriasis and obesity have been proposed, including increased social isolation, increased unhealthy dietary habits, increased alcohol consumption and decreased physical activity.[133,137]

In addition, understanding hormonal and cytokine biology can also explain the association between psoriasis and obesity. Increased levels of leptin, IL-6 en TNF- α are contributing to the pro-inflammatory state in both psoriasis and obesity. In contrary, adiponectin is an anti-inflammatory hormone that suppresses the effects of TNF-α, IL-6 and improves insulin sensitivity. This adipocytokine is decreased in obese psoriasis patients.[138,139]

It would appear reasonable to suggest that weight loss, could contribute positively to reducing the pro-inflammatory state and improving the clinical course of obese patients with psoriasis.

1.4.3 Physical activity

There is increasing evidence that physical activity plays an important role in psoriasis. Frankel et al showed in a study of US women, that vigorous physical activity was independently associated with a decreased risk of new-onset psoriasis. More specific, they found that participation in at least 20.9 metabolic equivalent task-hours per week of vigorous exercise, the equivalent of 105 minutes of running or 180 minutes of swimming or playing tennis, is associated with a 25% to 30% reduced risk of psoriasis. The reduced risk of incident psoriasis was not seen with low to moderate physical activity such as walking. This may be due to the effect of vigorous physical activity on systemic inflammation.[140]

The mechanism whereby physical activity decreases psoriasis risk deserves further investigation. Physical activity is known to reduce chronic inflammation and particularly decreases levels of proinflammatory cytokines, such as tumor necrosis factor[141] and interleukin 6.[142] In addition, physical activity is known to upregulate adiponectin and downregulate leptin.[143] These are two adipokines originating from adipose tissue and known to play a major role in psoriasis and obesity.[70] Furthermore, the protective effects of physical activity could also be mediated through its effect on mood. Exercise reduces anxiety and stress and improves emotional well-being.[144]

Thereby, it is shown that physical and psychosocial impairments common in psoriasis may make it problematic to adhere to physical activity. Three studies have found that 38%, 36% and 34% of psoriatics reported difficulty participating in sports.[145-147]

Because of the importance of physical activity and the difficulty participating in sports for psoriasis patients, additional support on this matter should be given. For example, creating a setting for psoriasis patients to participate in sports can be a valuable solution. Future studies should aim to determine if physical activity interventions improve health related outcomes in psoriasis.

1.4.4 Smoking

Smoking increases the risk of development of psoriasis. Higher intensity and duration of smoking was associated with increased clinical severity of psoriasis.[17,148-150] Chronic palmoplantar pustulosis – a subtype of psoriasis – has been shown to have the strongest association with smoking.[149]

Several mechanisms behind smoking's negative impact on psoriasis have been proposed. Firstly, smoking-induced oxidative stress resulting from increased reactive oxygen species production along with insufficient capacity of antioxidant mechanisms may be involved in the pathogenesis of psoriasis.[151] Secondly, psoriasis involves a neutrophil-predominant inflammatory infiltrate and smoking can alter the morphology and function of neutrophils.[152] Thirdly, genetic–environmental interactions involving smoking have been proposed. Duffin et al presented evidence that polymorphisms in the IL13/IL4 region (especially rs1800925*T) may be associated with protection from developing psoriatic arthritis and that this effect may be abrogated by smoking.[153] Thus, smoking cessation may be an important target for prevention and management of psoriasis.[154]

1.5 Adherence to therapy in psoriasis

Poor adherence to therapy is a complex problem existing for many chronic diseases such as diabetes, hypertension and heart disease. This can result in poorer prognosis, more hospitalizations and significantly higher health care costs. Improving adherence to therapy - whether it be medication, behavioural or lifestyle changes- can lead to improved patient outcomes and reduced health care costs.[155]

Especially in psoriasis, adherence to therapy is a major problem. Up to 50% of patients do not use their medication as prescribed.[156] Several factors can influence patient's adherence to therapy. (Figure 4) Patients characteristics, disease characteristics and treatment characteristics all influence medication adherence and treatment outcomes. Also, physician interaction and enabling factors are playing a role in this complex cycle.[157]

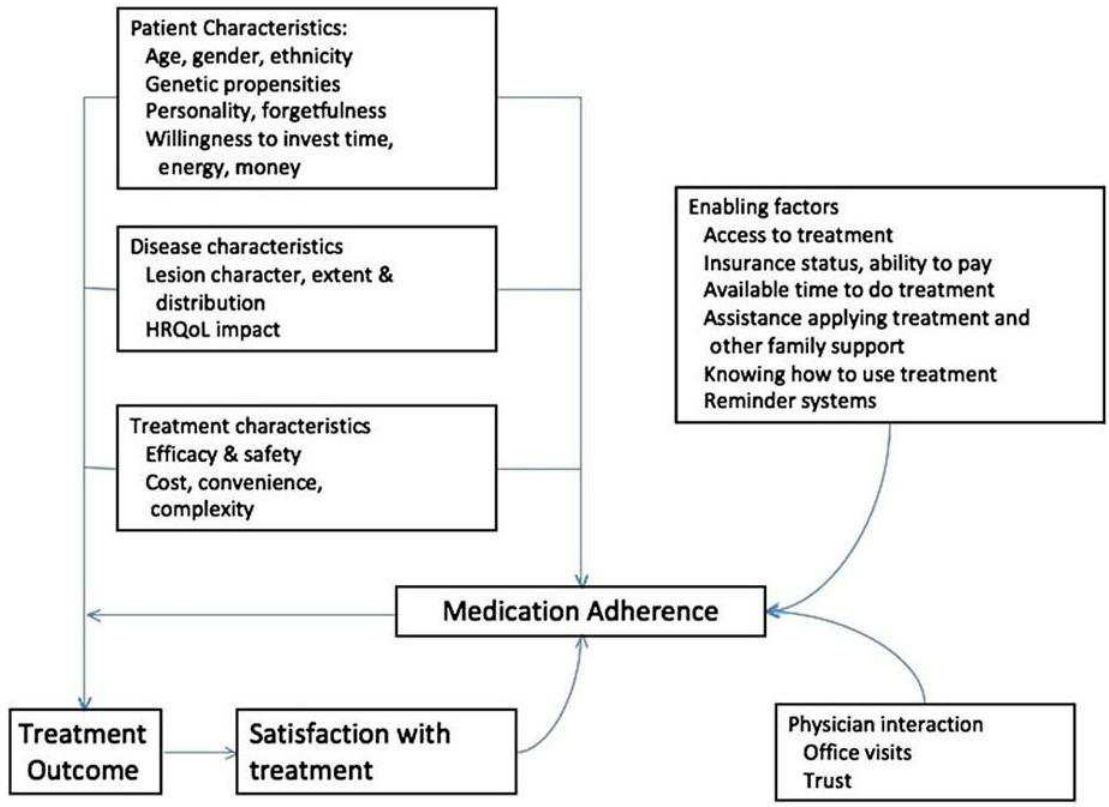


Figure 4 - Adherence to medication is influenced by multiple factors; HRQoL, Health-related quality of life. (Figure adapted from Feldman 2008)[157]

For example, topical treatment regimens can be complex. Simplifying the treatment regimen by shorten the duration of treatment and advise once-daily application, can improve adherence and hence outcome. Besides, patient's interaction with the physician plays a major role in treatment adherence. Good two-way communication and education of the patient about psoriasis and its therapy can establish a trusting relationship and higher level of adherence. Next to this, adherence to treatment increases before and after physician visits. Therefore, scheduling a follow-up visit shortly after treatment initiation may be of help.[158] Another option to enhance adherence to therapy after treatment initiation is regular phone calls by a health care provider. (e.g specialist nurse)[155]

Nurses are in a good position to occupy a key role in patients management. A dermatology specialist nurse can give additional education, support and be a point of contact for follow-up care throughout the long-term course of the disease.[159,160]

In conclusion, we may say that improving adherence to therapy in psoriasis is still at an early stage. Future research is needed to find the right approach to promote adherence to therapy in patients with psoriasis.

1.6 Conclusion

In conclusion, we can say that psoriasis is not merely a skin disease but is associated with several comorbidities and an impaired health-related quality of life. A holistic and multidisciplinary approach with attention for lifestyle modifications and adherence to therapy is essential. In Chapter 2 we discuss the aims and outline of this thesis with focus on improving the quality of care for psoriasis patients.

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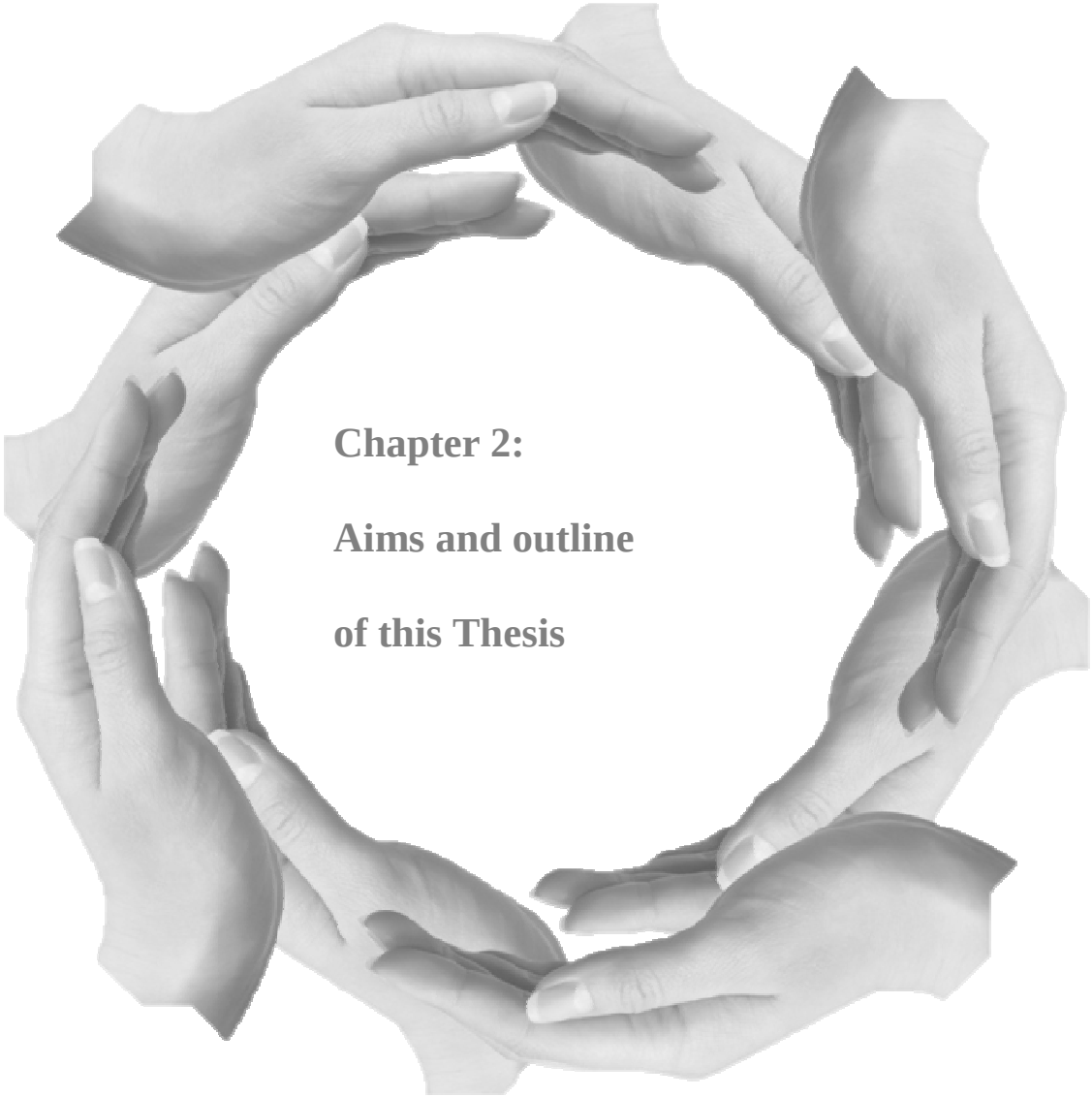

Chapter 2:

Aims and outline of this Thesis

Chapter 2: Aims and outline of this Thesis

Aims

The general objective of this research project is to improve the quality of care for psoriasis patients by evaluating following items in our patient population:

Our first aim is to acquire new insights in the complex association between psoriasis, psoriatic arthritis and metabolic syndrome. Therefore, we performed a prospective, cross-sectional study in 123 psoriasis patients. The main objective of this study was to examine the difference in prevalence of metabolic disease burden between patients with psoriasis who lack arthritic manifestations and psoriatic arthritis patients. A better understanding of these associations may have implications for psoriasis management. (Chapter 3)

Our second aim is to evaluate whether our educational programme has its added value in the care for psoriasis patients. Patient education and motivation play an increasingly important role in the long term management of psoriasis. We conducted a prospective, randomised controlled trial in 66 patients with psoriasis and atopic dermatitis to investigate whether our educational programme is of added value to medical therapy. Effect on disease severity and quality of life were measured as primary endpoints at different time points. Furthermore, level of depression, lifestyle changes and effect on medical consumption were followed during 9 months. (Chapter 4)

Lastly, we give an overview of updated relevant aspects in the clinical dermatological assessment of psoriasis patients, emphasizing the importance of a multidisciplinary and holistic clinical approach. In this review, a template is proposed which can be integrated in the currently used electronic patient file, thereby creating the potential of gathering information for future research. (Chapter 5)

Outline

In the last decade, the view on psoriasis as skin disease has shifted towards seeing it as a systemic disease with association of several comorbidities. In addition, substantial advances have been made in elucidating the molecular and immunological mechanisms of psoriasis. These improved insights into pathogenesis in psoriasis has resulted in major benefits for patients, including the introduction of several targeted therapies.[1]

Introduction of health-related quality of life instruments in the assessment of disease severity has led to a greater awareness of the true impact of psoriasis. These have shown that the impact of psoriasis is similar to other chronic diseases, including hypertension, diabetes and depression, and is ranked as one of the diseases that has the greatest impact on physical and mental health.[2] Due to these new insights, medical management of psoriasis has changed over the last decade. Lots of effort has been put in improving quality of care in psoriasis. Multidisciplinary collaboration receives more attention by setting up combined dermatology-rheumatology clinics[3] and psoriasis disease centers.[4] There is also a greater focus on patient centered care which allows health-related quality of life to be integrated in clinical management. The hallmarks of this concept are education of the patient and an effective two-way communication required to better integrate physician and patient perspectives. Patient centered care is especially valuable in psoriasis because of chronicity of the disease, lack of treatment adherence and need for lifestyle adjustments and psychological support.[5]

Next to this, definition of treatment goals[6] and establishment of treatment guidelines[7-9] can improve quality of care in psoriasis. A recent review of the European Expert Working Group for Healthcare in Psoriasis (EEWGHP) defined following action points to improve quality of care for psoriasis patients (see Table 2).[10] The ultimate goal is to provide early access to high quality care for all psoriasis patients and thereby preventing cumulative life course impairment.

Table 2: Actions points defined by EEWGHP as required from stakeholders or specific audiences to improve quality of care for psoriasis patients.[10]

Actions	Stakeholders/Audiences
1. Raise awareness of psoriasis and ensure that it is officially recognised as a serious medical condition	Patient advocacy groups, healthcare organisations, government, industry, academia, healthcare professionals
2. Promotion the development, awareness and use of treatment guidelines	Healthcare organisations, healthcare professionals, patient advocacy groups, European bodies
3. Raise awareness of assessments tools and their standard use, whilst identifying the potential for new assessment tools	Healthcare professionals, industry, healthcare organisations, academia
4. Define treatment goals and associated management strategies and encourage patients to be involved in setting their individual goals and strategies	Healthcare professionals, industry, healthcare organisations, patients
5. Drive data collection on the impact of earlier intervention with systemic therapies and proactively manage psoriasis through provision of timely therapeutic monitoring and a multidisciplinary team approach to ongoing care	Healthcare organisations, governments, industry, academia, primary and secondary care healthcare professionals, European bodies
6. Drive patient advocacy groups engagement with guideline- and policy-making parties	Healthcare organisations, governments, industry, healthcare professionals, health technology assessment agencies, patients, patient advocacy groups

With our work we want to contribute to this improvement in quality of care in psoriasis by acquiring new insights in comorbidities, evaluating our educational programme and giving an overview of relevant aspects in the assessment of psoriasis patients.

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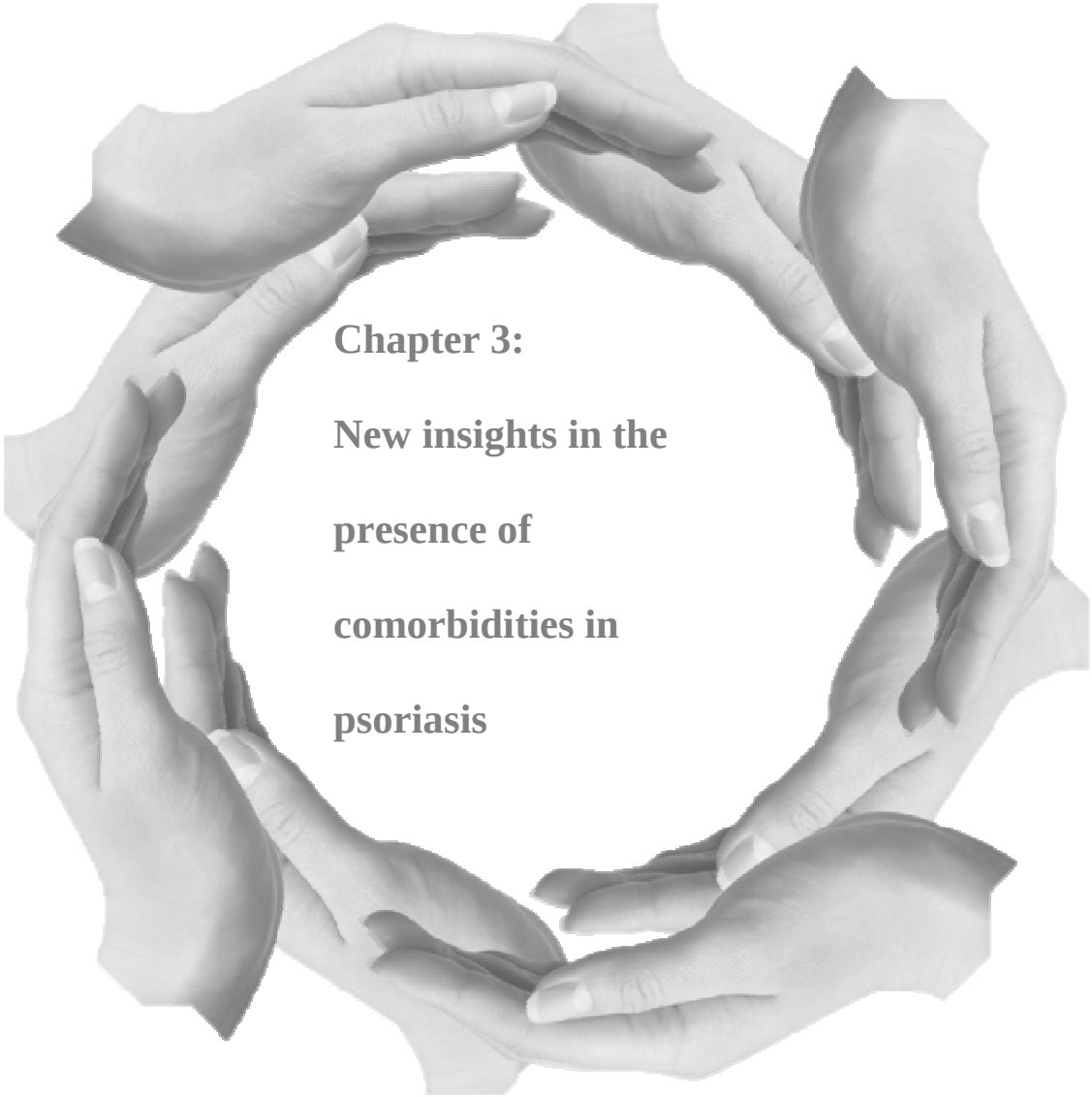

Chapter 3:

New insights in the presence of comorbidities in psoriasis

Chapter 3: New insights in the presence of comorbidities in psoriasis

Introduction

Several comorbidities are frequently associated with psoriasis such as psoriasis arthritis, cardiovascular disease and psychiatric disease. These comorbidities are discussed in Chapter 1 in more detail. Early detection of these comorbidities in psoriasis can improve outcomes. This can be accomplished by creating increased awareness and appropriate screening methods. Next to this, multidisciplinary collaboration makes early referral to a specialist possible.

In the following chapter, we discuss the similarities and differences between psoriasis and psoriatic arthritis with respect to epidemiology, genetics, immunology and biomarkers. Furthermore, we present our first paper on the association of metabolic syndrome in psoriasis versus psoriasis arthritis.

3.1 Psoriasis and psoriasis arthritis separate entities or one and the same?

Increasing evidence arises for a common etiology of skin psoriasis (PsO) and psoriatic arthritis (PsA) based on shared genetic markers, common immunological features and epidemiological similarities.[1] Although, the underlying factors which predispose patients to develop cutaneous or articular disease or both are unexplored.

Early detection of PsA can lead to better outcomes. Patients seen at a rheumatology clinic within two years of diagnosis have less joint damage progression compared to those with longer disease duration at first clinic visit.[2] Therefore, next to screening questionnaires, biomarkers may be useful to screen PsO patients for PsA.[3]

In this section, we discuss the similarities and differences between PsO and PsA with respect to epidemiology, genetics, immunology and biomarkers.

Epidemiology

PsO and PsA occur equally in men and women.[4] The majority of the patients (circa 70%) develop PsO before PsA. In contrast, PsA precedes the onset of PsO by more than 1 year in circa 15% of cases.[5] This last setting characterizes the so-called subset of psoriatic arthritis ”sine psoriasis”.[6] In addition, in another 15% the two conditions occur together within a 12 months period.[5]

The correlation of skin and joint symptoms in patients with PsO and PsA can vary significantly. Early studies suggested that PsA was linked with more severe cases of PsO.[7] On the contrary, Cohen et al showed that most patients with psoriatic arthritis have mild skin disease (n=221).[8] Additional to this, Jones et al found no association between severity of skin lesions and severity of arthritis among 100 consecutive patients with PsA.[9] However, a recent study found a highly significant correlation between skin and joint disease in 70 cases where the initial onset of both diseases was simultaneously.[10]

Genetics

A common genetic etiology for psoriasis and psoriatic arthritis has long been suspected. Associated HLA antigens for both diseases (B13, B17, B57, Cw6, DR7) have been described.

However, there are several differences in susceptibility loci between PsO and PsA. In PsO there are associations with HLA B37 and in PsA with HLA B7, B27, B38, B39, CR4, DR4, DR5, DR8.[1] HLA-Cw*0602 risk allele is stronger associated with PsO compared to PsA.[11] In addition, multiple susceptibility loci (PSORS 1 – PSORS7) to PsO have been reported which were not consistently reproducible in PsA cohorts.[12-14] Furthermore, several genome-wide association studies have been published. Genes implicated in skin barrier function including LCE3, DEFB4, and GJB2 are playing an important role in PsO but not in PsA.[15-17] Lastly, Bowes et al found 2 IL13 SNP (rs20541 and rs1800925) that were highly associated with susceptibility to PsA but not to PsO.[18]

Immunology

The inflammatory infiltrate in the skin and joints has been subject of detailed investigation. In both tissues there is a prominent lymphocytic infiltrate, localised in the epidermis and dermis of the skin and in the synovial fluid of the joints. T lymphocytes are most occurring inflammatory cells in the skin and joints. CD4+ Tcells are the most common lymphocytes in the tissues. In contrast with the synovial fluid compartment, where CD8+ Tcells are the most common lymphocytes.[19,20] Also, specific vascular changes have been reported in psoriasis skin and synovial membrane. Angiogenesis is dysregulated and angiogenic growth factors are upregulated in both PsO and PsA.[21] In addition, similarities in expression of neuropeptides in skin and joints have been described.[22] This may suggest a common neurovascular pathway. Furthermore, it is likely that cytokines, especially TNF-α and many others, may be involved in driving the inflammation in both PsO and PsA.[23]

Biomarkers

Chandran et al found that increased serum levels of receptor activator of nuclear factor-κB ligand, tumor necrosis factor superfamily member 14, matrix metalloproteinase-3 and cartilage oligomeric matrix protein are independently associated with psoriatic disease (PsA and PsO). A combination of biomarkers - high-sensitivity CRP (hs-CRP), osteoprotegerin (OPG), matrix metalloproteinase 3 (MMP-3) and the ratio of C-propeptide of type II collagen to collagen fragment neoepitopes (CPII/C2C)- is independently associated with PsA. This combination was able to distinguish patients with PsA from patients with PsO. Although these biomarkers are promising, they still need validation in prospective studies.[3]

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3.2 Paper 1: A cross-sectional study on the prevalence of metabolic syndrome in psoriasis compared to psoriatic arthritis. (Submitted to J Eur Acad Dermatol Venereol, 2012)

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Abstract

Background

Increasing epidemiological evidence suggests associations between psoriasis, psoriatic arthritis and metabolic disease. Elucidating the complex relationship between these comorbidities may have important management implications.

Objective

The aim of this study was to examine the difference in prevalence of metabolic disease burden between patients with psoriasis who lack arthritic manifestations (PsO) and psoriatic arthritis patients (PsA).

Methods

We performed a cross-sectional study in 123 patients with psoriasis only (PsO) and psoriasis arthritis (PsA). Metabolic syndrome was defined using the new criteria developed by the International Diabetes Foundation (IDF) in 2004. Therefore, clinical examination, standard survey and fasting blood samples were collected.

Results

One hundred and four patients were analysed of which 49 PsO and 55 PsA patients. We found that prevalence of the metabolic syndrome according to the IDF criteria was significantly higher in the PsO (44,9%) compared to the PsA group (25,5%) (p=0,037). Looking closer at the individual components of the metabolic syndrome, this difference can mainly be attributed to the significantly higher prevalence of abdominal obesity in PsO (83,7%) versus PsA (65,5%) (p= 0,034). For other individual components of the metabolic syndrome such as triglycerides, high density lipoproteins, hypertension and plasma glucose, we could not show statistically significant differences between the groups.

Conclusion

Metabolic syndrome is more prevalent in patients with PsO than in PsA patients, mainly determined by the higher prevalence of abdominal obesity in PsO compared to PsA group. These findings suggest that screening for metabolic syndrome should be considered especially in group of PsO patients.

Introduction

Psoriasis is a chronic inflammatory skin disease with a genetic and immunologic background. Its prevalence has been estimated at 2% of the population.[1] Psoriasis is a disabling disease affecting the physical and emotional well being of patients, and its effect on quality of life is similar to that seen within other major medical diseases such as diabetes, rheumatoid arthritis, and cancer.[2] Recently, it is increasingly being recognized that psoriasis is probably associated with other co-morbidities. In 1% up to 39% of patients, psoriasis may be accompanied by arthritis. The majority of the patients (circa 70%) develop psoriasis before articular involvement; in contrast arthritis precedes the onset of psoriasis by more than 1 year in circa 15% of cases, and in another 15% the two conditions occur together within a 12 months period.[3]

Increasing epidemiological evidence suggests independent associations between psoriasis and cardiovascular and metabolic disease. This association increases with increasing disease severity.[4] Among patients with rheumatological disease (rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis), psoriatic arthritis patients show the highest risk for presence of metabolic syndrome, in particular obesity, impaired glucose tolerance, and hypertriglyceridemia.[5]

The basis for the relationship between psoriasis, psoriatic arthritis and metabolic syndrome is complex, with the effects of chronic systemic inflammation, psychosocial issues, and potential adverse effects of therapies likely to be important. A better understanding of these associations may have management implications.

The main objective of this study was to examine the difference in prevalence of metabolic disease burden between patients with psoriasis who lack arthritic manifestations (PsO) and psoriatic arthritis patients (PsA).

Patients and Methods

We performed a prospective, cross-sectional study in patients with psoriasis only (PsO) and psoriasis arthritis (PsA). 123 patients were recruited from 3 different sources: dermatology clinic of the Ghent University Hospital (n=43), rheumatology clinic of the Ghent University Hospital (n=41) and patient advocacy groups (n=39). Data collection and analysis were performed during the period from January 2011 through May 2012. Eligible criteria were: 1) patients who fulfilled the ClASssification criteria for Psoriatic ARthritis (CASPAR)[6] defined by a rheumatologist or were diagnosed with skin psoriasis by a dermatologist; 2) age ≥ 18 years; and 3) patients who were able to give informed consent. The study was approved by the ethics committee of the Ghent University Hospital.

In a face-to-face interview using a standard data collection protocol all patients were questioned about their medical history (including items related to psoriasis, with and without arthritis) as well as current and past medication, comorbidities and known risk factors. Blood pressure was measured twice and the average of 2 blood pressure readings was calculated. Body weight, body height, and waist circumference were also measured. Skin disease severity was determined by the Psoriasis Area and Severity Index (PASI) and nail abnormalities were investigated. Fasting blood was taken for assay of glucose, lipid levels (total cholesterol, high-density lipoprotein [HDL] and low-density lipoprotein [LDL] cholesterol, and triglycerides level) and inflammatory parameters.

Metabolic syndrome was defined using the new criteria developed by the International Diabetes Foundation (IDF) in 2004.[7] This definition was based on a consensus between previous existing definitions of the WHO diabetes group, European Group for the Study of Insulin Resistance and US National Cholesterol Education Program: Adult Treatment Panel III. Ethnic-specific waist circumference cut-offs were incorporated into the definition. The criteria comprise central obesity (waist circumference ≥94 cm in men or ≥80 cm in women), plus two of the following: elevated triglycerides (≥150 mg/dL) or specific treatment for this lipid abnormality, reduced high-density lipoprotein cholesterol (<40 mg/dL for men; <50 mg/dL for women) or specific treatment for this lipid abnormality, elevated blood pressure (≥130 mmHg systolic or ≥85 mmHg diastolic) or treatment of previously diagnosed hypertension, and elevated fasting plasma glucose (≥100 mg/dL) or previously diagnosed type 2 diabetes. The use of waist circumference as parameter for obesity is preferred above body mass index because the latter lacks consideration of body composition and gender differences.[8]

Statistics

Power calculation showed a total of 110 patients were needed for this cross-sectional study in order to obtain a 90 percent probability to detect a 0,25 prevalence difference between 2 groups at a two-sided 0,05 significance level. Data were analyzed by using the Statistical Package for Social Sciences software, version 19. Chi-square test and Mann-Whitney U test were used to compare proportions between groups. Univariate and multivariate logistic regression models were used to calculate the odds ratio (OR) for metabolic syndrome. $P < 0.05$ was considered significant.

Results

One hundred and ten patients were assessed for eligibility. Six patients were excluded because diagnosis of psoriatic arthritis according to CASPAR criteria was not fulfilled. One hundred and four patients were analysed of which 49 had psoriasis (PsO) and 55 psoriasis arthritis (PsA) (Fig. 1).

The characteristics of the included study population are described in Table 1. Both groups are comparable concerning age, onset and duration of psoriasis. All patients with psoriatic arthritis also had psoriasis of the skin, except for 1. The majority of these patients developed skin manifestations before articular involvement (n=44, 81%).

In the PsO group 40,8% of the patients were treated systemically compared to the PsA group in which 81,8% of patients was under systemic therapy (Chi-square test; p<0,001). There were more patients on cardio-protective medication in the PsO group, especially lipid-lowering drugs and anticoagulants. Median PASI is significantly higher in the PsO [5,2 (IQR 2,5-11,6)] versus the PsA patients [3,4 (IQR 0,6-5,5)] (Mann-Whitney U test; p<0,05).

Family history for skin psoriasis is 71% versus 57% in PsA compared to PsO and for psoriasis arthritis 33% compared to 4% in PsA versus PsO. There were more smokers in the PsO group (30,6%) compared to PsA group (18,2%) and the use of daily alcohol was higher in PsA patients (32,7% vs 26,5%) but this did not reach significance. Physical activity level was almost the same in both groups: approximately half of the patients performed moderate to intensive physical activity. Psychological distress (as asked by history) was higher in the PsO group (67%) compared to PsA group (42%) (Chi-square test; p<0,01) and antidepressant use was higher in the PsO group but did not reach significance. (14,3% vs 7,3%).

The prevalence of metabolic syndrome according to the IDF criteria was significantly higher in the PsO (44,9%) compared to the PsA group (25,5%) (Chi-square test; p=0,037). Looking closer at the individual components of the metabolic syndrome, this difference was mainly attributable to the significantly higher prevalence of abdominal obesity in PsO (83,7%) versus PsA (65,5%) (Chi-square test; p= 0,034). For other individual components of the metabolic syndrome such as triglycerides, high density lipoproteins, hypertension and plasma glucose, we could not show statistically significant differences between the groups.

The prevalence of the metabolic syndrome in the analysed population could be influenced by other factors such as age, disease severity (PASI), disease duration, systemic therapy or systemic inflammation (CRP). Older age was significantly correlated with a higher prevalence of metabolic syndrome [OR=1,1 (1.0,1.1)]. No significant difference was seen in prevalence of the metabolic syndrome for the other factors. Univariate and multivariate analyses adjusting for these factors reveiled persistent differences between PsA en PsO (Table 2).

PsA patients (n=55) can be divided in different types according to clinical pattern: oligoarticular (n=21) or polyarticular (n=17) peripheral disease and axial disease with (n=13) or without (n=4) associated peripheral arthritis. We did not find significant differences in prevalence of metabolic syndrome nor the individual components of the metabolic syndrome in the different subtypes of PsA.

PsO patients treated with biologics (n=13) have significantly higher prevalence of the metabolic syndrome compared to PsA patients treated with biologicals (n=26) [OR=11,1 (2.3,54.0)] and compared to PsO patients not treated with biologics (n=36) [OR=6,7 (1.5,28.8)]. PsA patients treated with biologicals (n=26) had a longer use of biologicals (4,8 years ±4,3) compared to the PsO patients on biologicals (n=13) (2,5 years ±1,9).

Discussion

In this study we observed a significantly higher prevalence of the metabolic syndrome according to the IDF criteria in patients with psoriasis of the skin compared to patients with psoriasis arthritis. Looking closer at the different components of metabolic syndrome, the difference was mainly attributable to a significantly higher prevalence of abdominal obesity in PsO versus PsA. This association was even enhanced after multivariate adjustments for confounding factors such as age, disease severity, disease duration, systemic therapy and systemic inflammation.

To our knowledge this is the first study that compares prevalence of metabolic syndrome in PsO compared to PsA. Little data exist on individual components of the metabolic syndrome or cardiovascular morbidity between PsO and PsA. Husted et al found that the prevalence of hypertension was significantly higher in PsA patients than in PsO patients after multivariate analysis.[9] Ahlehoff et al reported a similar cardiovascular risk in patients with severe PsO and PsA.[10]

Our results show high prevalence of hypertension in both PsO (85,7%) and the PsA (80%) group compared to what is known from literature (38.8%).[11] That may be due to three factors: firstly, high mean age of our study population (49,5±12,9 years), secondly white coat hypertension may overestimate the prevalence of hypertension in our study and thirdly due to the stringent criteria of hypertension (≥130/85) by IDF definition. Accordingly, Langan et al found a prevalence of hypertension in 87,9% of the psoriasis population compared to 59,5% in the control group with similar criteria and age range.[4] We believe a definition with strict criteria for cardiovascular disease is clinically important because severe psoriasis and/or psoriatic arthritis carry a risk of cardiovascular disease comparable to that of patients with diabetes mellitus.[10]

According to literature, the correlation of skin and joint symptoms in patients with psoriasis and psoriatic arthritis can vary considerably. Early studies suggested that arthritis was more common in more severe cases of psoriasis.[12] In contrast, Cohen et al showed that most patients with psoriatic arthritis have mild skin disease.[13] Consistent with the last study, we found a median PASI that was significantly higher in PsO compared to PsA patients.

A limitation of our study is the difficulty of defining our groups, PsO versus PsA patients. Although, we assured that clinically we made the best distinction between those groups by appointing a dermatologist and a rheumatologist specialised in this matter, we can not be certain of our distinction between the groups because of two reasons: First of all, there are no serologic tests available to aid in the diagnosis of psoriatic arthritis such as rheumatoid factor in rheumatoid arthritis.[14] Classification of PsA was based on CASPAR criteria but this has the disadvantage that early PsA can be missed.[15] Secondly, PsO patients can develop arthritis in the future although most patients have a long disease duration of psoriasis (23 years), so definition of the groups might change over time.

Several factors may be the cause of the complex association between psoriasis, psoriatic arthritis and metabolic syndrome. Firstly, the psychological burden associated with psoriasis

can make it more difficult to watch lifestyle behaviour such as diet and have a negative influence on metabolic syndrome. In this study, the psychological impact was higher in the PsO than PsA group. Secondly, we cannot exclude the influence of past or current medication on metabolic syndrome. For example, acitretin use can be associated with lipid abnormalities.[16] So far, there is limited evidence on the role of biologics on the prevalence of metabolic syndrome in psoriasis.[17] In this study, PsO patients treated with biologics have higher prevalence of the metabolic syndrome compared to PsA patients treated with biological or compared to PsO patients not treated with biologics. This implies that skin psoriasis plays an independent role in the risk of metabolic syndrome. Thirdly, a different genetic background between PsO and PsA patients could explain this difference in prevalence of metabolic syndrome. For example, overlapping susceptibility loci has been demonstrated in skin psoriasis and diabetes type 2 (CDKAL-1).[18] Fourthly, adipokines such as adiponectin, leptin, originating from adipose tissue, could play a pathogenetic role in the association between psoriasis and metabolic disease. Leptin is upregulated and adiponectin downregulated in both psoriasis and obesity.[19,20] At last, also systemic inflammation might have an influence on prevalence of metabolic syndrome.[21] Unfortunately, because of the cross-sectional design of the study, no causal relationship can be deduced from this analysis.

The metabolic burden is high in the psoriasis population, especially in the PsO group (44,9 %). This comorbidity is associated with an increased cardiovascular risk beyond traditional risk factors.[22] Additional to this, we suspect an undertreatment of the cardiovascular risk factors in our study population. Accordingly, Ahlehoff et al and Kimball et al showed an undertreatment of cardiovascular risk factors in psoriasis patients.[23,24]

Therefore we and others[21,25] recommend that physicians treating moderate to severe psoriasis are instructed on how to screen for comorbid conditions, more specifically metabolic syndrome. Patient education with regard to lifestyle modifications (such as physical activity and diet) should be integrated in the general approach of psoriasis patients at risk.[26]

Acknowledgments

The study has been financially supported by Abbott.

Tables

Table 1: Characteristics of the included study population, psoriasis (PsO) compared to psoriatic arthritis patients (PsA) (n=104)

Variables	**PsO (n=49)**	**PsA (n=55)**
Gender (male),n (%)	29(59,2)	38(69,1)
Age (years), mean (± SD)	49,4 (±12,7)	49,7 (±13,3)
Duration of psoriasis (years), mean (± SD)	23,0 (±14,4)	22,9 (±11,4)
Duration of psoriasis arthritis (years), mean (± SD)		14,5 (±11,1)
Age at onset of psoriasis (years), mean (± SD)	26,1 (±12,4)	26,7 (±12,9)
PASI, median (IQR)	5,2 (2,5-11,6)	3,4 (0,6-5,5)
CRP (mg/dl), median (IQR)	0,2 (0,1-0,35)	0,2 (0,1-0,5)
Current smokers, n (%)	15(30,6)	10(18,2)
Current daily drinkers, n (%)	13(26,5)	18(32,7)
Therapy psoriasis and psoriatic arthritis		
Topical therapy,n (%)	37(75,5)	27(49,1)
Light therapy,n (%)	5(10,2)	3(5,5)
Systemic therapy,n (%)	20(40,8)	45(81,8)
Biologics,n (%)	13(26,5)	26(47,3)
Duration on biologics (years), mean (± SD)	2,5 (±1,9)	4,8 (±4,3)
Methotrexate,n (%)	2(4,1)	19(34,5)
Leflunomide,n (%)	0(0)	8(14,5)
Sulfasalazine,n (%)	0(0)	1(1,8)
Acitretin,n (%)	4(8,2)	0(0)
Fumaric acid esters,n (%)	1(2)	0(0)
Past biologics,n (%)	10(20,4)	11(20)
Past methotrexate,n (%)	20(40,8)	26(47,3)
Cardio-protective medication		
Lipid-lowering medication,n (%)	8(16,3)	5(9,1)
Antihypertensive medication,n (%)	13(26,5)	12(21,8)
Anti-diabetic medication,n (%)	1(2)	1(2)
Anticoagulants,n (%)	6(12,2)	4(7,3)

SD= standard deviation; IQR= interquartile range; PASI= Psoriasis Area and Severity Index; CRP= C-reactive protein.

Table 2: Prevalence of metabolic syndrome and individual components according to the criteria of the International Diabetes Federation (IDF) in psoriasis (PsO) compared to psoriatic arthritis (PsA) patients and univariate and multivariate adjusted analyses.

	PsO (n=49) n(%)	PsA (n=55) n(%)	Unadjusted OR (95%CI)	P	Multivariate adjusted OR (95%CI)*	P	Multivariate adjusted OR (95%CI)**	P
Metabolic syndrome	22(44,9)	14(25,5)	2,4 (1.0,5.5)	0,039	2,6 (1.1,6.1)	0,031	5,9 (1.9,17.8)	0,002
Abdominal obesity	41(83,7)	23(65,5)	2,7 (1.1,6.9)	0,038	2,8 (1.1,7.1)	0,036	6,4 (0.9,1.1)	0,003
Hypertriglyceridemia	13(26,5)	12(21,8)	1,3 (0.5,3.2)	NS	1,3 (0.5,3.2)	NS	1,8 (0.6,5.2)	NS
HypoHDL	6(12,2)	4(7,3)	1,8 (0.5,6.7)	NS	1,8 (0.5,6.8)	NS	2,9 (0.5,15.3)	NS
Hypertension	42(85,7)	44(80)	1,5 (0.5,4.2)	NS	1,6 (0.5,4.6)	NS	2,9 (0.8,10.9)	NS
Elevated plasma glucose or type 2 diabetes	4(8,2)	6(10,9)	0,7 (0.2,2.7)	NS	0,8 (0.2,3.0)	NS	0,8 (0.2,4.4)	NS

OR = odds ratio; 95% CI=95% confidence interval; HDL=high density lipoproteins; *Multivariate adjusted model included age; **Multivariate adjusted model included age, disease severity, disease duration, systemic therapy or systemic inflammation.

Figures

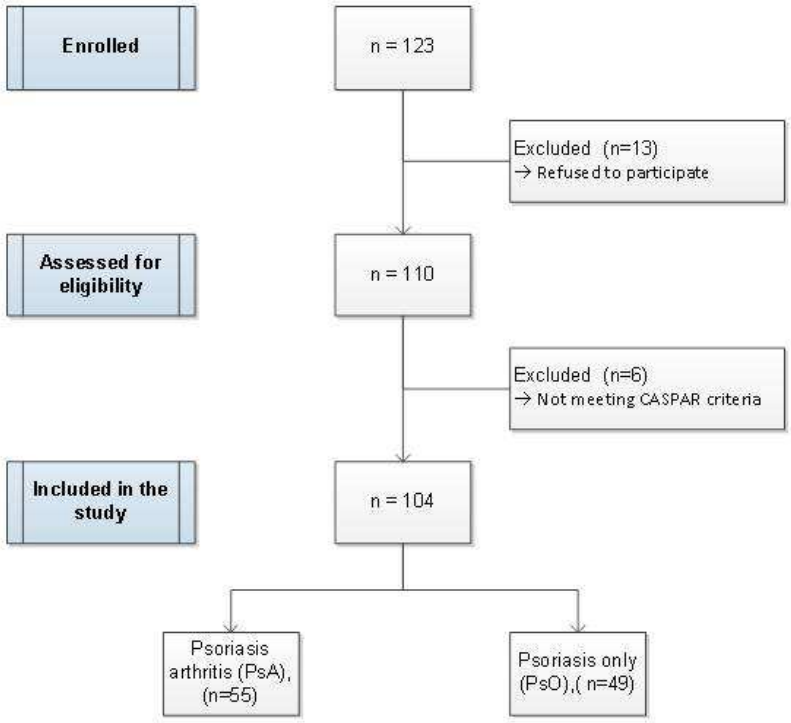

Fig.1 Flow diagram of the progress of the patients through the trial: patients enrolled, assessed for eligibility and included in the study.

CASPAR = Classification criteria for psoriatic arthritis.

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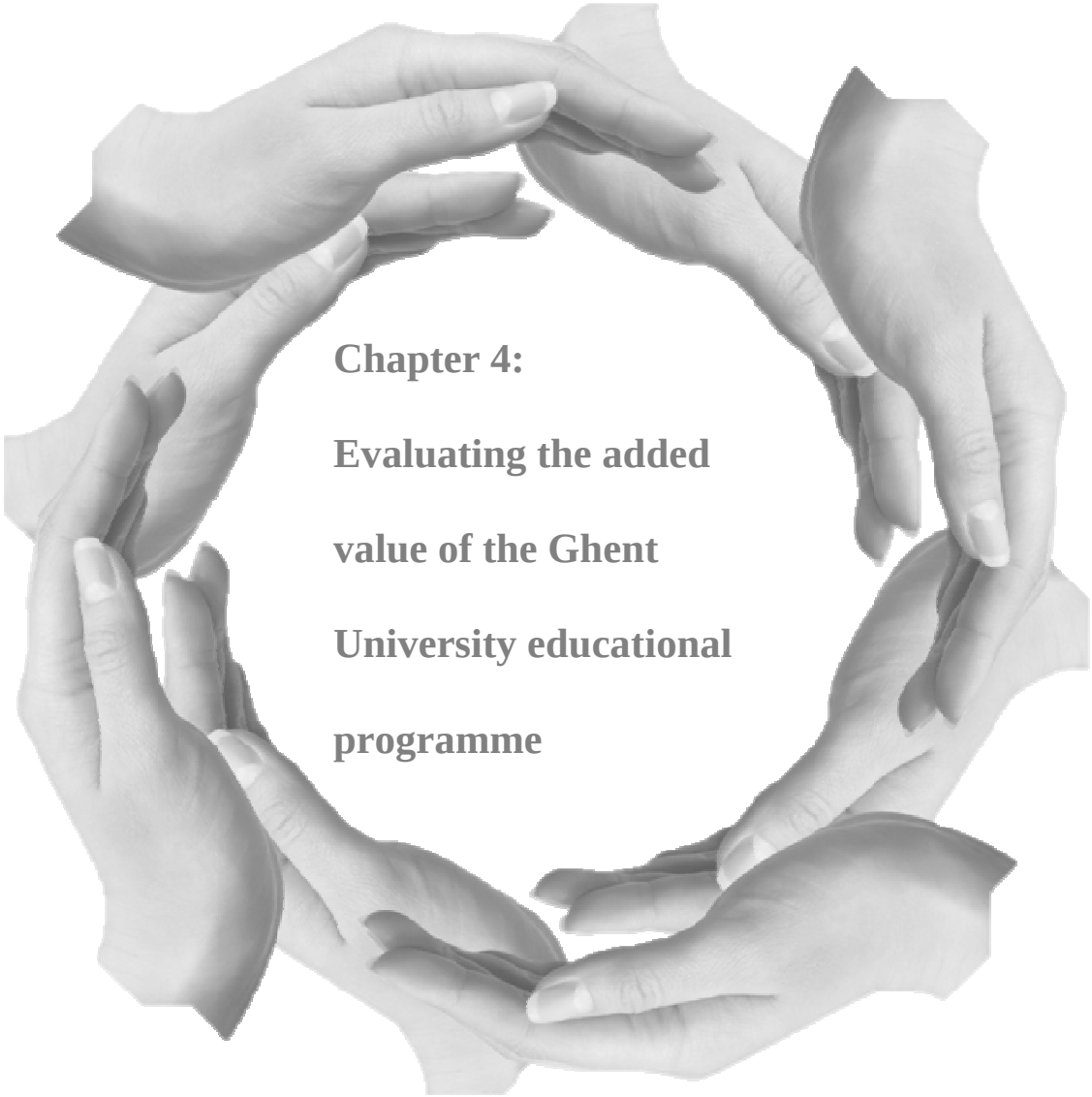

Chapter 4:

Evaluating the added value of the Ghent University educational programme

Chapter 4: Evaluating the added value of the Ghent University educational programme

Introduction

Patient education plays an increasingly important role in the long term management of psoriasis. As discussed in the introduction, psoriasis has a major impact on quality of life and is associated with several comorbidities and lifestyle factors. Besides, a great problem of non-adherence to therapy exists in psoriasis patients. In addition to this, psoriasis patients find it difficult to self-manage their disease. Ersser et al found that there is a need for educational programmes who enables psoriasis patients to develop the knowledge, skills and confidence to self-manage effectively. Key features of such an educational programme are resource efficient, individualized, person-centred and systematic.[1]

The ultimate goal of our educational programme is to enable patients to achieve good quality of life despite having a chronic skin disease. In the following chapter, we present our educational programme for chronic skin diseases in paper 2 and our randomized, controlled trial for psoriasis and atopic dermatitis patients in paper 3.

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4.1 Paper 2: A novel multidisciplinary educational programme for patients with chronic skin diseases: Ghent pilot project and first results. (Published in Arch Dermatol Res, 2011)

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Abstract

Chronic inflammatory skin disorders have a major impact on patients' health related quality of life. Preliminary studies to date have suggested that additional educational and psychological training programmes may be effective in the management of chronic skin diseases, although more rigid methodology is needed. Our purpose was to investigate the effect on quality of life of a novel multidisciplinary educational programme for patients, 18 years or older, with chronic skin diseases. The 12-week intervention encompasses cognitive education on skin and general health issues, and stress-reducing techniques. Quality of life questionnaires were used to assess the participants at baseline and at the end of the program. These comprehend Dermatology Life Quality Index (DLQI), Skindex-29, Psoriasis Disability Index (PDI) and Quality of Life Index for Atopic Dermatitis (QoLIAD). Fifty-five patients participated in six programmes since 2006. Forty-three patients completed the programme. Overall, compared to baseline, DLQI (n=39) improved by 5.64 points ($p<0.001$; SD ±6.09), Skindex-29 (n=27) by 19.67 points ($p<0.001$; SD ±17.37), PDI (n=9) improved by 7.44 points ($p=0.019$; SD ±7.60) and QoLIAD (n=13) improved by 4.39 points ($p=0.036$; SD ±6.69) by the end of the intervention. Preliminary results show that quality of life of patients with chronic skin diseases improved significantly after participation to the programme. These positive initial results are stimulating to set up a prospective controlled randomised trial investigating the impact on quality of life, the clinical efficacy and the cost-effectiveness of this educational intervention programme.

Introduction

Patients with chronic inflammatory skin disorders like psoriasis, atopic dermatitis, chronic urticaria, etc. are prone to psychological distress.[11] The chronic relapsing character of these diseases and the need for continuous, sometimes unsatisfactory treatment causes frustration and disappointment in patients, which in turn might negatively influence the disease course. In periods of stress, exacerbations are often triggered or worsened. The importance of the brain-skin interaction in the etiology of these diseases has therefore received much attention the last years.[2,3,7] Increasing the knowledge of the patient about their skin disease and treatment can stimulate participation in the treatment decision and this can have positive effects on patients satisfaction, compliance and health outcomes, as shown by Renzi et al.[17]

In Ghent, we came up with the concept of an educational programme that could be added to our standard treatment approaches for chronic dermatoses. Offering more support and education in the format of group sessions will improve the comprehension of the skin condition, change the attitude towards the disease, improve the adherence to prescribed therapy and improve quality of life. The novelty of this programme is that it is open to all diagnoses and that it combines cognitive educational sessions, stress reduction techniques and additional skin workshops. Our programme runs 2 or 3-hour sessions twice weekly for 12 weeks. It was set up in 2006 and runs twice yearly. Our purpose was to investigate the effect on quality of life of this educational programme for patients with chronic skin diseases. Preliminary results of six runs of the programme are presented here.

Patients and methods

Patient population

Patients from any gender or race with a chronic skin disease such as psoriasis, atopic dermatitis or other types of eczema, chronic urticaria, acne, hidradenitis suppurativa, vitiligo… can enter the programme. Age range for inclusion is from 18 years onwards.

Content of the educational programme

The educational programme consists of 2-hour sessions twice weekly for 12 weeks. An interdisciplinary team of trainers is involved: dermatologist; dermatologic nurse; pharmacist; psychiatrist; psychologist; dietician; philosopher; training expert; sports, mindfulness and yoga teacher. An overview of the activities, and their share in the whole programme, is given in Table 1. The programme activities can be divided into 4 groups.

1. Specific information on skin disease conditions

In the first 1-h session, a dermatologist gives basic medical information on all diagnoses present in the patient group. Topics such as the definition of the different diseases, basic pathogenetic mechanisms, clinical symptoms, prognosis, and treatment of a given skin disease are carefully explained.

Furthermore, three skin care sessions of 2-h are offered. A pharmacist together with a dermatologic nurse present information on structure, biological and social functions of skin; specific skin disease problems such as xerosis, itch and scaling are tackled.

2. Stress-reduction techniques

Physical training Patients get acquainted with a variety of group and individual sports during 12 weeks, 1 hour per week. The aim is to enhance the motivation for physical training on a regular basis and let patients find what type of sports is best of fit for them. This training scheme is preceded by a physical fitness assessment as a method for screening health risk prior to exercise and sport.[4,24]

Yoga Yoga combines many stress-reducing techniques, including exercise and learning to control the breath, clear the mind and relax the body. This group training is given in 9 sessions of 1 hour each. [22]

Mindfulness-based stress reduction This technique is a behavioural intervention based on insight meditation. It aims to be alert for itch, pain and other sensations or moods and it prevents to be carried away by negative thoughts and reaction patterns. This is educated in 8 sessions of 2,5 hours each on a weekly basis. [16]

3. Information sessions on life style factors and psycho-dermatology

(a) Diet

Two information sessions on composing a balanced diet are given by a dietician. The lessons accentuate the importance of healthy and varied nutrition. Moreover specific topics about nutrition and skin are highlighted, such as food allergy, psoriasis and the metabolic syndrome….

(b) Responsible physical training

In one session the elements of building condition and responsible training are explained. This session is given by a training expert.

(c) Sleep hygiene

A session about sleep hygiene highlights the importance of good sleep and discusses sleep disorders. The different treatment options to optimize sleep are discussed. This session is given by a psychiatrist specialized in sleeping disorders.

(d) Smoking cessation

In this session more insight is given in the association between smoking and skin diseases. Moreover, smoking cessation counseling is offered to the participants that smoke.

(e) Substance abuse

Substance abuse is sometimes the consequence of the burden of a chronic disease which again has a negative influence on the course of the disease. During this session, information is given about alcohol abuse, the short- and longterm effects and treatment. This session is given by a psychiatrist.

(f) Psycho-dermatology

A session psycho-dermatology informs about the common underlying psychopathological disorders that often accompany chronic dermatoses, and ways to counter them. This session is given by a psychiatrist.

(g) Practical philosophy

Two philosophical sessions are included in the programme to inspire the patients on a paradigm shifting with regard to their disease. These lessons are given by a philosopher.

Of all cognitive interventions, including the skin information sessions, a syllabus is offered to the patients.

4. Feedback

The dermatologist also sees the patients halfway the programme on an individual basis to answer more individual questions, and at the end, in a group evaluation session.

Evaluations

Patients complete the following validated, self-administered quality of life questionnaires before start of the programme and immediately after the programme: Dermatology life quality index (DLQI), Skindex-29, Psoriasis disability index (PDI) and Quality of Life Index for

Atopic Dermatitis (QoLIAD). DLQI and Skindex-29 are dermatology-specific quality of life instruments. DLQI consists of 10 questions concerning patients' perception of the impact of skin diseases on different aspects of their quality of life over the last week. The results of a few studies investigating the clinical meanings of the DLQI score show a minimal clinical important difference between 2.2 and 6.9 depending on the skin disease.[5] The Skindex-29 consists of 30 items divided in 3 scales, assessing burden of symptoms, social functioning and emotional state. The questions refer to the previous 4-week period, and scores are given on a 5-point scale, from 'never' to 'all the time'.[1] PDI and QoLIAD are disease specific quality of life instruments for psoriasis and atopic dermatitis respectively. The PDI is a 15-item scale that specifically addresses self-reported disability in areas of daily activities, employment, personal relationships, leisure and treatment effects.[14] The QoLIAD consist of 25 questions and measures the impact of atopic dermatitis on quality of life in adults. In these four questionnaires a higher score indicates a greater negative impact of the skin disease on quality of life.[23]

The physical fitness assessment preceding participation to the programme measures body mass index (BMI), fat percentage and the physical condition of the patients based on VO2 max. For the determination of the fat percentage, the Parizkova-method was used. In this method the skin fold thickness is measured at ten different locations on the body. For the determination of the VO2 peak, the subjects perform an incremental ramp exercise test on a cycle ergometer (Lode Excalibur Sport, The Netherlands) with a rate of increase in work rate ranging between 10 and 25 Watt.min-1 depending on the anthropometrics and the fitness level of the individuals. The pulmonary gas exchange is registered breath-by-breath by means of the Jaeger Oxycon Pro (Germany) and the VO2 max is determined as the highest VO2 over a period of 30s. The condition of the participants based on the VO2 max is divided into five categories (weak, low, average, good and very good) according to gender and age.

Statistical analysis

Statistical analysis of the data were performed using PASW software version 18. The paired student t-test was used to compare continued variables. Parametric tests could be performed because the continue variables were distributed normally.

Results

Currently six runs of the programme have been completed. A total of 55 patients participated. Forty-three patients completed the programme, twelve dropped out, including eight men and

four women. (nine psoriasis, one atopic dermatitis, one prurigo, and one acne). The reasons for drop-out were lack of time, depression, infection or locomotor disability.

Included diagnoses were: psoriasis, atopic dermatitis, prurigo, alopecia areata, pemphigus, hidradenitis suppurativa, acne , chronic urticaria, morphea and seborrhoic dermatitis. In Table 2 the number of patients are given that started and completed the programme, completed the physical fitness assessment and completed the quality of life questionnaires. Mean age of the total group (n=55) was 45 years (range 25-69 years). The physical fitness test preceding participation to the programme revealed the following values for BMI, fat percentage and patient physical condition (based on VO_2 max): for women (n=28), mean BMI was 26.3 kg/m² (SD ±5.4), mean fat percentage was 26.5% (SD ±6.6) and mean VO_2 max was 27.5 ml/min.kg (SD ±7.5). For men (n=25), mean BMI was 25.9 kg/m² (SD ±4.0), mean fat percentage was 19.4% (SD ±6.0) and mean VO_2 max was 35.9 ml/min.kg (SD ±9.8). The mean condition in women is weak in 21%, low in 46%, average in 25% and good in 7%. In men the mean condition is weak in 12%, low in 24%, average in 32%, good in 28% and very good in 4%. The mean BMI of psoriasis patients was 27.5 (n=25, SD ±4.9) and mean BMI of atopic dermatitis patients was 23.8 (n=15, SD ±3.0).

Quality of life

For 39 patients a DLQI score and of 27 patients a Skindex-29 score was obtained before and after the programme. Overall, mean DLQI improved by 5.64 points (p<0,001; SD ±6.09) and mean Skindex-29 by 19.67 points (p<0,001; SD ±17.37).

Additionally, a PDI score was obtained from nine psoriasis patients and a QoLIAD score was obtained from 13 atopic dermatitis patients before and after the programme. In psoriasis patients, mean DLQI (n=15) improved by 3.93 points (p=0.015; SD ±5.50), mean Skindex-29 (n=9) improved by 23.33 points (p=0.020; SD ±24.15) and mean PDI (n=9) improved by 7.44 points (p=0.019; SD ±7.60). In atopic dermatitis patients mean DLQI (n=15) improved by 6.33 points (p=0.003; SD ±6.73), mean Skindex-29 (n=14) improved by 17.50 points (p<0,001; SD ±9.97) and mean QoLIAD (n=13) improved by 4.39 points (p=0.036; SD ±6.69).

The mean values of the questionnaires before and after the programme for each diagnosis are given in Table 3 and Table 4.

Discussion

In the present article, we have described the goals, content and preliminary results of a novel educational programme that we introduced as an additional therapy to the standard treatment for chronic skin diseases.

The results of the physical fitness test before the programme showed overweighed patients (n=53, mean BMI = 26.1 kg/m²). Mean fat percentage in men (19.4%) and women (26.5%) was higher than in normal healthy population (17% in men and 23% in women). The mean condition in women was weaker than in men, however, 36% of male participants have also a weak or low condition. The results of the physical condition test therefore emphasizes the importance of managing lifestyle factors such as diet and exercise.

Furthermore, validated questionnaires revealed that the health related quality of life significantly improved after the intervention. Specifically, women with atopic dermatitis (n=9) seemed to benefit most from the programme with regard to quality of life.

An important goal of our educational programme is to improve patients adherence to therapy. Good evidence shows that office visits drive patients adherence behaviour. Even independent of the content of the visits, our twice weekly visits could have an effect on patients compliance to treatment.

Several concepts of educational and behavioural interventions have been described for skin diseases, in particular for psoriasis[12,15], atopic dermatitis[9,18] and chronic pruritus.[6,10,20] These programmes have in common that they contain education on the skin disease, education on lifestyle factors and stress-reducing techniques but they slightly differ in their approach depending on the skin disorder. They are conducted ranging from 1 to 6 sessions during up to 6 weeks. The overall results of these studies show improved quality of life and clinical outcome compared with a control group.

The major difference with our concept is the intensity and the diversity of our programme: our programme runs 2-hour sessions twice weekly for 12 weeks including education about skin diseases, skin care work-shops, education about lifestyle and stress-reduction techniques such as yoga, physical training and mindfulness-based stress reduction. Limitations to our preliminary data are lack of a control group and lack of a clinical outcome measurement. Finally, we could not control for changes in other aspects of the patients' managements, such as changes in the pharmacological therapy.

Conclusions and future perspectives

The objective of our programme was to support patients in the self-management of their skin disease in a holistic manner. Education about skin diseases and stress-reduction techniques were the basic elements of our programme. In addition we wanted to accentuate the approach of lifestyle factors as diet, exercise, sleep, alcohol and smoking.[19] Lifestyle factors can influence the course of skin diseases especially in psoriasis in which an increased incidence of the metabolic syndrome and cardiovascular disease has recently drawn attention.[13]

With the description of the elaboration of the programme and its preliminary outcome we want to be of help in defining and setting up future standardized preferably multi-center trials with a critical set-up for evaluation. Warsi et al.[21], Ersser et al.[9] and Chida et al.[8] emphasize the need for rigorously designed trials with well-validated interventional instruments, maximal reduction of possible bias, and better description of important variables such as patient educational level, disease duration and severity and social support.

This initiative for patients with chronic dermatoses was experienced as a valuable addition to classical treatment. Quality of life with regard to specific skin problems was improved. These positive initial results are stimulating to set up a prospective controlled randomised trial investigating the impact on quality of life, the clinical efficacy and the cost-effectiveness (in light of restricted health care budgets) of this educational intervention programme, in a group of patients with chronic skin diseases. In view of all this, we call for a multi-center European study in this field.

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Tables

Table 1: An overview of the activities and their part in the whole programme.

Overview of activities	Teacher	Number of sessions	Duration one session	Total duration
1. Specific information on skin disease conditions				
1.a Information session about skin diseases	Dermatologist	1	60min	1h
1.b Skin care	Pharmacist and dermatologic nurse	3	120min	6h
2. Stress-reduction techniques				
2.a Physical training	Sports teacher	12	60min	12h
2.b Yoga	Yoga teacher	9	60min	9h
2.c Mindfulness-based stress Reduction	Mindfulness teacher	8	150min	20h
3. Information sessions on life style and psychodermatology				
3.a Diet	Dietician	2	60min	2h
3.b Responsible physical training	Training expert	1	60min	1h
	Psychiatrist	1	90min	1.5h
3.c Sleep hygiene	Psychologist	1	60min	1h
3.d Smoking cessation	Psychiatrist	1	90min	1.5h
3.e Substance abuse	Psychiatrist	1	90min	1.5h
3.f Psycho-dermatology	Philosopher	2	60+90min	2.5h
3.g Practical philosophy				
4. Feedback				
4.a Individual	Dermatologist	1	15min	15min
4.b In group	Dermatologist	1	1h	1h
				Total: 60h15min

Table 2: Number of patients that started and ended the programme, completed the physical fitness assessment, and completed the quality of life questionnaires before and after the programme: Dermatology life quality index [DLQI], Skindex-29, Psoriasis disability index [PDI] and Quality of life index for atopic dermatitis [QoLIAD].

Diagnosis	**Number of patients**						
	Started programme	Completed physical fitness assessment	Ended programme	Completed DLQI before and after	Completed Skindex-29 before and after	Completed PDI before and after	Completed Qoliad before and after
Psoriasis	26	25	17	15	9	9	0
Atopic dermatitis	16	15	15	15	14	0	13
Prurigo	3	3	2	2	0	0	0
Alopecia areata	2	2	2	1	1	0	0
Pemphigus	2	2	2	1	1	0	0
Hidradenitis suppurativa	2	2	2	2	1	0	0
Acne	1	1	0	0	0	0	0
Chronic urticaria	1	1	1	1	0	0	0
Morphea	1	1	1	1	0	0	0
Seborrhoic dermatitis	1	1	1	1	1	0	0
Total	**55 (25 men/ 30 women)**	**53 (a)**	**43**	**39 (b)**	**27 (c)**	**9 (d)**	**13 (e)**

(a) Two patients did not take part in the physical fitness assessment at the start of the programme; (b) Of 43 patients who completed the programme, 4 patients did not fill out DLQI questionnaire; (c) Only 27 of 43 patients filled out Skindex-29 because this questionnaire was only introduced since the second programme; (d) Only 9 of the 17 psoriasis patients who ended the programme filled out a PDI because this questionnaire was only introduced since the second programme; (e) Of 15 atopic dermatitis patients who completed the programme, two patients did not complete QoLIAD.

Table 3: Mean values and standard deviation (±SD) of Dermatology life quality index [DLQI] and Skindex 29 outcomes are given for each diagnosis.

Diagnosis	**Mean DLQI before (±SD)**	**Mean DLQI after (±SD)**	**Mean Improve-ment in DLQI (±SD)**	**Mean Skindex 29 before (±SD)**	**Mean Skindex 29 after (±SD)**	**Mean Improve-ment in Skindex 29 (±SD)**
Psoriasis	9.87 (±6.63)	5.93 (±6.01)	3.93 (±5.50; *p=0.015)	54.78 (±22.47)	31.44 (±19.99)	23.33 (±24.15; *p=0.020)
Atopic dermatitis	14.80 (±6.77)	8.47 (±3.29)	6.33 (±6.73; *p=0.003)	70.36 (±11.96)	52.86 (±10.30)	17.50 (±9.97; *p<0.001)
Prurigo	9.50 (±9.19)	3.00 (±0.00)	6.50 (±9.19; *p=0.500)			
Alopecia areata	6.00	0.00		38.00	19.00	
Pemphigus	9.00	11.00		46.00	52.00	
Hidradenitis suppurativa	17.50 (±3.54)	6.00 (±0.00)	11.50 (±3.54; *p=0.136)	91.00	40.00	
Acne						
Chronic urticaria	18.00	10.00				
Morphea	14.00	0.00				
Seborrhoic dermatitis	6.00	2.00		37.00	25.00	
Total	**12.23 (±6.75)**	**6.59 (±4.82)**	**5.64 (±6.09; *p<0.001)**	**62.59 (±19.25)**	**42.93 (±17.68)**	**19.67 (±17.37; *p<0.001)**

Mean improvement in DLQI and Skindex-29 is calculated by the difference in mean values before and after the programme . * significance value

Table 4: Mean values and standard deviation (±SD) of Psoriasis disability index [PDI] and Quality of life index for atopic dermatitis [QoLIAD] outcomes are shown.

	Mean before (±SD)	**Mean after (±SD)**	**Mean improvement (±SD)**
Psoriasis : PDI	12.00 (±6.78)	4.56 (±5.25)	7.44 (±7.60;*p=0.019)
Atopic dermatitis: QOLIAD	13.15 (±3.85)	8.77 (±5.60)	4.39 (±6.69;*p=0.036)

Mean improvement in PDI and QoLIAD is calculated by the difference in mean values before and after the programme . * significance value

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4.2 Paper 3: An educational programme for patients with psoriasis and atopic dermatitis: a prospective randomized controlled trial. (Accepted in Br J Dermatol, 2012)

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Summary

Background Patient education in addition to standard treatment, with the aim of affecting care through courses is a relatively new concept in dermatology. Here we introduce a randomized controlled trial (RCT) regarding a previously described 12-week educational programme for chronic skin diseases.

Objective The primary objective of the RCT was to measure the effect of an educational programme on disease severity and quality of life in patients with psoriasis or atopic dermatitis.

Methods We recruited 50 patients from the Ghent University Hospital. Patients with diagnosed psoriasis or atopic dermatitis were randomized (1:1) to the intervention or control group. The clinical outcome was measured by two blinded observers using Psoriasis Area and Severity Index (PASI), Scoring Atopic Dermatitis or the Eczema Area and Severity Index. Quality of life was measured by dermatology-specific quality of life questionnaires. There was a follow-up period of 9 months.

Results We found that disease severity and quality of life improved significantly for patients with psoriasis (n=29) but not for patients with atopic dermatitis (n=21) at 3 months. Patients in the intervention group showed a significant reduction in mean PASI (P=0.036), mean Dermatology Life Quality Index (P=0.019) and in mean Psoriasis Disability Index (P=0.015), compared with the control group at 3 months. This improvement continued for at least 6 months, i.e. 3 months after the intervention, but was lost at follow-up after 9 months.

Conclusion Evaluating this form of educational programme, by means of a single-centre RCT, indicates its added value in the longer term management of psoriasis.

Introduction

Chronic skin diseases, such as psoriasis and atopic dermatitis, have a profound negative impact on patient's quality of life.[1,2] Because treatment is highly self-demanding, we see a low compliance to therapy, resulting in poor clinical outcomes.[3,4] Therefore, patient education and motivation plays an increasingly important role in the long-term management of chronic skin diseases. Successful education increases patient satisfaction and improves health outcomes and adherence to treatment.[5,6] As more studies are needed within this context, we set up further research on our previously described group-based educational programme.[7] We conducted a prospective, single-blinded, randomized controlled trial (RCT) in adult patients with psoriasis and atopic dermatitis, to investigate whether our educational programme is of added value to medical therapy. Effect on disease severity and quality of life were measured as primary end points at different time-points. Furthermore, the level of depression, lifestyle changes and the effect on medical consumption were followed over 9 months.

Patients and methods

Patient population and study procedures

From February 2010 to 2011, 50 patients were recruited from three different sources: Ghent University Hospital (n=18), patient advocacy groups (n=26) and peripheral dermatologists (n=6). Patients older than 18 years with psoriasis or atopic dermatitis were eligible to participate in the trial. At inclusion, patients were checked for diagnosis by a dermatologist. Exclusion criteria were other severe illnesses, psychiatric disorders and cognitive disorders. The patients were randomized (1:1) to the intervention or control group. This procedure involved computer-generated randomization of lists in which allocation was indicated, and stratified by diagnosis using a block size of two. Sequentially numbered envelopes were used by the investigator to assign patients to the intervention or control group. Patients assigned to the intervention group participated in the educational programme while still receiving medical therapy, whereas patients assigned to the control group received only medical therapy. Three runs of the programme were included in the trial: 14 patients started in spring 2010, 23 in autumn 2010 and 13 in spring 2011. Patients were assessed at four study visits: before the start of the programme (baseline), after the programme (3 months) and at two follow-up visits at 6 and 9 months after the start. The study was approved by the local ethical committee (registration number B67020097924) and was registered on http://www.clinicaltrials.gov (NCT01077882).

Intervention: group-based educational programme

The 12-week educational programme consisted of 2-h sessions twice a week, including several components: (i) education on the patient's skin disease; (ii) education on a healthy lifestyle; (iii) application of stress-reducing techniques and (iv) feedback. The first part included an information session on the patient's skin disease given by a dermatologist, and three skin care sessions given by a dermatological nurse and pharmacist. The second part contained education on diet, responsible physical training, sleep hygiene, smoking, substance abuse, psychodermatology and practical philosophy, given by a team of trainers: a dietician, training expert, psychiatrist, psychologist and philosopher. The third part consisted of weekly physical training, yoga and mindfulness meditation taught by a sports, yoga and mindfulness teacher. The fourth and final part contained two feedback sessions with a dermatologist. Detailed content of the programme is described in Lambert et al.[7]

Primary outcomes

Disease severity

Two clinicians performed assessments of disease severity at the four study visits and were blinded for randomization. The clinical severity of psoriasis was assessed by the Psoriasis Area and Severity Index (PASI),[8] and the severity of atopic dermatitis by Scoring Atopic Dermatitis (SCORAD) and the Eczema Area and Severity Index (EASI).[9] Clinicians were trained to define the PASI, SCORAD and EASI before start of the trial. The level of agreement between both clinicians' assessments on PASI, SCORAD and EASI was very good. The intraclass correlation coefficient was 0.86 (95% confidence interval (CI) 0.72-0.94) for PASI, 0.89 (CI 0.74-0.96) for SCORAD and 0.92 (CI 0.82-0.97) for EASI.

Quality of life

Patients completed the following validated, self-administered quality-of-life questionnaires at the four study visits: Dermatology Life Quality Index (DLQI),[10] Skindex-29,[11] Psoriasis Disability Index (PDI)[12] and Quality of Life Index for Atopic Dermatitis (QoLIAD).[13] DLQI and Skindex-29 are dermatology-specific quality of life instruments. DLQI is a historical comparator and focuses on disability, thereby not fully capturing the emotional aspects of patients' lives. Skindex-29 is a more sensitive instrument for different dimensions of quality of life, including emotions. PDI and QoLIAD are disease-specific quality-of-life questionnaires. More information about the questionnaires is given in Lambert et al.[7]

Secondary outcomes

Depression severity

The Beck Depression Inventory (BDI) is a self-completed questionnaire with 21 questions. It is one of the most widely used instruments for measuring depression severity.[14] Patients were categorized as having minimal (0-9), mild (10-18), moderate (19-29) or severe (30-63) depression. BDI scores were collected during four study visits.

Lifestyle

Patients were queried monthly for changes in smoking behaviour and physical activity. Physical activity was categorized as: sedentary activity (i), light physical activity (walking, biking) < 4h weekly (ii), or at least 4h weekly (iii), and moderate physical activity (sports) < 4h weekly (iv), or at least 4h weekly (v).[15] Stress was examined by the Everyday Problem Checklist during four study visits.[16] Patients were categorized as having a low (men ≤ 6 , women ≤ 4), normal (men 7-36, women 5-33) or high (men ≥ 37, women ≥ 34) stress level.

Medical consumption and cost-effectiveness evaluation

The medical therapy of the patients was divided into topical therapy, systemic therapy, combination of topical and systemic therapy or no therapy. Topical therapy included: corticosteroids with or without calcipotriol, calcineurin inhibitors, tar ointment and hydration. Systemic therapy included: methotrexate, ciclosporine, acitretin, oral corticosteroids and ultraviolet (UV)-B. Patients were asked about changes in medical therapy monthly. Also, medical consumption was followed,i.e. costs for medication and doctor visits related to the management of the skin disease. EuroQol-5D (EQ-5D) questionnaires were used as a standardized instrument to measure health outcomes. For cost-utility analysis, the gain in quality-adjusted life years utility was plotted against time, using the area under the curve approach (cost in euro/EQ-5D gain).

Statistics

Power calculation showed that 34 patients were needed for this RCT. There is an 80% probability that the study would detect a treatment difference at a 0.05 significance level if the mean difference between treatments is 2 and the standard deviation is 2. Data were analysed using SPSS software (SPSS Inc., Chicago, IL, U.S.A.). Mixed modeling analysis was performed to identify differences in time between the intervention and control groups for each outcome variable. These data were presented as mean and 95% CI. Intraclass correlation

coefficient was the measured level of agreement between both clinicians. The Spearman correlation coefficient measured the correlation between quality of life and disease severity.

Results

Patient population

Fifty patients participated in our trial, 29 with psoriasis and 21 with atopic dermatitis. There were 24 men and 26 women. The mean age was 39.6 ± 12.2 years, with a range of 21-63 years. The mean duration of disease was 19.5 ± 11.1 years. At baseline, the average disease severity was mild for psoriasis; mean PASI was 7.7 ± 3.9. For atopic dermatitis, the average disease severity was moderate; mean SCORAD was 38.9 ± 16.3 and mean EASI was 11.1 ± 9.3. The average quality of life for the total group was moderately to severely affected at baseline; mean DLQI was 8.5 ± 5.5 and mean Skindex-29 was 44.4 ± 16.8. Beck depression inventory showed a mean value of 9.8 ± 7.4, which represents a minimally depressive state. The highest educational attainment of the total group was low in 4%, medium in 38% and high in 58%; 57% were professionally active and 43% were professionally inactive (including students and pensioners); 71% had a multiperson household and 29% were living alone. Regarding treatment modalities, 76% of the patients were on topical therapy, 2% on systemic therapy, 14% on topical and systemic therapy and 8% had no therapy at baseline. Table 1 shows the baseline characteristics of the patients in the intervention and control groups.

Up to 3 months, there were nine dropouts, and a further three patients dropped out during the following 6 months. Reasons for dropout in the intervention group included lack of time, the programme being too intensive and moving house. In the control group, worsening of skin disease and loss of motivation were reasons given for dropout. Figure 1 shows a flow diagram of progress through the phases of the trial.

Primary outcomes

Disease severity and quality of life improved significantly after participation in the programme in the psoriasis group, but not in the atopic dermatitis group. These effects were maintained for at least 6 months but were lost at 9 months follow-up. Moreover, we saw a moderate correlation between quality of life and disease severity in the patients with psoriasis and atopic dermatitis. At baseline, the Spearman correlation coefficient between PASI and DLQI was 0.6, and between SCORAD and DLQI was 0.5.

Disease severity and quality of life in patients with psoriasis

We analysed data from 29 patients with psoriasis at 3 months. At 6 and 9 months, data from 28 patients with psoriasis were analysed. One patient was excluded from analysis because her condition deteriorated severely due to stress caused by workplace bullying.

Psoriasis area and severity index

At 3 months: intervention patients showed significant reduction (P=0.036) in mean PASI going from 8.4 (CI 6.0-10.8) at baseline to 6.8 (CI 4.3-9.3) at 3 months, compared with the control group, which had mean PASI going from 7.1 (CI 4.8-9.4) at baseline to 8.1 (CI 5.8-10.4) at 3 months.

At 6 months: intervention patients showed significant reduction (P=0.017) in mean PASI going from 8.6 (CI 5.8-11.4) at baseline to 6.5 (CI 3.6-9.4) at 3 months ,and 5.9 (CI 3.0-8.9) at 6 months compared with the control group, which showed mean PASI going from 7.1 (CI 4.6-9.7) at baseline to 8.1 (CI 5.6-10.7) at 3 months and 7.8 (CI 5.2-10.3) at 6 months.

At 9 months: intervention patients showed reduction in mean PASI going from 8.6 (CI 5.6-11.6) at baseline to 6.5 (CI 3.3-9.8) at 3 months, 6.0 (CI 2.7-9.2) at 6 months and 7.0 (CI 3.8-10.3) at 9 months, compared with the control group, which showed mean PASI going from 7.1 (CI 4.3-9.9) at baseline to 8.1 (CI 5.3-10.9) at 3 months, 7.8 (CI 5.0-10.6) at 6 months and 7.0 (CI 3.8-10.3) at 9 months, but this did not reach significance (P=0.116, Fig. 2a)

Dermatology life quality index

At 3 months: patients in the intervention group showed significant reduction (P=0.019) in mean DLQI going from 8.4 (CI 5.6-11.2) at baseline to 4.4 (CI 1.3-7.4) at 3 months, compared with the control group, which showed mean DLQI going from 6.6 (CI 3.9-9.3) at baseline to 6.4 (CI 3.6-9.2) at 3 months.

At 6 months: patients in the intervention group showed reduction in mean DLQI going from 8.0 (CI 5.0-11.0) at baseline to 4.8 (CI 1.4-8.2) at 3 months and 4.7 (CI 1.3-8.0) at 6 months, compared with the control group, which showed mean DLQI going from 6.6 (CI 3.8-9.4) at baseline to 6.4 (CI 3.5-9.3) at 3 months and 6.9 (CI 4.1-9.8) at 6 months, but this did not reach significance (P=0.089).

At 9 months: intervention patients showed reduction in mean DLQI going from 8.0 (CI 4.9-11.1) at baseline to 4.8 (CI 1.4-8.2) at 3 months, 4.7 (CI 1.3-8.0) at 6 months and 4.0 (CI 0.6-

7.4) at 9 months, compared with the control group, which showed mean PASI going from 6.6 (CI 3.7-9.5) at baseline to 6.4 (CI 3.5-9.3) at 3 months, 6.9 (CI 4.0-9.8) at 6 months and 5.8 (CI 2.9-8.8) at 9 months, but this did not reach significance (p=0.100, Fig. 2b)

Psoriasis disability index

At 3 months: intervention patients showed significant reduction (P=0.015) in mean PDI going from 9.0 (CI 5.0-13.0) at baseline to 4.3 (CI 0.1-8.4) at 3 months compared with the control group, which had mean PDI going from 7.6 (CI 3.8-11.5) at baseline to 6.7 (CI 2.9-10.6) at 3 months.

At 6 months: intervention patients showed significant reduction (P=0.020) in mean PDI going from 8.8 (CI 4.5-13.0) at baseline to 4.5 (CI 0.1-9.0) at 3 months and 4.2 (CI -0.3-8.6) at 6 months, compared with the control group, which showed mean PDI going from 7.6 (CI 3.7-11.6) at baseline to 6.7 (CI 2.7-10.7) at 3 months and 7.3 (CI 3.3-11.3) at 6 months.

At 9 months: intervention patients showed significant reduction (P=0.021) in mean PDI going from 8.8 (CI 4.3-13.2) at baseline to 4.5 (CI -0.1-9.1) at 3 months, 4.1 (CI -0.5-8.7) at 6 months and 4.9 (CI 0.3-9.5) at 9 months, compared with the control group, which showed mean PDI going from 7.6 (CI 3.6-11.7) at baseline to 6.7 (CI 2.6-10.8) at 3 months, 7.3 (CI 3.2-11.4) at 6 months and 7.4 (CI 3.3-11.6) at 9 months (Fig. 2c).

Skindex-29

No significant differences in Skindex-29 were seen between the intervention and control groups of patients with psoriasis.

Disease severity and quality of life of atopic dermatitis

We analysed data of 21 atopic dermatitis patients. No significant differences were seen between intervention and control group of atopic dermatitis for SCORAD, EASI, DLQI, Skindex-29 nor for QoLIAD.

Secondary outcomes

Depression severity

At 9 months, we analysed depression data from 29 patients with psoriasis. Patients in the intervention group showed a significant reduction (P=0.029) in mean BDI going from 12.3 (CI 8.3-16.4) at baseline to 10.5 (CI 6.1-14.9) at 3 months, 9.1 (CI 4.7-13.5) at 6 months and 6.1 (CI 1.7-10.5) at 9 months, compared with the control group, which had mean BDI going from 7.4 (CI 3.5-11.3) at baseline to 6.3 (CI 2.3-10.3) at 3 months, 8.1 (CI 4.1-12.0) at 6 months and 7.3 (CI 3.2-11.3) at 9 months (Fig. 3). No significant differences for BDI were seen between the intervention and control groups for atopic dermatitis.

Lifestyle

Patients were queried on a monthly basis for changes in smoking behavior and physical activity. At baseline 13 patients were smokers (26%), of whom seven were randomized to the intervention group. In the intervention group one patient stopped smoking after 3 months and one patient reduced to half the amount of cigarettes after 6 months. There were no changes in smoking behavior in the control group (n=6). Figure 4 shows the physical activity of the patients. The intervention group had a significantly higher physical activity level (P=0.035) than the control group during the entire study. At baseline, 64% of participants agreed on the negative influence of stress on their skin disease. The Everyday Problem Checklist (n=27) revealed low stress levels in 7.4%, normal stress levels in 44.4% and high stress levels in 48.1% at baseline. However, we could not show significant differences in stress level between the control and intervention groups during the study.

Medical consumption and cost-effectiveness evaluation

Treatment interventions were allowed in both intervention and control groups. We monitored treatments by questionnaire and found no major differences between study arms over the period of the study (Table 2). We could not show significant differences in medical consumption between the control and intervention groups over the period of study. EQ5D values in the intervention group were not significantly better than in the control group at 6 months. Cost-utility analysis taking into account programme cost per patient and medical resource use per individual patient did not show cost-effectiveness at 6 months.

Discussion

In this RCT, at 3 months we found that our educational programme contributed to an improved disease severity and quality of life in patients with psoriasis. This improvement continued for at least 6 months, i.e. 3 months after the intervention, and was not related to major changes in medical therapy or influence of seasonal variation. Furthermore, an improvement in physical activity was seen in the intervention group but not in the control group. Lastly, there was a longer positive effect on the depression status of patients with psoriasis.

These findings support previous studies showing that patient education contributes to improved quality of life and clinical outcomes. In a multicenter RCT, Staab et al.[17] showed that education for children with atopic dermatitis resulted in an improved quality of life and disease severity (n=992). Also, Fortune et al.[18] found that a cognitive-behavioural symptom management programme for adult patients with psoriasis is beneficial in the management of psoriasis (n=93). De Bes et al.[5] critically evaluated studies regarding educational programmes in patients with chronic skin diseases conducted between 2000 and 2008. Interventions that were more intensive and were delivered over a longer time scale (3 months or more) were more successful than briefer interventions. [19]

Important limitations of our study are the influence of confounding factors such as changes in therapy. Treatment interventions were not restricted in either the intervention or control group. Most patients were receiving topical therapy, as they had mild disease. We monitored treatments by questionnaire and found no major imbalances between study arms (Table 2), but we cannot exclude an influence of minor changes in therapy. Furthermore, the use of self-administered quality of life questionnaires could lead to bias because patients are not blinded for the treatment allocation. Nevertheless, bias by seasonal variation was reduced by staggering recruitment across seasons. There were 27 patients participating in spring and 23 participating in autumn.

No attempt was made with regard to our educational programme on eliciting the effects of individual components of the intervention. It would be interesting to study this in the future, especially with regard to psoriasis.

Evaluating this form of educational programme, through the means of a single-centre RCT, indicates its added value in the longer term management of psoriasis. We cannot provide a

satisfactory explanation for the absence of effect in patients with atopic dermatitis. Certain disease-specific factors in psoriasis, such as metabolic comorbidities and susceptibility to addiction, might make diet and substance abuse of greater importance for patients with psoriasis than for patients with atopic dermatitis. However, we believe that these skin diseases have enough common ground with regards to their need for education.

Further research is needed on how education is best offered, especially as regards the frequency of contacts and the intervals between them. As the beneficial effects seems to wane after 6 months after the end of the programme, and as the programme is perceived to be very intensive, it might be an option to offer components on a more continuous basis. We do believe that the group (vs. individual) format offers an advantage, and can in practice be better reconciled with the time-consuming aspects of organizing patient education.

In conclusion, our data indicate that this format of patient education deserves more investigation in order to obtain more robust data, especially in psoriasis.

What's already known about this topic?

Patient education plays an increasingly important role in the long-term management of chronic skin diseases, such as psoriasis and atopic dermatitis.

What does this study add?

Evaluating this form of educational programme, by means of a prospective randomized controlled trial, indicates its added value in the long-term management of psoriasis.

Acknowledgments

The organization of the educational programme was supported by unrestricted grants from Pierre Fabre SA, Schering-Plough, Abbott, LEO Pharma and Johnson & Johnson.

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Tables

Table 1: Baseline characteristics of patients in the intervention and control group.

Variables	Intervention	Control
Gender: M/F (%)	48/52	48/52
Diagnosis: psoriasis/atopic dermatitis (%)	60/40	56/44
Age (years), mean (± SD)	38,5 (±12,3)	40,6 (±12,2)
Duration of disease (years), mean (± SD)	18,9 (±11,0)	20,1 (±11,4)
Age at onset of disease (years), mean (± SD)	19,6 (±17,3)	20,5 (±17,4)
Education: low/medium/high (%)	4/22/74	4/52/44
BMI, mean (± SD)	24,4 (±4,2)	25,3 (±4,9)
PASI, mean (± SD)	8,9 (±4,3)	7,1 (±3,8)
SCORAD, mean (± SD)	38,9 (±18,0)	38,8 (±15,5)
EASI, mean (± SD)	11,9 (±10,9)	10,4 (±8,1)
DLQI, mean (± SD)	9,7 (±6,0)	7,5 (±5,0)
Skindex29 total, mean (± SD)	45,5 (±16,1)	43,3 (±17,7)
Skindex29 symptoms, mean (± SD)	58,1 (±15,4)	55,8 (±18,4)
Skindex29 emotions, mean (± SD)	48,9 (±19,6)	49,0 (±22,7)
Skindex29 functioning, mean (± SD)	35,2 (±20,4)	30,8 (±21,4)
Qoliad, mean (± SD)	9,1 (±5,6)	9,6 (±6,1)
PDI, mean (± SD)	9,0 (±6,8)	7,6 (±7,8)
BDI, mean (± SD)	11,3 (±8,2)	8,4 (±6,5)

BMI, Body mass index; PASI, Psoriasis Area and Severity Index; SCORAD, Scoring Atopic Dermatitis; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; QoLIAD, Quality of Life Index for Atopic.

Table 2: The numbers (n) of patients undergoing particular types of medical therapy (topical, systemic, combination of topical and systemic therapy, no therapy) over the time of the study in the intervention and control groups, and by diagnosis.

		Intervention		**Control**	
Time point	**Type of therapy**	**N**		**n**	
		Psoriasis	**Atopic dermatitis**	**Psoriasis**	**Atopic dermatitis**
Baseline	Topical	9	8	12	9
	Systemic	-	-	1	-
	Combination	2	2	1	2
	No	4	-	-	-
	Total	15	10	14	11
3 months	Topical	5	7	12	8
	Systemic	-	-	-	-
	Combination	2	1	-	2
	No	2	1	1	-
	Total	9	9	13	10
6 months	Topical	4	6	12	7
	Systemic	-	-	-	-
	Combination	2	1	-	2
	No	2	1	1	-
	Total	8	8	13	9
9 months	Topical	3	7	10	7
	Systemic	-	-	1	-
	Combination	2	1	1	1
	No	3	-	1	-
	Total	8	8	13	8

Figures

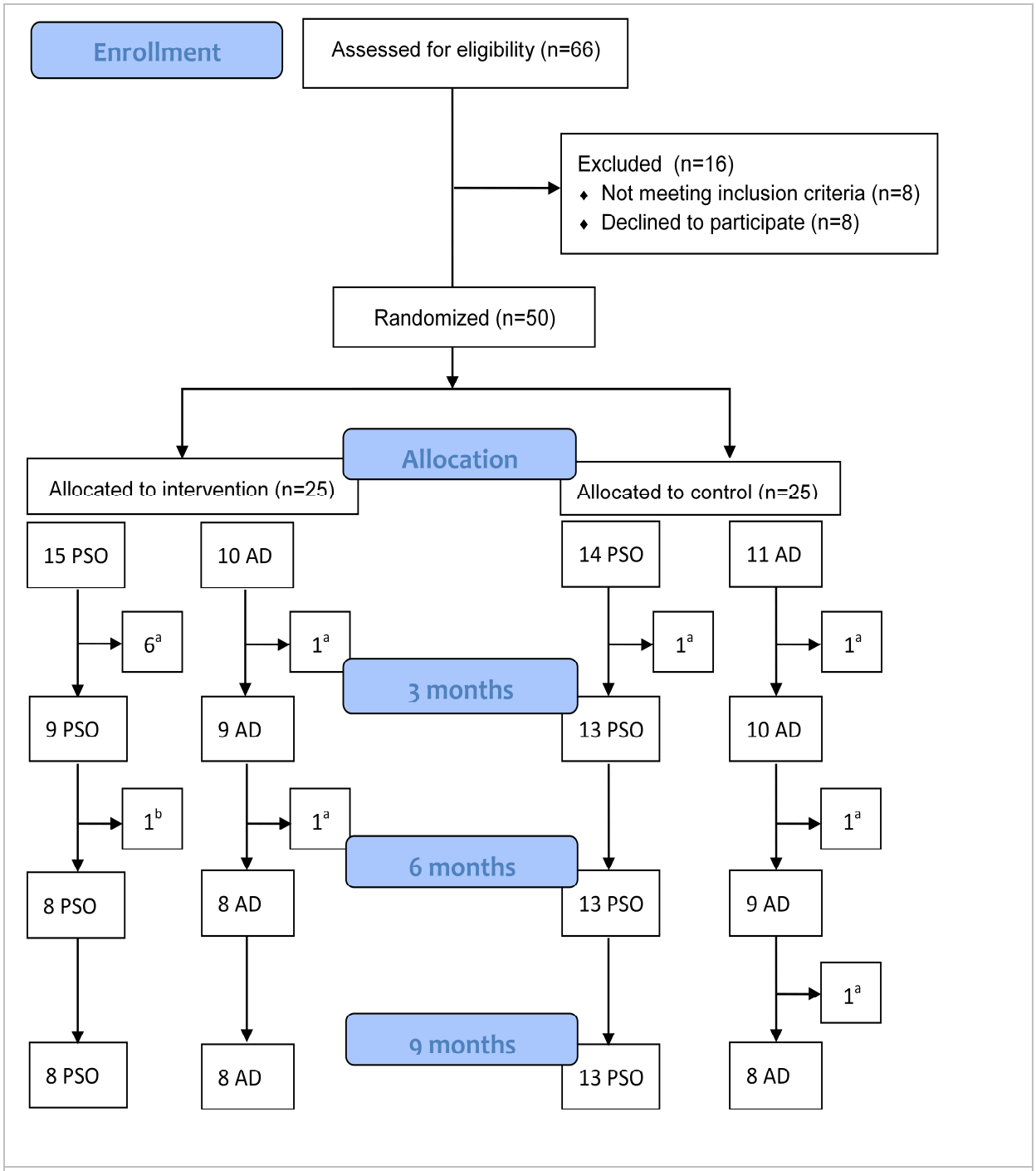

Fig.1 Flow diagram of the progress through the phases of the trial. [a]Drop-outs ;[b] Excluded from analysis; PSO, patients with psoriasis; AD, patients with atopic dermatitis

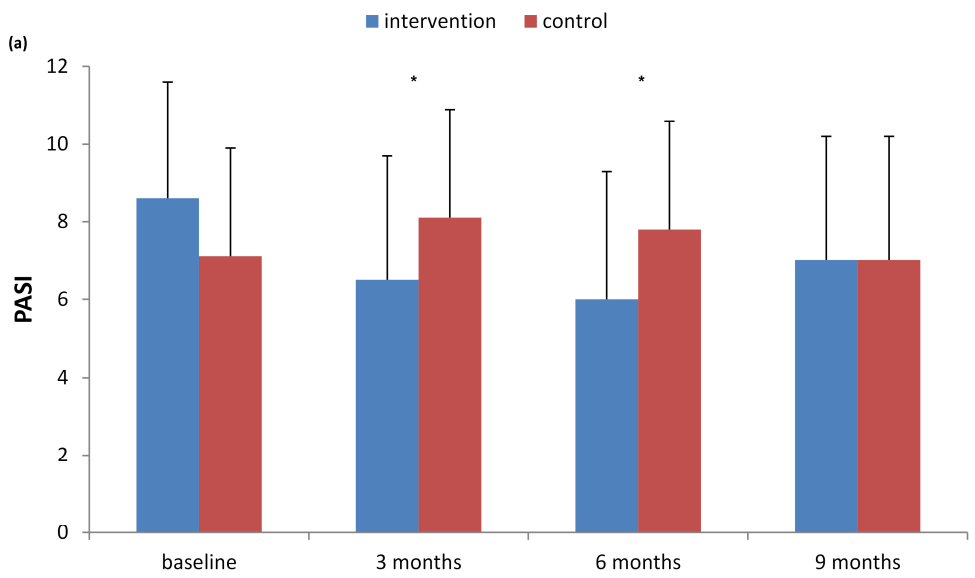

Fig.2a Disease severity of psoriasis, as assessed by Psoriasis Area and Severity Index (PASI), for intervention patients (blue columns) and control patients (red columns) at baseline, 3, 6 and 9 months follow-up. All values are mean and 95% confidence interval. *P <0.05

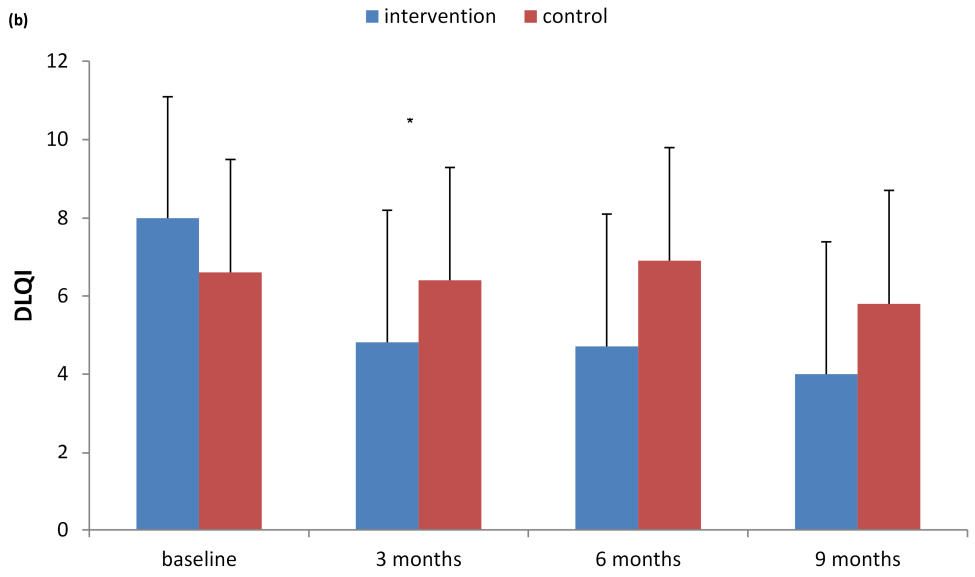

Fig.2b Quality of life of psoriasis, as assessed by Dermatology Life Quality Index (DLQI), for intervention patients (blue columns) and control patients (red columns) at baseline, 3, 6 and 9 months follow-up. All values are mean and 95% confidence interval. *P <0.05

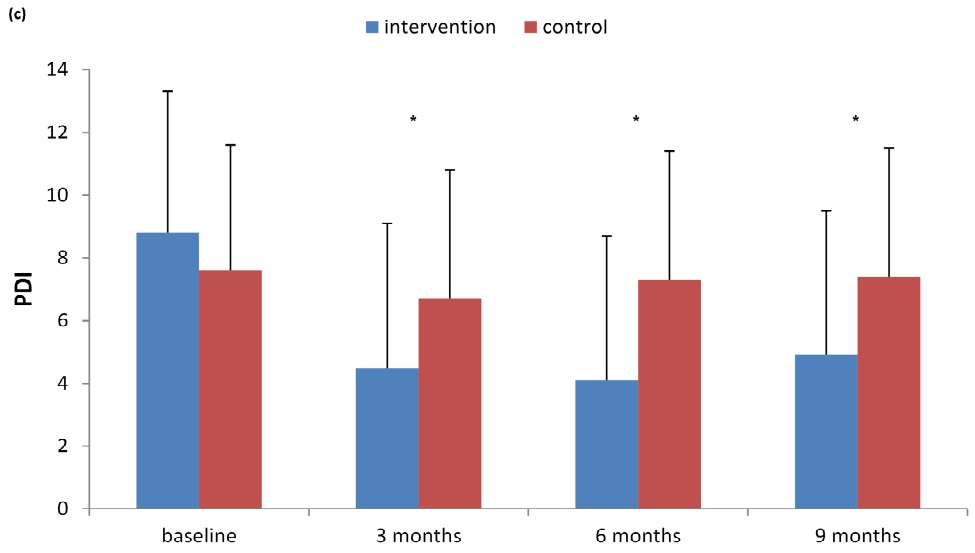

Fig.2c Quality of life of psoriasis, as assessed by Psoriasis Disability Index (PDI), for intervention patients (blue columns) and control patients (red columns) at baseline, 3, 6 and 9 months follow-up. All values are mean and 95% confidence interval. *P <0.05

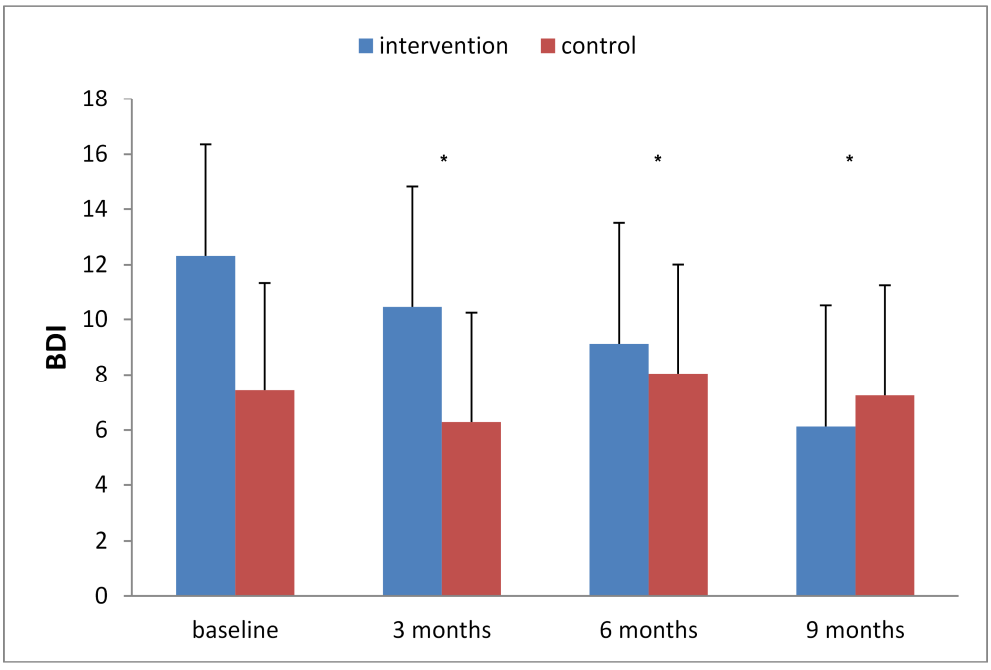

Fig. 3 Mean depression scores for psoriasis, as assessed by Beck Depression Inventory (BDI), for intervention patients (blue columns) and control patients (red columns) at baseline, 3, 6 and 9 months follow-up. All values are mean and 95% confidence interval. *P <0.05

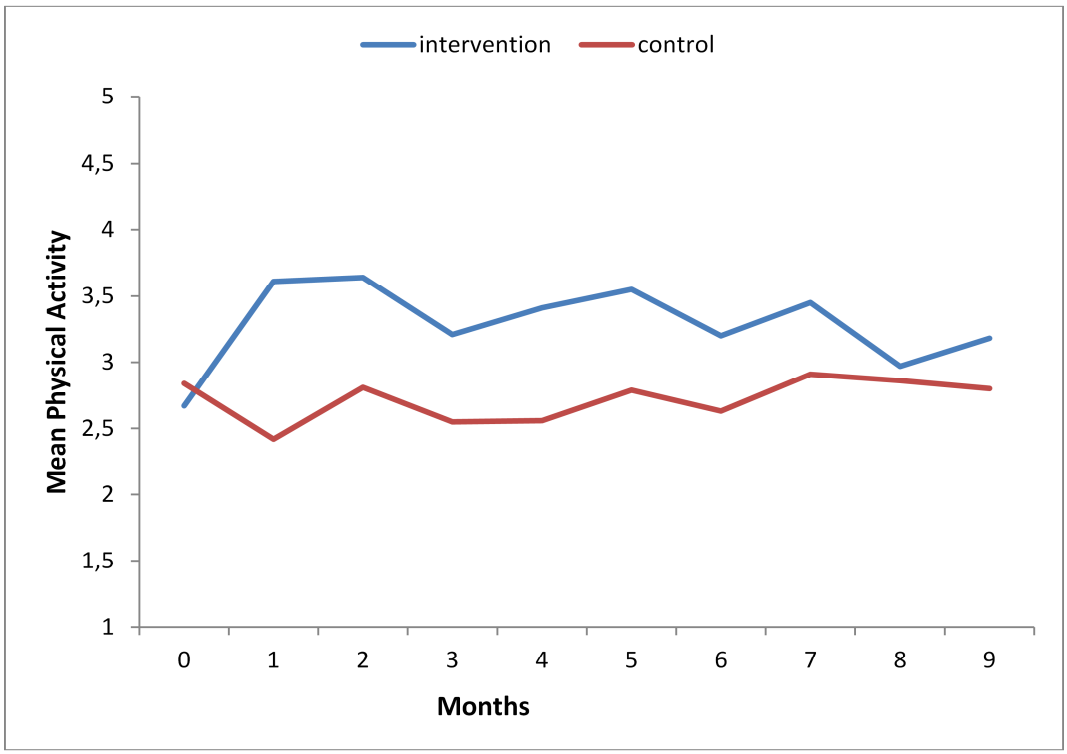

Fig. 4 The intervention group has significant more physical activity (p=0.035) than the control group during the 9 months of the study. Physical activity: 1, sedentary; 2, light <4h/week; 3, light >4h/week; 4, moderate <4h/week; 5, moderate >4h/week.

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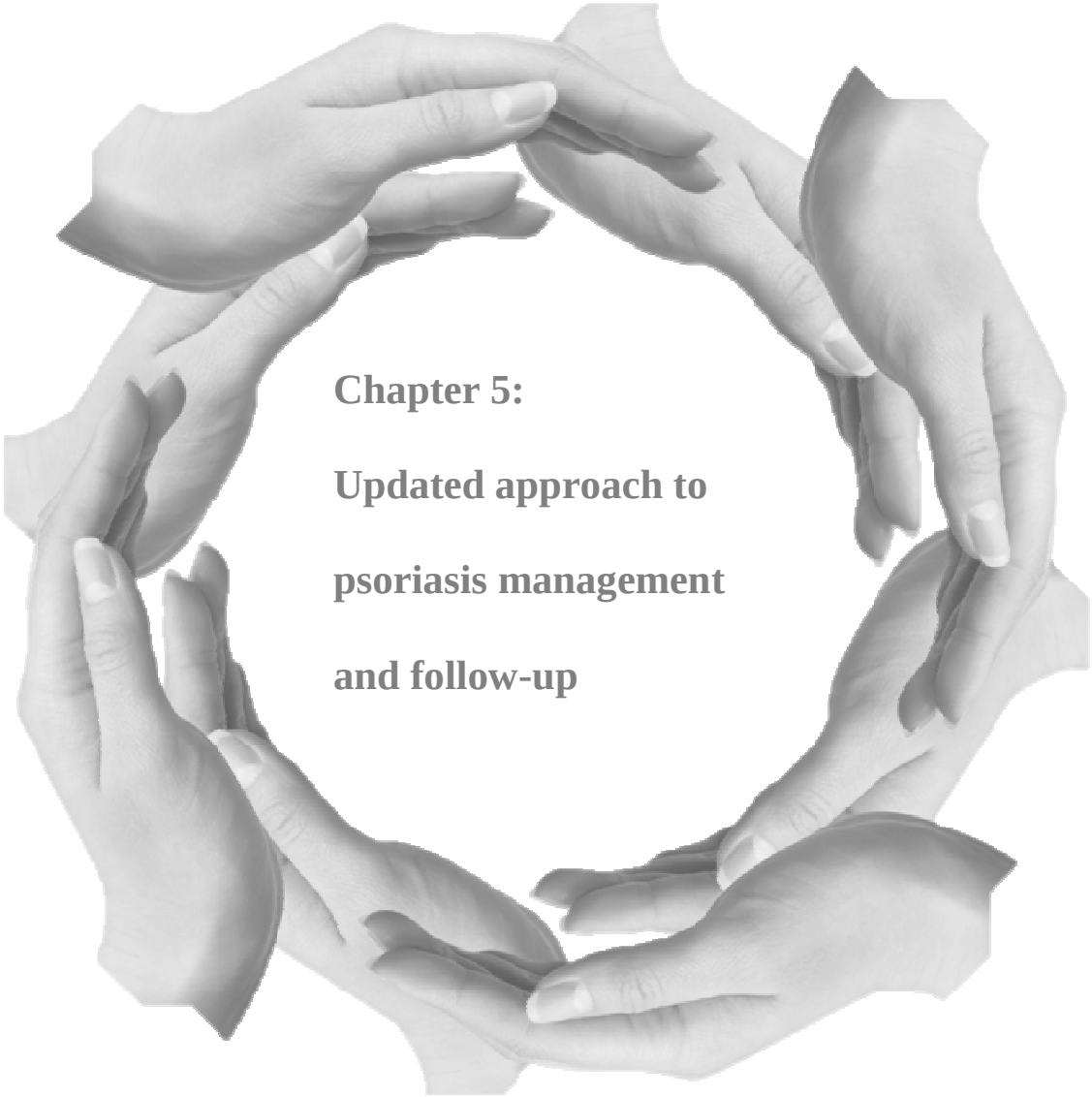

Chapter 5:

Updated approach to psoriasis management and follow-up

Chapter 5: Updated approach to psoriasis management and follow-up

5.1 Paper 4: A comprehensive approach to psoriasis management in the dermatological practice: a template for patient report anno 2012. (Submitted to J Am Acad Dermatol, 2012)

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Abstract

Psoriasis is a common chronic inflammatory skin disease, with complex interactions between genetic, immunological, systemic and environmental factors. Several comorbidities have been associated with psoriasis, such as immune-mediated inflammatory diseases, cardiovascular and metabolic diseases, different types of cancer and psychosocial problems. In addition, it should be mentioned that some of the medications in psoriasis has potentially severe side effects, warranting good pretreatment screening and therapy follow-up.

Consequently this implies that dermatologists need to address several health-related aspects when assessing psoriasis patients, going far beyond just optimal skin care. This article offers an overview of the various relevant aspects in the clinical dermatological assessment of psoriasis patients, emphasizing the importance of a multidisciplinary and holistic clinical approach. It can be used as a template for good clinical practice in psoriasis.

Introduction

Psoriasis is a common chronic inflammatory skin disease, approximately affecting 2% of the population[1]. It is characterized by intense proliferation and abnormal differentiation of keratinocytes, resulting in erythematous plaques and scaling. Complex interactions exist between genetic, immunological, systemic and environmental factors. Furthermore, several disorders have been associated with psoriasis. These comorbidities frequently only become clinically manifest several years after the beginning of psoriasis and tend to occur more often in more severe psoriasis [2]. Therefore, dermatologists need to approach psoriasis as a multisystem disorder, with health-related aspects going beyond the skin. Regular follow-up with full evaluation of the impact on quality of life, the comorbid conditions and if appropriate multidisciplinary care has the potential of optimizing long-term patient outcomes.

This text offers an overview of the various relevant aspects in the dermatological psoriasis assessment, while emphasizing the importance of a holistic approach. In concordance with real practice, the structure of a clinical consult is respected throughout this manuscript. The demographics of the patient as well as the personal and family history, the drug history, current psoriasis-related history and clinical examination are addressed. Finally guidelines are provided for further investigations, treatment initiation and follow-up. Gathering this information in a preset electronic patient file template (see Tables 1 to 7) has the advantage of offering an anchor during consultation. Additionally it has the potential of creating a database on which information can be retrieved retrospectively.

Demographics (Table 1)

Basic demographic information includes sex, age, ethnicity, skin phototype and family planning. *Sex and age* influence treatment choices and dosage of certain drugs[3]. Ethnicity has an impact on the pharmacokinetics of an individual[4] as well as psoriasis prevalence[5]. *Employment status* and work productivity on the other hand, can be negatively influenced by psoriasis and psoriasis arthritis [6,7]. S*kin phototype* offers information about the ability to burn or tan when exposed to ultraviolet (UV) radiation, and is classified using the Fitzpatrick scale [8]. This needs to be considered in phototherapy risk assessment, where pigmented skin may confer more protection against skin cancer[9]. When recording past UV exposure it is also important to find out about UV habits (ea. sunbeds and sunny holidays).

Asking about the *family planning* is of importance because hormonal changes in pregnancy and post partum influence psoriasis. In the study of Murase et al 55% of the patients reported improvement of psoriasis during pregnancy, 21% reported no change and 23% reported worsening.[10] Furthermore, there are pregnancy-related complications that can be caused by both disease and treatment [11]. Therefore, the minimum recommended drug-free interval before conception is 3 months for men and women taking methotrexate and 2 years for women with retinoids[12]. It is also advised to stop biologic agents in advance, assuring the fetus is drug free during the first 12 weeks of critical development. Though, recent data suggest that pregnancies in women exposed to TNFα antagonists seem to have similar outcomes to those of unexposed pregnancies [13]. During the pregnancy itself emollients, topical steroids (mild to potent), dithranol and ultraviolet B are safe. Relatively safe are very potent topical steroids (in small quantities) and oral cyclosporine. Topical coal tar products are not recommended in the first trimester of the pregnancy because of teratogenicity but are

probably safe for use in the second and third trimesters. Prohibited treatments are retinoids , calcipotriol derivates, methotrexate and psoralen plus ultraviolet A (PUVA) therapy. Fumaric acid esters and biological agents still have unknown effects. In breastfeeding moms cyclosporine, retinoids, calcipotriol derivates, methotrexate, PUVA, fumaric acid esters and biologic agents should be avoided[12]. As family planning is a dynamic piece of information that may change over time Table 1 needs to be revisited frequently while bearing this in mind.

Personal and family medical history (Table 2)

The personal history of the patient should comprise onset of psoriasis, presence of related diseases, psychosocial problems and other comorbidities. Additionally, a concise family history should be obtained.

Although possible at any age, a bimodal distribution of *age of onset* is observed. Type I is the early onset type, beginning before or at the age of 40 years, with a peak at the age of 15 to 20 years. It accounts for more than 75% of the psoriasis patients and disease tends to be more severe. Furthermore, more relatives seem to be affected in this type and associations have been reported with human leucocyte antigen (HLA)-CW6. Type II psoriasis begins after the age of 40 years, mostly occurring at 55 to 60 years [14-16].

One of the psoriasis related diseases is *psoriatic arthritis (PsA),* a chronic inflammatory joint disease, usually negative for rheumatoid factor. Its prevalence among psoriasis patients is about 11% [17], but varies widely [18]. Because cutaneous lesions frequently precede joint manifestations, dermatologists are uniquely positioned for early detection[19]. Additionally, psoriasis is considered to be one of the *immune-mediated inflammatory disorders* (IMIDs)[20], intrinsically having a higher risk for the development of other IMIDs[21]. Among others, associations have been made for psoriasis with inflammatory bowel disease [22,23], multiple sclerosis [24,25], uveitis[26], lupus erythematosus [27], rheumatoid arthritis[27], alopecia areata [28] and coeliac disease[29].

Other comorbidities include *multiple malignancies*[30-34] such as non melanoma skin cancer and lymphomas. Responsible factors could comprise behavioral risk factors, psoriasis itself and/or the psoriasis treatment (e.g. PUVA[35,36], cyclosporine [35,37], methotrexate [35,38,39], and some biologic therapies[35]). *Metabolic disorders* such as hypertension[40], insulin resistance [40-44], obesity [45-48] and hyperlipidemia[49,50] have also been associated with psoriasis. Taken together, the metabolic syndrome is far more prevalent compared to the general population [51-54],

increasing the risk for type 2 diabetes[55] and *cardiovascular diseases* [56-58]. Next to obvious behavioral risk factors, it is hypothesized that chronic systemic inflammation in psoriasis would be the cause of insulin resistance, leading to endothelial cell dysfunction and atherosclerosis [59]. In addition, severity of psoriasis seems to be related in a positive dose-response manner with the severity of complications [53,58,60]. As a result, dermatologists should take a pro-active role in cardiovascular prevention in this population at risk[61], starting screening in moderate to severe psoriasis from the age of 20 years [62,63]. Further investigations regarding surveillance these possible comorbidities will be discussed in detail in a separate section later in this text.

The psychosocial burden of psoriasis affects all facets of a patient's life including relationships, social activities, work and emotional wellbeing [64-67]. There is an increased risk of depression, anxiety, and suicide [68,69], even in pediatric patients [70]. *Other aspects* of potential importance in the personal history, especially when giving certain drugs, are serious infections (e.g. tuberculosis), liver disease, heart failure, neurologic disease, uncontrolled hypertension, renal disease or malignancy [3,71].

Next to a personal history, *family history* of psoriasis or related diseases (e.g. IMIDs) should be asked for, as psoriasis is a condition that is frequently seen in patients with genetic predisposition. It is estimated that the risk for a child to develop psoriasis is one chance on four when one parent has psoriasis. If one of two identical twins has psoriasis, there is a 70% risk of developing the condition for the other twin[72].

Drug history and vaccination status (Table 3)

Medical treatments and vaccinations could also be important for future treatment decisions. Knowledge of *current and past psoriasis medication* with their effects and side-effects, is important to correctly adjust the treatment of the patient. As PUVA poses a risk of cutaneous carcinogenicity, patients' cumulative exposure to therapeutic UV light should be monitored and limited[73]. Biologic therapy or cyclosporine treatment is relatively contraindicated in patients with a high cumulative dose of previous PUVA [3]. *Non-psoriasis medication* gives valuable information about the existing comorbidities as well as potential drug interactions[3]. In addition, some treatments can provoke or aggravate psoriasis, such as beta blockers, angiotensin-converting enzyme-adrenorecepter inhibitors, gold salts, non-steroidal anti-inflammatory drugs, anti-malaria medicines, lithium and mepacrine. Exacerbation of psoriasis

due to adrenergic antagonists, interferon, gemfibrozil, iodine, digoxin and clonidine has also been observed [74].

The *vaccination status* is of importance when giving immunosuppressive medication [3,71]. Administration of the standard vaccinations preferably at least 2 weeks before starting therapy, is recommended to ensure optimal immune responses. However, inactivated or subunit-based vaccines (e.g. the human papilloma, influenza and pneumococcal vaccine) are generally safe and can be considered sufficiently effective during immunosuppression[73,75]. Because of the risk of reactivation, live and live-attenuated vaccines (e.g. varicella, yellow fever, and typhoid) should be avoided [75].

Current history (Table 4)

The current history offers the dermatologist a good idea of the disease course, while correlating this with treatment and environmental influences. Special attention is also warranted for the psychosocial impact of the disease.

The *stability of the skin lesions* should be evaluated at every visit, so proper adjustments to the therapy can be made. Ask for common triggers for psoriasis such as stress, infections, skin trauma, medication and cold weather [76,77]. Screening for *psoriatic arthritis* should include asking about joint pain, morning stiffness, swelling, decreased range of motion and fatigue[78]. The interested dermatologist can also use validated screening questionnaires for assessment of joint status, e.g. the Toronto Psoriatic Arthritis Screening or the Psoriatic Arthritis Screening and Evaluation [79].

Environmental influences seem to have a crucial role as trigger for psoriasis. For example smoking is linked to psoriasis onset (especially pustular [80,81]) [46,82,83] as well as clinical severity [84,85]. Likewise alcohol consumption is related to the onset [86], severity [87] and reduced treatment response[88] in psoriasis, with even an increased risk of death [89]. A healthy diet also positively influences skin lesions[90] and response to therapy (e.g. cyclosporine [91]). Additionally, life style behavior can also influence cardiovascular risk.

Adequate *drug surveillance* includes assessing patient adherence to the treatment as well as potential side-effects. It can be necessary to ask for symptoms of concurrent infections (e.g. tuberculosis), heart failure, neurological disease, liver disease, malignancies or other complications[92]. Dermatologists should verify whether major surgery is foreseen in the future, and if so discontinue biologic therapy at least four half-lives prior to the surgery[92].

The *psychosocial impact* of psoriasis plays a substantial role in the perception of disease severity, quality of life, and disease course. Nevertheless, this topic remains largely unrecognized and undertreated[93], as the impact experienced by patients is not always proportional to standard measurements of disease severity [94]. Simply asking questions about depressed mood, anxiety or suicidal intentions could help detecting a need for psychosocial help [95]. Several health-related quality of life indicators have also been reported, of which the dermatology life quality index (DLQI) and the Skindex-29 are the two most commonly used outcome parameters in dermatology [96].

Clinical examination (Table 5)

Clinical examination should not be limited to skin, nail and joint investigations. Signs related to the drug treatment or cardiovascular comorbidity also need to be considered.

The localization, phenotype and severity of the *psoriasis skin lesions* must be monitored. Chronic plaque psoriasis, inverse psoriasis, guttate psoriasis, erythrodermic psoriasis and generalized or palmoplantar pustular psoriasis all have their specific trigger factors and prognosis[97]. However, there is a possible overlap in symptoms and sometimes one type can evolve into another throughout a patient's life. When assessing the clinical disease severity of the skin the most commonly used tools are the body surface area (BSA) and the psoriasis area and severity index (PASI) [96].

Coexistent *nail involvement* is found in up to 55% of the psoriasis patients, and even up to 90% of the patients with psoriatic arthritis [77]. The Nail Psoriasis Severity Index (NAPSI) is a reproducible, objective simple scale used to evaluate the severity of nail bed psoriasis and nail matrix psoriasis [98]. *Rheumatologic examination* includes screening for psoriatic arthritis when complaints of joint problems are present. Redness, swelling and pain, indicating characteristics such as enthesopathy, dactylitis and arthritis should be investigated, since early treatment interventions can prevent irreversible joint destruction and disability [99-101].

Drug- related examination implies looking for clues of infection or malignancy, especially when taking immunosuppressant therapy. Total body examination comprises exclusion of actinic damage, cutaneous malignancies, herpes and viral warts, or managing these conditions appropriately. Signs related to liver, neurologic, cardiac or hematological diseases are also of relevance [71]. Blood pressure measurement and regular weighing can be appropriate e.g. in cyclosporine treatment [3]. Implementation of *cardiovascular screening* for psoriasis patients is

only very limited, despite the existence of various guidelines[62,63,79,103]. At least every 2 years a measurement of blood pressure, pulse, body mass index (BMI) and abdominal circumference should be done, with referral to a specialist if necessary (see Table 5 for target values) [62,63,79,102].

Further investigations (Table 6)

Depending on the individual situation, further investigations can include e.g. laboratory studies, medical imaging, skin tests and biopsies.

Rheumatologic investigations such as laboratory studies (e.g. rheumatoid factor) and medical imaging (e.g. ultrasonography for swollen joints and radiography for joint malformations) can be done by the dermatologist or a rheumatologist in referral, depending on the personal expertise. As dermatologists have a primary role in the prevention, screening and follow-up of cardiovascular diseases in psoriasis, c*ardiovascular surveillance* became a hot topic [103]. Several guidelines have been suggested, however with different target values and screening intervals [102,104]. Summarized, a yearly standard fasting lipid profile and at least 3-yearly fasting blood glucose measurement are recommended. C-reactive protein (CRP) or high-sensitivity CRP should also be determined as they represent the activation of cytokines driving inflammation, linking them to atherosclerosis[105]. CRP assays only report levels > 3 mg/L. However, the hs-CRP assay reports levels as low as 0.1 mg/L, and is of better use in cardiovascular risk stratification. Patients with hs-CRP levels < 1 mg/L are categorized as having lower relative risk, while those with levels of 1 to 3 mg/L are at intermediate risk, and those with levels > 3 mg/L are at higher relative risk for cardiovascular events.[106] Optional screening parameters (e.g. hemoglobin A1c, microalbuminuria, lipoprotein-associated phospholipase A2 and sex hormone binding globulin [107,108]) can be used, but the gains over conventional cardiovascular risk factors are minimal[109].

Drug surveillance is warranted to detect associated side-effects. As methotrexate, retinoids and cyclosporine represent the first line systemic treatment in Europe for psoriasis insufficiently controlled with topical agents or phototherapy, these treatments will be discussed in further detail as well as the frequently used biologic therapies.

Patients on biologicals [71,75,110] need laboratory studies at baseline, month 3 and then every 6 months with determination of complete blood count, kidney and liver function and pregnancy testing. Baseline hepatitis panel and Human Immunodeficiency Virus (HIV) serology can be

periodically reassessed in those at risk. Measuring antinuclear antibodies should be limited only to situations suspicious for a lupus-like syndrome [75,111]. An echocardiogram is recommended in patients with NYHA class I and II cardiac failure, as TNF antagonist therapy should not be given if the ejection fraction is lower then 50% of the normal. Screening for tuberculosis consists of a chest radiograph, purified protein derivative skin test or interferon gamma release assay in suspicious cases (suspicion of false positive or false negative Mantoux testing). Although not mandatory, annual tuberculosis testing is recommended.

Baseline evaluations for methotrexate [112-114] include a chest radiograph and blood examination with blood count, renal function tests, liver chemistry, procollagen III (PIIINP), pregnancy testing, and hepatitis B, C and HIV serology tests if indicated. Folic acid supplementation is necessary. In selected cases baseline liver biopsy (e.g. in persistently abnormal PIIINP) and tuberculosis screening are considered. Laboratory studies (blood count, liver and renal function) should be continued every 2 weeks for 6 weeks after the last dose change, monthly thereafter until stabilized and then every 2 to 3 months. In the presence of risk factors or a cumulative dose of methotrexate greater than 1.5 g, monitoring of hepatic fibrosis may include either measuring PIIINP every 3 to 6 months or performing a Fibroscan and/or Fibrotest once a year [114]. Hepatologist opinion and liver biopsy are considered in patients with chronically elevated PIIINP [114] or every 3.5 to 4.0 g of total cumulative methotrexate dose [112].

Patients treated with cyclosporine require screening of renal function at baseline, weeks 2, 4, 6 and 8 and then monthly thereafter [3]. Other laboratory investigations should be taken initially monthly and thereafter pending the course of therapy. Determination of cyclosporine serum concentrations is not part of the routine monitoring. Baseline tuberculosis screening and pregnancy testing are recommended. Patients should also attend their dentist at 6-month intervals to monitor for gingival hypertrophy [3].

In acitretin therapy [115] a pregnancy test within 2 weeks prior to therapy is crucial. At baseline one should also check the liver function, fasting cholesterol and triglycerides. These investigations should be repeated every 2 to 4 weeks for the first 2 months, and then every 3 months. Other baseline investigations include complete blood count, renal function and fasting glucose. Musculoskeletal pain is common and targeted radiographic investigation is only recommended if the pain is atypical [114]. Children taking acitretin should have their growth charted.

Skin biopsy is sometimes necessary for histologic confirmation of the diagnosis of psoriasis or skin side effects during therapy[116].

Treatment (Table 7)

Optimal psoriasis management begins with educating the patient, making shared decision making possible. The treatment can comprise pharmacotherapy, behavioral modifications and multidisciplinary assessments. Clear recommendations should be given concerning the next follow-up appointment.

Education and patient empowerment make it possible for patients to participate in the decision-making process, leading to improved adherence[117] and better quality of life[118]. Better understanding of the complex relationship with other health issues such as cardiovascular risk, may make patients more motivated for behavioural modifications such as a healthy diet, physical activity, smoking cessation and cutting down on alcohol consumption. *Pharmacotherapy* includes local or systemic psoriasis treatments and vaccinations (e.g. influenza and pneumococcal vaccination during immunosuppressant therapy)[71]. Additionally it can be necessary to deal with comorbidities (e.g. lipid lowering drugs) or side-effects of psoriasis therapy (e.g. folic acid supplementation and methotrexate[113]).

Referral to a specialist team of interest can be necessary, as management of psoriasis patients is shifting towards a more multidisciplinary approach. *Regular assessments* are advised to monitor disease severity, comorbidity, adverse-effects of the treatment, and patient adherence. Evaluation of well-controlled localized disease with moderate-strength topical steroids or topical retinoids can be done every 6 to 12 months[77]. Potent topical steroids, systemic treatment or complications require more frequent follow-up depending on the individual situation.

Conclusion and discussion

Psoriasis is a complex multisystem disease, complicated with comorbidities and complex treatment options warranting good clinical and biochemical follow-up. Therefore dermatologists are in need of a comprehensive practice guidance addressing all relevant aspects for a holistic approach to the psoriasis patient. In this manuscript, a template is proposed which can be integrated in the currently used electronic patient file, thereby minimizing the chances of forgetting certain aspects of psoriasis management. Additionally it

gives the potential of retrospectively gathering information out of the electronic system based on certain prefixed indexes (ea. gathering all patients with a family history of psoriasis).

However, to make this consultation proposal practical one might have to reevaluate current practice organization. There is a potentially important role for a specifically trained psoriasis nurse practitioner in educating, measuring and weighing the patient, as well as taking questionnaires and clinical severity scores. The advantage of much of this would be for audit and research purposes. If not feasible in the private dermatological practice, one can use an adapted “light” version of this exhaustive proposal for the electronic patient file. However, it does serve to remind dermatologist and patient of the wider implications of the disease. A potential application of this would be for the patient to have a hand held or electronic record which could serve as a checklist for the whole team caring for the patient. As a busy dermatologist does not always have the time (or sometimes skills) to assess or initiate therapy for certain comorbidities, the patient’s general practitioner could assume responsibility for assessment of these factors, working as a team.

Additionally, there is a continuous need for updating and optimizing every aspect of the consultation as new evidence and knowledge arise. The example as provided here, should therefore not be seen as a static and rigid example for a patient file. It is rather an attempt to foresee in a dynamic and adaptable prototype of how to address the individual patient, with differing emphasis for one person to the other depending on patient-specific factors.

Tables

Table 1: DEMOGRAPHICS			
Parameter	**Prefixed choice options**		**Text space**
Age			Specify
Sex	Male		
	Female		
Ethnic group	Caucasian		
	Asian		
	African		
	Other		Specify
Phototype	I		
	II		
	III		
	IV		
	V		
	VI		
UV habits	use of tanning parlors	Yes	
		No	
	regular total body sun exposure	Yes	
		No	
Employment	Active		Specify
	Non-active		Specify
Family planning	Current pregnancy		Specify
	Pregnancy plans		Specify
	Breast feeding		Specify
Multiple choice boxes can be checked for one parameter.			

Table 2: PERSONAL AND FAMILY MEDICAL HISTORY		
Parameter	**Prefixed choice options**	**Text space**
Psoriasis	Age start skin lesions	*Specify*
	Evolution	*Specify*
Psoriatic artritis	Absent	
	Present	*Specify treating rheumatologist*
	Unknown	*Specify*
Immune-mediated disorders	Other joint suffering then PsA (ea. Rheumatoid arthritis)	*Specify diagnosis and treating rheumatologist*
	Uveitis	*Specify*
	Spondylarthropathy	*Specify*
	Inflammatory bowel disease	*Specify: Crohn/colitis ulcerosa*
	Coeliac disease	*Specify*
	Vitiligo	*Specify*
	Diabetes mellitus type 1	*Specify*
	Multiple sclerosis	*Specify*
	Lupus	*Specify*
	Alopecia areata	*Specify*
	Thyroid disease	*Specify*
	Other	*Specify*
Cardiovascular and metabolic disorders	Ischemic heart disease	*Specify*
	Cerebrovascular accident	*Specify*
	Peripheral artery disease	*Specify*
	Hypertension	*Specify*
	Diabetes mellitus type 2	*Specify*
	Obesity (BMI >30)	*Specify*
	Hyperlipidemia	*Specify*
Malignancies	Lymphoma	*Specify*
	Non melanoma skin cancer	*Specify*

	Melanoma skin cancer	*Specify*
	Other	*Specify*
Mental health	Depression	*Specify*
	Suicidal ideations	*Specify*
	Anxiety disorders	*Specify*
	Other	*Specify*
Other personal history	Dermatological	*Specify*
	Non-dermatological	*Specify*
	Allergy	*Specify*
Family history	Psoriasis	*Specify*
	Psoriatic artritis	*Specify*
	Immune-mediated disorders	*Specify*
	Cardiovascular and metabolic disorders	*Specify*
	Malignancies	*Specify*
	Mental health	*Specify*
	Other	*Specify*

Table 3: DRUG HISTORY AND VACCINATION STATUS

Parameter	**Prefixed choice options**	**Text space**
Vaccination status	Pneumococcus	*Specify date last administration*
	BCG	*Specify date last administration*
	Influenza	*Specify date last administration*
	Other	*Specify vaccine and date of administration*
Non-psoriasis medication		*Specify*
Past psoriasis treatments	Topical	*Specify (effect, side-effects, period)*
	Systemic	*Specify (effect, side-effects, period)*
	UV light therapy	*Specify (effect, side-effects, total dose to date, date of last treatment, course lenght)*
Current topical psoriasis	Corticosteroids	*Specify (effect, side-effects, period)*

treatment		
	Vitamin D3	*Specify (effect, side-effects, period)*
	Retinoids	*Specify (effect, side-effects, period)*
	Tar Products/Dithranol	*Specify (effect, side-effects, period)*
	Other	*Specify (treatment, effect, side-effects, period)*
Current systemic psoriasis treatment	Methotrexate	*Specify (effect, side-effects, period)*
	Cyclosporin	*Specify (effect, side-effects, period)*
	Retinoids	*Specify (effect, side-effects, period)*
	Corticosteroid	*Specify (effect, side-effects, period)*
	Leflunomide	*Specify (effect, side-effects, period)*
	Sulfasalazine	*Specify (effect, side-effects, period)*
	Infliximab	*Specify (effect, side-effects, period)*
	Etanercept	*Specify (effect, side-effects, period)*
	Adalimumab	*Specify (effect, side-effects, period)*
	Ustekinumab	*Specify (effect, side-effects, period)*
	Fumaric acid	*Specify (effect, side-effects, period)*
	Other	*Specify (treatment, effect, side-effects, period)*
Current light therapy	PUVA	*Specify (effect, side-effects, total dose to date, date of last treatment, course lenght)*
	Broadband UVB	*Specify (effect, side-effects, total dose to date, date of last treatment, course lenght)*
	Narrowband UVB	*Specify (effect, side-effects, total dose to date, date of last treatment, course lenght)*
	Excimer laser	*Specify (effect, side-effects, period)*
BCG: Bacille Calmette Guérin, PUVA: psoralen plus ultraviolet A, UVB: Ultraviolet B		

Table 4: CURRENT HISTORY		
Parameter	**Prefixed choice options**	**Text space**
Disease course		

Skin lesions	Stable		*Specify*
	Positive evolution		*Specify*
	Negative evolution		*Specify*
Current skin symptoms	Itch		*Specify*
	Pain		*Specify*
	Bleeding		*Specify*
Triggers	Infection		*Specify*
	Stress		*Specify*
	Medication		*Specify*
	Koebner phenomenon		*Specify*
	Cold weather		*Specify*
	Other		*Specify*
Joint complaints	Absent		
	Peripheral	nocturnal pain with awakening	*Specify*
		morning stiffness	*Specify*
		swelling 1 or multiple joints	*Specify*
	Axial	nocturnal pain with awakening	*Specify*
		morning stiffness	*Specify*
		swelling 1 or multiple joints	*Specify*
Behavioral risk factors and lifestyle			
Activity	No activity		
	Mild activity		
	Moderate activity (<4x/week during 30 min)		
	Intense activity (>4x/week during 30 min)		
Alcohol	No		
	Yes		*Specify*
Smoking	No		
	Yes		*Specify*
Diet	No		

	Yes	*Specify*
Drug surveillance		
Side-effects	No	
	Skin problems	*Specify*
	Non-skin problems	*Specify*
Future elective surgery	No	
	Yes	*Specify*
Adherence	No	*Specify*
	Yes	*Specify*
Psychosocial impact		
Psychological problems	Depression	*Specify*
	Anxiety Disorder	*Specify*
	Suicidal ideations	*Specify*
Dermatological life quality index (DLQI)		*Specify score*
Skindex-29		*Specify score*

Table 5: CLINICAL EXAMINATION		
Parameter	**Prefixed choice options**	**Text space**
Psoriasis phenotype	Psoriasis vulgaris	*Specify if necessary*
	Inverse psoriasis inversa	*Specify if necessary*
	Guttate psoriasis	*Specify if necessary*
	Erythrodermic psoriasis	*Specify if necessary*
	Generalized pustular psoriasis	*Specify if necessary*
	Pustular psoriasis on palms and soles	*Specify if necessary*
Localization psoriasis	Hairy scalp	*Specify if necessary*
	Facial	*Specify if necessary*
	External auditory	*Specify if necessary*
	Genital and/or perianal	*Specify if necessary*
	Hand and feet	*Specify if necessary*

	Nails	*Specify if necessary*
	Intertriginous areas	*Specify if necessary*
	Lower limbs	*Specify if necessary*
	Upper limbs	*Specify if necessary*
Scores	PASI	*Specify score*
	BSA	*Specify score*
	NAPSI	*Specify score*
Joints	Absent	
	Dactylitis	*Specify*
	Enthesitis	*Specify*
	Arthtitis	*Specify*
Drug- related examination	Viral skin infections	*Specify*
	Skin (pre)canceroses	*Specify*
	Signs of infection	*Specify*
	Signs of malignancy	*Specify*
	Other	*Specify*
Tension (mmHg) *(target value: < 140-120 mmHg systolic and < 90-80 mmHg diastolic)*		*Specify*
Pulse (pm)		*Specify*
Length (m)		*Specify*
Weight (kg)		*Specify*
BMI *(target value: < 25kg/m2)*		*Calculated*
Abdominal circumference *(target value: < 102 cm in male and < 88 cm in women)*		*Specify*
Additional remarks		*Specify*
PASI: Psoriasis Area and Severity Index, BSA: Body Surface Area, NAPSI: NailPsoriasis Severity Index, BMI: Body Mass Index		

Table 6: FURTHER INVESTIGATIONS		
Parameter	**Prefixed choice options**	**Text space**
Cardiovascular profile	Fasting lipid profile *(target values: total cholesterol < 200 mg/dL,*	*Specify*

	high-density lipoprotein cholesterol ≥ 50 mg/dL, low-density lipoprotein cholesterol < 100 mg/dL)	
	Fasting blood glucose *(target value: < 100 mm/dL)*	*Specify*
	CRP	*Specify*
Drug surveillance	Acitretin	
	Liver function	*Specify*
	Fasting serum cholesterol and triglycerides	*Specify*
	Renal function	*Specify*
	Fasting glucose	*Specify*
	Sedimentation	*Specify*
	Creatin kinase	*Specify*
	Pregnancy test	*Specify*
	Radiological investigations	*Specify*
	Methotrexate	
	Complete blood cell and platelet count	*Specify*
	Renal function	*Specify*
	Liver function	*Specify*
	Procollagen III	*Specify*
	Hepatitis B and C and HIV serology	*Specify*
	Pregnancy test	*Specify*
	Chest radiograph	*Specify*
	Tuberculosis screening	*Specify*
	Liver biopsy	*Specify*
	Cyclosporine	
	Complete blood cell and platelet count	*Specify*
	Renal function	*Specify*
	Glomerular filtration rate	*Specify*
	Uric acid	*Specify*
	Magnesium and potassium	*Specify*

		Liver function	*Specify*
		Fasting lipid profile	*Specify*
		Pregnancy test	*Specify*
		Urinalysis	*Specify*
		Tuberculosis screening	*Specify*
		Dental screening	*Specify*
	Biological		
		Complete blood cell and platelet count	*Specify*
		Renal function	*Specify*
		Liver function	*Specify*
		Hepatitis B and C and HIV serology	*Specify*
		Anti-nuclear antibodies	*Specify*
		Anti-drug antibodies	*Specify*
		Pregnancy test	*Specify*
		Urine analysis	*Specify*
		Chest radiograph	*Specify*
		Tuberculosis screening	*Specify*
		Echocardiogram	*Specify*
	Other		*Specify*
Biopsy	No		
	Yes		*Protocol*
CRP: C-reactive proteine			

Table 7: INITIATED TREATMENT		
Parameter	**Prefixed choice options**	**Text space**
Topical treatment	Corticosteroids	*Specify (period and frequency)*
	Vitamin D3	*Specify (period and frequency)*
	Retinoids	*Specify (period and frequency)*
	Tar Products/Dithranol	*Specify (period and frequency)*

	Other	*Specify (treatment, period and frequency)*
Systemic psoriasis treatment	Retinoids	*Specify (period and frequency)*
	Methotrexate and folic acid	*Specify (period and frequency)*
	Cyclosporin	*Specify (period and frequency)*
	Corticosteroid	*Specify (period and frequency)*
	Infliximab	*Specify (period and frequency)*
	Etanercept	*Specify (period and frequency)*
	Adalimumab	*Specify (period and frequency)*
	Ustekinumab	*Specify (period and frequency)*
	Other	*Specify(treatment, period and frequency)*
Light therapy	PUVA	*Specify (period and frequency)*
	UVB	*Specify (period and frequency)*
	Excimer laser	*Specify (period and frequency)*
New vaccinations		
Other		
Information and advise		*Specify lifestyle advise*
Referral	No	
	Yes	*Specify reason and advice*
Next appointment		*Specify follow-up interval*

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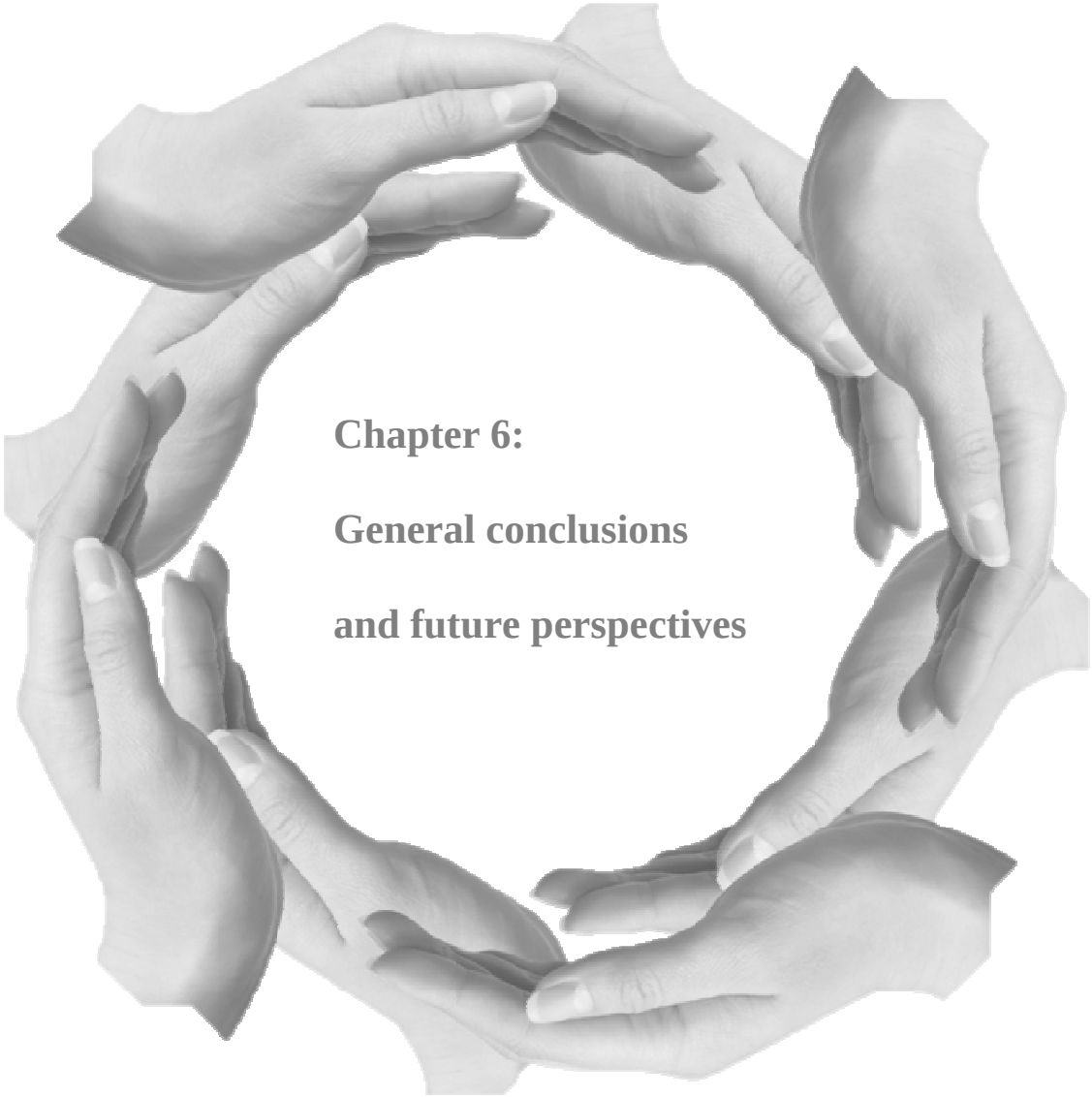

Chapter 6:

General conclusions

and future perspectives

Chapter 6: General conclusions and future perspectives

The present thesis intended to gain more insight in improving the quality of care for psoriasis patients. Therefore, three aims were formulated in Chapter 2.

In this chapter, a summary of the major conclusions and future perspectives of the presented articles will be given and discussed. In addition, we will discuss what we learned from this thesis and what could be improved. Lastly, clinical implications of this thesis will be given.

Aim 1: To acquire new insights in the complex association between psoriasis, psoriatic arthritis and metabolic syndrome (Chapter 3)

We performed a cross-sectional study in 123 patients with psoriasis of the skin (PsO) and psoriasis arthritis (PsA). We found that prevalence of the metabolic syndrome according to the criteria of the International Diabetes Foundation was significantly higher in the PsO (44,9%) compared to the PsA group (25,5%) (p=0,037). Looking closer at the individual components of the metabolic syndrome, this difference can mainly be attributed to the significantly higher prevalence of abdominal obesity in PsO (83,7%) versus PsA (65,5%) (p= 0,034). This association was even enhanced after multivariate adjustments for confounding factors such as age, disease severity, disease duration, systemic therapy and systemic inflammation. These findings suggest that screening for metabolic syndrome should be considered especially in the group of PsO patients. Furthermore, we suspect an undertreatment of the cardiovascular risk factors in our study population. Managing cardiovascular risk by initiating preventive cardiovascular pharmacotherapy and life style modifications is essential in these patients.

In future studies, the causality of the association between PsO, PsA and metabolic syndrome should be further elucidated. Long-term data should be acquired on the impact of earlier intervention with systemic therapies in psoriasis. In particular, the effect of biologics on cardiovascular and metabolic comorbidities should be elucidated. This may have important implications for the choice of treatment.

Furthermore, future prospective studies should aim at validating biomarkers differentiating PsA from patients with PsO. This enables early detection of PsA in PsO patients. In addition, it allows differentiating PsO from PsA for future research.

Aim 2: To evaluate the added value of the Ghent University educational programme (Chapter 4)

We conducted a randomized controlled trial (RCT) in adult patients with psoriasis and atopic dermatitis to evaluate the added value of our 12 week educational programme consisting of education about skin diseases and life style factors and stress-reduction techniques. We found two major conclusions of this study: Firstly, in our RCT we found an improvement in disease severity, quality of life and depression status after the educational programme for psoriasis patients but not for atopic dermatitis patients. Psoriasis patients in the intervention group showed a significant reduction in mean PASI (p=0.036), mean Dermatology Life Quality Index (p=0.019), mean Psoriasis Disability Index (p=0.015) and mean Beck Depression Inventory (p=0.029), compared with the control group after the programme. Similar to this, we found that in general there is more evidence according to literature for the effectiveness of the different components of the educational programme for psoriasis compared to atopic dermatitis. (Table 1)

Table 1: Evidence for different components of the educational programme in patients with psoriasis and atopic dermatitis according to literature.

	Psoriasis	**Atopic dermatitis**
1. Specific information on skin disease		
a. Information session on skin disease	a[2-4]	a[3,5,6]
b. Skin care	a[2-4]	a[3,5,6]
2. Stress-reduction techniques		
a. Physical training	a[7]	c
b. Yoga	c	c
c. Mindfulness-based stress reduction	b[8]	c
3. Information sessions on life style		
a. Diet	a[9]	c
b. Responsible physical training	a[7]	c
c. Sleep hygiene	b[10]	a[6,11]
d. Smoking cessation	a[12,13]	b[14]
e. Substance abuse	a[15]	c
f. Psycho-dermatology	a[16,17]	b[18]
g. Practical philosophy	c	c
4. Feedback		
a. Individual dermatologist	?	?
b. In group	?	?
a = strong evidence; b = preliminary results; c = no evidence		

Secondly, the improved outcomes for psoriasis patients after the programme continued for at least 3 months after the intervention, but seems to wane after 6 months after the intervention. Therefore, we can conclude that it would be interesting to offer the components of the programme on a more continuous basis.

In our RCT we found that the positive effect of intensive physical activity in the intervention group waned after 9 months follow-up. Hereby, we can conclude that moderate physical activity incorporated in the daily lives of the patients would be a better alternative to maintain these positive effects. This hypothesis should be validated in future studies.

Additional to this, it would be interesting to study the effects of the individual elements of the programme in psoriasis patients. The impact of different stress-reducing techniques and their biological effects on brain and immune function can be an important research topic. Also, the educational part of the programme and its effect on patient outcomes and adherence to therapy should be examined separately.

Furthermore, determination of the external validity of the programme is an important issue. The review of De Bes et al summarises evidence concerning the effects of patient education in patients with chronic skin diseases.[19] They found a moderate external validity in 9 of the 10 RCT's and only 1 had a sufficient external validity. The most important factor that interferes with the generalisability of our educational programme is the resource intensity of the programme. Therefore, we might suggest to organise the educational part of the programme by the centre itself and to work in collaboration with existing centres for sports, yoga and mindfulness. In this context, it is important to agree on a common setting for groups of patients with skin diseases with these centres.

Aim 3: To give an overview of updated relevant aspects in the clinical dermatological assessment of psoriasis patients (Chapter 5)

In this review paper we give a structured summary of relevant aspects in the clinical assessment of psoriasis patients anno 2012. At first, relevant aspects about patient's demographics, personal and family medical history, drug history and vaccination status are discussed. Secondly, clinical examination to assess disease severity and impact on quality of life is reviewed. Special attention is given in the first two items to detect comorbidities and adverse effects of therapy. Thirdly, further investigations are discussed with emphasis on

good pre-treatment screening and therapy follow-up. Lastly, emphasis is given on patient education that makes shared decision making possible and a multidisciplinary approach in the management of psoriasis.

Based on this information, a template is proposed which can be integrated in the currently used electronic patient file. Hereby, we want to give an anchor during consultation and create the potential of gathering information for future research.

What have we learned? What could be improved?

The design of this thesis is oriented to the clinical question: "What can be improved in the care for psoriasis patients?". Therefore, it is of practical use for the clinician treating psoriasis patients. As many different subfields are included, the knowledge of these different areas is difficult to maintain.

Overall, we learned that a good selection of the measurement methods will help to reduce labour-intensiveness of the studies. For this and for the preparation of the design of the study, enough time and experience is needed. Concerning measurement methods, an important part of the process for developing an effective educational intervention is measuring self-efficacy levels. Self-efficacy has been shown to be one of the most consistent predictors of successful self-care behaviour and should therefore be incorporated in future studies on educational programmes.[20] Also, an accurate sample size calculation in advance can prevent difficulties in the progress of the study. Next to this, we noticed that the recruitment of the patients takes a lot of effort, this should not be underestimated in time and labour-intensiveness.

In particular for the RCT about our educational programme, we encountered some difficulties in conducting a pragmatic randomised controlled trial. First of all, randomisation of the patients caused sometimes disappointment when ending up in the control group. Along the way, the patients were better prepared to this randomisation and the disappointment was not as large. Also blinding of the assessors was not an easy task. Patients were told not to mention in which group they were randomised to the assessors but sometimes revealed something about the programme.

In addition, in the reporting of the feasibility study on the Ghent University educational programme (paper 2), we jumped to conclusions too soon. This concerns the following part on page 59 "Furthermore, validated questionnaires revealed that the health related quality of life significantly improved after the intervention. Specifically, women with atopic dermatitis

(n=9) seemed to benefit most from the programme with regard to quality of life." These conclusions are surpassed by the results of our RCT which shows effectiveness in psoriasis patients but not in atopic dermatitis patients.

Unfortunately, we could not show cost-effectiveness of the programme at 6 months. The EQ-5D questionnaire was used to calculate quality adjusted life years needed to measure cost-utility of the programme. Our first problem was that EQ-5D values in intervention group were not significantly better than in the control group. For future studies in dermatology, dermatology life quality index (DLQI) should be a better questionnaire to calculate quality adjusted life years and ultimately cost-utility of an intervention.[21] Next to this, we did not see any difference in medical consumption nor absenteeism between the groups. Therefore, the cost programme per patient could not be lowered by gain in medical resource spending or taking into account absenteeism. In addition, a larger sample size and a longer follow-up period are needed to draw conclusions with regard to cost-effectiveness of the programme.

In the future it could be of help to take this comments into account when setting up and conducting similar studies.

Clinical implications

The results of this thesis show the importance of screening for metabolic and cardiovascular disease, especially in patients with psoriasis of the skin. Besides, previous research showed that early detection of other comorbidities such as psoriatic arthritis is essential to improve outcomes in psoriasis.[22] This can be achieved by increasing awareness among physicians treating psoriasis patients and establishing appropriate screening methods. In addition, psoriasis patients should be supported in lifestyle modifications if indicated such as weight loss, physical activity, stress-reduction, smoking cessation and tackling alcohol abuse. Therefore, organising sports for groups of patients with psoriasis or in general, skin diseases, can be of help. Also, patients at increased risk at developing psoriasis, such as a familial affliction, should be encouraged to maintain a healthy lifestyle (regular physical activity, healthy diet, participation to stress-reduction exercises, smoking cessation and alcohol limitation). Furthermore, patient education improves health outcomes and adherence to therapy and should therefore be integrated in the management of psoriasis.

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Summary

Samenvatting

Résumé

Summary

Psoriasis is a common chronic inflammatory disease affecting approximately 2% of the population in Europe and the United States and is less prevalent elsewhere. Although traditionally psoriasis has been considered a dermatologic disease, it is being recognized that psoriasis is associated with other comorbidities. They may arise from a genetic predisposition, from the side effects of antipsoriatic treatments, from the lifestyles of psoriatic patients or more recently being hypothesized, from the chronic inflammatory nature of psoriasis. The comorbidities in psoriasis may be linked by common inflammatory pathways involving cytokine dysregulation or share a genetic basis. In addition, conditions linked with psoriasis have been associated with increasing rates of considerable morbidity and mortality.

Furthermore, psoriasis has a significant physical, social, and psychological burden. This major impact on patient's quality of life can lead to disruption of daily activities, social relationships and negative self-image. Also, lifestyle factors such as physical inactivity, smoking, alcohol consumption, obesity and stress are of greater importance because of their negative influence on psoriasis and its comorbidities.

In Chapter 1 we look closer at psoriasis anno 2012. The comorbidities associated with psoriasis are discussed. In addition, we discuss the health-related quality of life of psoriasis patients and the lifestyle factors which have an influence on the onset and course of psoriasis. Next to this, we elaborate on the problem of adherence to therapy in psoriasis patients and what can be changed to improve this.

Most common comorbidity in psoriasis is inflammatory arthritis. Psoriatic arthritis usually follows skin manifestations but in approximately 15% it may precede them. The correlation of skin and joint symptoms in patients with psoriasis and psoriatic arthritis can vary considerably. In Chapter 3 we discuss the similarities and differences between psoriasis and psoriatic arthritis with respect to epidemiology, genetics and immunology. Furthermore, we present our first paper on the association of metabolic syndrome in psoriasis versus psoriasis arthritis.

The presence of comorbid conditions in psoriasis patients has important implications for clinical management. The principal aim of therapy is to reduce the burden of the disease over time by controlling symptoms, helping patient to cope with the chronic nature of the disease, reducing psychologic and relational burden and preventing systemic complications and

comorbidities. Therefore, psychological support and support for lifestyle modifications should be given next to optimal medical care. Also, screening for comorbidities is important that makes essential referral possible. Besides, efficiently informing patients through education and improving adherence to therapy may complement standard care. In this context, we present our educational programme for chronic skin diseases in paper 2 and our randomized, controlled trial for psoriasis and atopic dermatitis patients in paper 3. (Chapter 4)

Lastly, in our fourth paper we give a summary of updated relevant aspects in the clinical dermatological assessment of psoriasis patients, emphasizing the importance of a multidisciplinary and holistic clinical approach. (Chapter 5)

In conclusion, with this approach we hope to improve the quality of care for psoriasis patients and ultimately the long-term quality of life in the psoriasis population.

Samenvatting

Psoriasis is een veelvoorkomende, chronische inflammatoire aandoening met een prevalentie van ongeveer 2% in Europa en de Verenigde Staten en komt minder voor elders. Alhoewel traditioneel psoriasis wordt beschouwd als een dermatologische aandoening, wordt het erkend dat psoriasis geassocieerd is met meerdere comorbiditeiten. Deze kunnen ontstaan vanuit een genetische voorbeschiktheid, door bijwerkingen van psoriasis behandelingen, door de levensstijl van de psoriasis patiënten of meer recent geopperd, door de chronische inflammatoire aard van psoriasis. De comorbiditeiten in psoriasis kunnen gemeenschappelijke inflammatoire pathways hebben waarbij cytokine dysregulatie een belangrijke rol speelt of kunnen een genetische basis delen. Daarnaast zijn deze comorbiditeiten in psoriasis geassocieerd met een aanzienlijke morbiditeit en mortaliteit.

Bovendien zorgt psoriasis voor een aanzienlijke fysieke, sociale and psychologische belasting. Deze grote impact op de kwaliteit van leven van de patiënt kan leiden tot verstoring van de dagelijkse activiteiten en sociale relaties en het creëren van een negatief zelfbeeld.

Daarnaast zijn ook de levensstijl factoren zoals fysieke activiteit, roken, alcohol misbruik, obesiteit en stress van groot belang omwille van hun negatieve invloed op psoriasis en de comorbiditeiten.

In hoofdstuk 1 gaan we dieper in op psoriasis anno 2012. De comorbiditeiten geassocieerd met psoriasis worden besproken. We bespreken de invloed van psoriasis op de kwaliteit van leven en de levensstijl factoren die een invloed hebben op het ontstaan en het verloop van psoriasis. Daarnaast, gaan we ook dieper in op het probleem van therapietrouw bij psoriasis patiënten en wat er kan veranderd worden om dit te verbeteren.

De meest voorkomende comorbiditeit in psoriasis is een inflammatoire arthritis. Psoriasis arthritis ontstaat meestal nadat de huidsymptomen reeds aanwezig zijn alhoewel in ongeveer 15% kan het de huidsymptomen voorafgaan. Het verband tussen huid- en gewrichtssymptomen in patiënten met psoriasis en psoriasis arthritis is onduidelijk. In hoofdstuk 3 bespreken we de gelijkenissen en de verschillen tussen psoriasis en psoriasis arthritis op vlak van epidemiologie, genetica en immunologie. Daarnaast, presenteren we ons eerste artikel over de associatie van het metabool syndroom in psoriasis versus psoriasis arthritis.

Het voorkomen van comorbiditeiten in psoriasis heeft belangrijke implicaties voor de klinische aanpak. Het voornaamste doel van de therapie is om de belasting van de ziekte te verminderen na verloop van tijd door beheersing van de symptomen, patiënten te helpen beter om te gaan met de chroniciteit van de aandoening, het verminderen van psychologische en relationele belasting and het voorkomen van systemische complicaties en comorbiditeiten.

Daarvoor zijn naast optimale medische zorg ook psychologische ondersteuning en ondersteuning voor levensstijl veranderingen noodzakelijk. Daarnaast is het belangrijk om te screenen voor comorbiditeiten in psoriasis wat verwijzing naar een specialist ter zake mogelijk maakt. Bovendien is het efficiënt informeren van de patiënten door educatie en hiermee het verbeteren van de therapietrouw een belangrijke aanvulling op de standaard zorg. In deze context, presenteren we ons educationeel programma voor patiënten met chronische huidziekten in artikel 2 en onze gerandomiseerde, gecontroleerde studie voor psoriasis en atopisch eczeem patiënten in artikel 3. (Hoofdstuk 4)

Als laatste geven we een samenvatting van de relevante aspecten in de klinische dermatologische beoordeling van psoriasis patiënten in ons vierde artikel. Hierbij ligt de nadruk op het belang van een multidisciplinaire en holistische klinische benadering. (Hoofdstuk 5)

Kortom, hopen we met deze aanpak de kwaliteit van zorg voor psoriasis patiënten en uiteindelijk de kwaliteit van leven in de psoriasis populatie op lange termijn te verbeteren.

Résumé

Le psoriasis est une affection inflammatoire chronique courante, avec une prévalence d'environ 2% en Europe et aux Etats-Unis. La maladie est moins répandue ailleurs. Bien que, traditionnellement, le psoriasis soit considéré comme affection dermatologique, il est admis qu'il est associé avec plusieurs comorbidités. Celles-ci peuvent être issus d'une prédisposition génétique, des effets secondaires du traitement du psoriasis, du mode de vie des patients, ou, comme suggéré récemment, du caractère inflammatoire de la maladie. Les comorbidités du psoriasis peuvent avoir des filières inflammatoires communes, ou partager une même base génétique. Par ailleurs, ces comorbidités du psoriasis sont associés à une morbidité et mortalité considérables.

Le psoriasis représente une charge physique, psychologique et sociale importante. Cet impact sur la qualité de vie du patient peut provoquer des perturbations dans les activités quotidiennes, les relations sociales et créer une image de soi négative.

Par ailleurs, les facteurs liés au mode de vie, tels que sédentarité, tabagisme, abus d'alcool, obésité ou stress sont encore plus importants de par l'effet négatif sur le psoriasis et ses comorbidités.

Dans le premier chapitre on approfondira le psoriasis anno 2012. Nous discuterons les comorbidités associés avec le psoriasis. De plus nous étudierons la qualité de vie des patients psoriasiques et nous parlerons des facteurs du mode de vie qui influencent l'origine et le cours de la maladie. De plus nous considèrerons le suivi thérapeutique par le patient et les facteurs qui peuvent être améliorés.

La comorbidité la plus courante du psoriasis est une arthrite inflammatoire. L'arthrite psoriasique apparaît en général après les symptômes cutanés; mais dans 15% des cas elle les précèdent. La corrélation entre symptômes cutanés et articulaires chez le patient psoriasique atteint d'arthrite psoriasique est très variable. Dans le troisième chapitre nous considèrerons les similitudes et les différences entre le psoriasis et l'arthrite psoriasique sur le plan épidémiologique, génétique et immunologique. De plus nous présenterons notre troisième article sur l'association du syndrome métabolique dans le psoriasis versus l'arthrite psoriasique.

La présence de comorbidités chez le patient psoriasique a des implications importantes sur la prise en charge clinique. L'objectif principal du traitement est la diminution du fardeau de la

maladie au fil du temps, en maîtrisant les symptômes, en aidant les patients à mieux prendre en charge la chronicité de leur maladie, en diminuant la charge psychologique et relationnelle et en assurant la prévention des complications systémiques et des comorbidités.

Pour cela, à côté de l'optimalisation des soins médicaux, il est nécessaire d'assurer le soutient psychologique et le suivi des modifications du mode de vie. De plus, il est important de détecter les comorbidités dans le psoriasis, afin d'assurer le renvoi du patient vers le spécialiste compétent. Enfin, il est important de compléter les soins de base par une éducation du patient par une information efficace, et ainsi améliorer le suivi thérapeutique par le patient. Dans ce contexte, nous présenterons notre programme éducatif du patient atteint d'une maladie chronique de la peau dans le deuxième article, et notre étude contrôlée et randomisée concernant le psoriasis et les patients atteint d'eczéma atopique dans le troisième article (chapitre 4).

Pour finir, nous donnerons un aperçu des aspects pertinents de l'évaluation dermatologique clinique du patient psoriasique dans notre quatrième article. Nous mettrons l'accent sur l'importance d'une approche clinique multidisciplinaire et holistique (chapitre 5).

Nous espérons améliorer de cette façon, à long terme, la qualité des soins et la qualité de vie de tous les patients atteint par le psoriasis.

Curriculum Vitae

Curriculum Vitae

Personalia

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Education

1995-2001: High school - OLV van Vlaanderen Kortrijk (Science-Mathematics 8h)
2001-2008: Final degree in medicine - University of Ghent (graduated 25/06/2008 with distinction)

Professional experience in dermatology

10/2008-10/2009: Internship dermatology: clinical practice – University Hospital of Ghent
10/2009-12/2012: PhD: Psoriasis more than skin deep: New insights in the presence of comorbidities and search for a better care

Thesis and essay in dermatology

2004-2007: Thesis: ‘Imiquimod in Dermatology’

2007: Essay in the context of acceptance to the dermatology program: ‘De rol van neuromediatoren in het ontstaan en onderhouden van psoriasis en atopische dermatitis en in het symptoom jeuk in deze dermatosen’

Publications

-Bostoen J*, Lambert J*,Geusens B, Bourgois J, Boone J, De Smedt D, Annemans L. A novel multidisciplinary educational programme for patients with chronic skin diseases: Ghent pilot project and first results. Arch Dermatol Res, 2011, 303(1):57-63. *equally contributed (IF_{2011}=2.279)

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-DeCoster E, **Bostoen J**, van Geel N, Lapeere H, Lambert J. A comprehensive approach to psoriasis management in the dermatological practice: a template for patient report anno 2012. Submitted to J Am Acad Dermatol, 2012. (IF_{2011}=3.991)

-Verhaeghe E, Ongenae K, Dierckxsens L, **Bostoen J**, Lambert J. Nonablative fractional laser resurfacing for the treatment of scars and grafts after Mohs micrographic surgery: a randomized controlled trial. Accepted in J Eur Acad Dermatol Venereol, 2012. (IF_{2011}=2.980)

-Nonablative fractional laser resurfacing for the treatment of hypertrophic scars: a randomized controlled trial. Verhaeghe E, Ongenae K, **Bostoen J**, Lambert J. Accepted in Dermatologic Surgery, 2012. (IF_{2011}=1.798)

Abstracts/Posters

- J. Bostoen, S. Bracke, S. De Keyser, J. Lambert. An educational programme for patients with psoriasis and atopic dermatitis: a prospective randomized controlled trial.

-1-3/12/2011: Psoriasis From Gene to Clinic (Londen)

-16-20/03/2012: American academy of dermatology (San Diego)

-18-19/10/2012: Pfizer Dermatology European Faculty Forum (Amsterdam)

-J. Bostoen, L. Van Praet, L. Brochez, H. Mielants, J. Lambert. A cross-sectional study on the prevalence of the metabolic syndrome in psoriasis compared to psoriatic arthritis.

-18-19/10/2012: Pfizer Dermatology European Faculty Forum (Amsterdam)

Lectures

-October 2008: 'Comorbidity' : psoriasis and metabolic syndrome (Psoriasis LigaVlaanderen – Affligem)

-April 2010: Meet-the expert session: psoriasis (Bruges)

-April 2010: 'OnderHUIDs' – an education programme in dermatology (Mechelen)

-June 2010: Psoriasis and metabolic syndrome (LOK group Artevelde 1 - Ghent)

-Sept 2010: Symposium psoriasis reumatology-dermatology: case presentations and literature review (Ghent)

-Dec 2010: Dermatological side-effects of anti-TNF medication (LOK group Gastroenterology –Bruges)

-March 2011: 2h Course about psoriasis for home nurses (Sint-Niklaas)

-Dec 2012: A cross-sectional study on the prevalence of the metabolic syndrome in psoriasis compared to psoriatic arthritis. (postgraduate rheumatology – Zwijnaarde)

Attended international psoriasis conferences

-March 2009: 'Progress en promise: changing practice, changing lives' – Amsterdam (The Netherlands)

-April 2009 : 'Psoriasis, European Accreditation Council For Continuing Medical Education' - Athens (Greece)

-Nov-Dec 2010: '5th European workshop on immune-mediated inflammatory diseases' congres - Sitges-Barcelona (Spain) + masterclass on psoriasis

Participation in Industry-Sponsered Clinical Trials

-2009: Subinvestigator of the TRANSIT study: Stelara for psoriasis

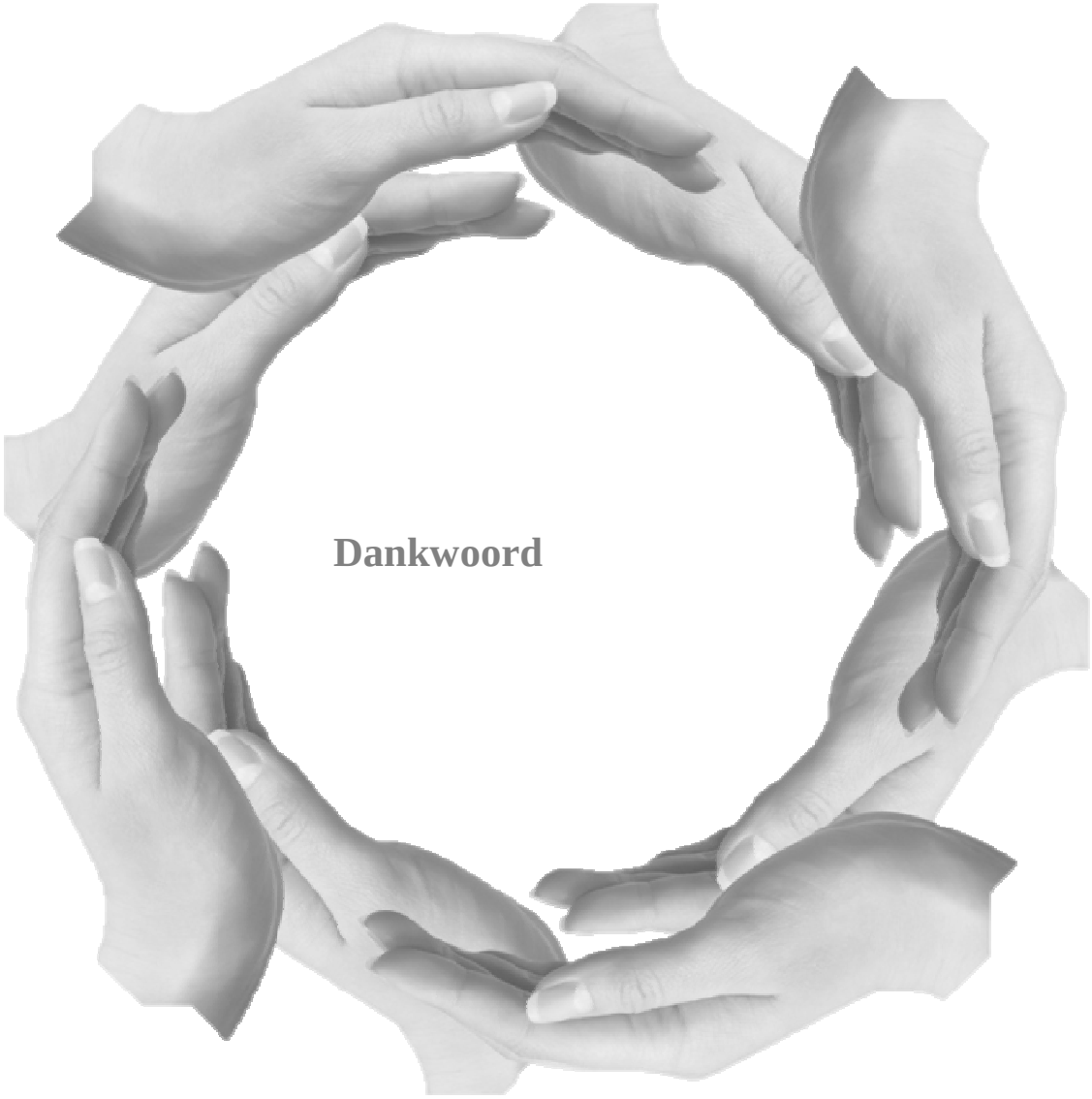
-2010: Subinvestigator of the CADMUS study: Stelara for adolescents

-2010: Subinvestigator of the PREPARE study: Prevalence of Psoriatic Arthritis in Adults with psoriasis

-2010: Subinvestigator of clinical study M04-717: A multicentre, randomised, double-dummy, double-blind study evaluating two doses of adalimumab versus methotrexate in paediatric subjects with chronic plaque psoriasis.

-2010: Subinvestigator of ESTEEM 1 study: A phase 3, multicenter, randomized, double-blind, placebo-controlled, efficacy and safety study of apremilast (CC-10004) in subjects with moderate to severe plaque psoriasis.

-2010: Subinvestigator of PMOS study: Evaluation of Humira retention rate in psoriasis patients in daily practice and assessment of work productivity and quality of life.



Dankwoord

Dankwoord

En natuurlijk geen proefschrift zonder dankwoord!

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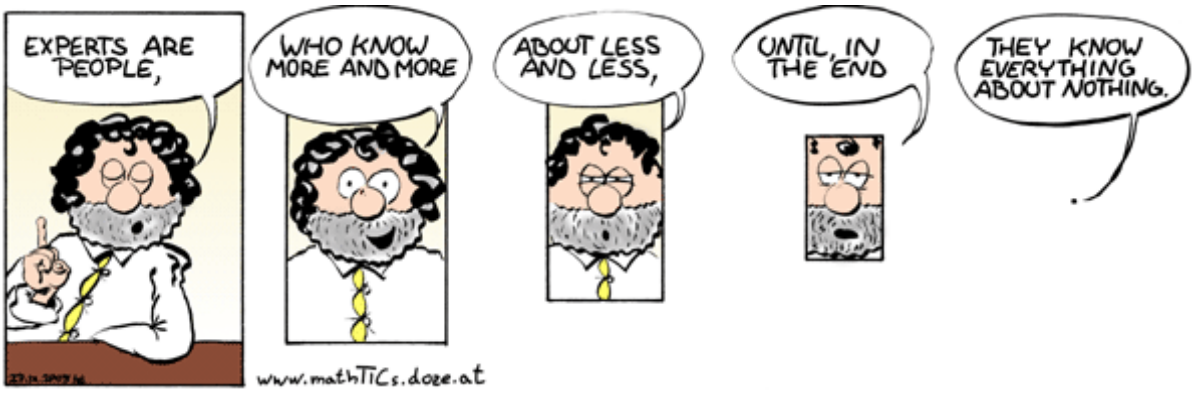
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