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PSORIASIS

Studies of phenotype at onset and of associated cardiovascular morbidity

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The Lotus flower grows in muddy water without adhering to it; a reminder of our inner divine potential to reach total concrete consciousness towards our spiritual perfection though our material life.

ABSTRACT

Psoriasis is a complex inflammatory skin disorder, affecting 2-3% of the population in the western world. The etiology of psoriasis is not yet known. However it is likely that its pathogenesis involves interplay between multiple genetic and environmental triggers.

The aim of this thesis was to study psoriasis phenotypes at disease onset, to explore putative precipitating factors and to investigate cardiovascular morbidity in psoriasis.

Firstly, we established the Stockholm Psoriasis Cohort (SPC), comprising 400 adults (<15 yr) with first-time incidence (<1 yr) of psoriasis disease: 74 had guttate psoriasis and 326 primarily had plaque psoriasis. Different environmental factors were implicated in different phenotypes: guttate psoriasis was associated with younger age and recent infection (84%), while the predominating factor associated with the onset of plaque psoriasis was a recent distinct life crisis (46%).

Secondly, we examined whether or not the prevalence of streptococcal infections in guttate and plaque phenotypes varies in HLA-Cw*0602 positive and negative individuals. Three hundred and seventy five individuals, either with guttate (n=68) or plaque (n=307) psoriasis, derived from the SPC, and a total number of 285 matched controls were included in the study. The study showed that, regardless of phenotype, the prevalence of streptococcal throat infections is double among HLA-Cw*0602 positive psoriatics compared with HLA-Cw*0602 negative patients. No increased prevalence of streptococcal infection was noted among control individuals.

Thirdly to assess the risk for cardiovascular death among psoriasis patients, we used Swedish nation-wide registries to follow up both inpatients and outpatients with psoriasis for cardiovascular mortality. In a cohort of 8991 psoriatic inpatients, followed until 1995, cardiovascular mortality was 50% greater compared with the general population. There was a gradual increase in risk with increasing duration of follow-up, and with increasing number of admissions. The relative risk of death from cardiovascular disease was highest among patients who were admitted at a young age, whereas psoriasis outpatients had no increase in risk. The underlying pathogenesis for such a correlation remains unclear. However multiple factors including systemic inflammation, oxidative stress, aberrant lipid profile and concomitant established risk factors have been discussed.

Fourthly, to assess the blood lipid profile in patients with psoriasis at the initial stage of the disease, 200 patients derived from the SPC were investigated, comparing plasma concentrations of lipids, lipoproteins and apolipoproteins with those of matched controls. Psoriasis patients manifested significant dyslipoproteinemia. Specifically, patients had significantly higher cholesterol concentrations in the very-low-density and high-density lipoprotein fractions compared with controls. Adjustment for established environmental risk factors did not affect the results.

Key words: Psoriasis, guttate psoriasis, precipitating factors, streptococcal infection, life change events, Histocompatibility Antigens Class I (HLA-C), cardiovascular death, atherosclerosis, cardiovascular disease, hyperlipidemia.

LIST OF ORIGINAL PAPERS

This thesis is based on the following papers,
which are referred to by their Roman numerals throughout the text

I ***Mallbris L***, Larsson P, Bergqvist S, Vingard E, Granath F and Stahle M: Psoriasis phenotype at disease onset: clinical characterization of 400 adult cases. Journal of Investigative Dermatology 2005;124 (3):499-504.

II ***Mallbris L***, Granath F, Sakuraba K, Sanchez F and Stahle M: HLA-Cw*0602 associates with a two fold higher prevalence of streptococcal throat infection at the onset of both guttate and plaque psoriasis. *In manuscript*.

III ***Mallbris L***, Akre O, Granath F, Yin L, Lindelof B, Ekbom A and Stahle-Bäckdahl M: Increased risk for cardiovascular mortality in psoriasis inpatients but not in outpatients. European Journal Epidemiology; 19: 225-230, 2004.

IV ***Mallbris L***, Granath F, Hamsten A and Stahle M: Psoriasis is associated with dyslipoproteinemia already at the onset of skin disease. *Submitted*.

CONTENTS

LIST OF ABBREVIATIONS

AGA	serum IgA antibody to gliadin
Apo	apolipoprotein
BMI	body mass index
C	cholesterol
CE	cholesteryl esters
CI	Confidence-interval
CM	chylomicrons
CVD	cardiovascular diseases
EmA	IgA antibodies to endomysium
HDL	high density lipoproteins
HLA	human leukocyte antigen
HR	hazard ratio
hs-CRP	sensitive-C reactive protein
ICD	International Classification of Diseases
IDL	intermediate density lipoprotein
LDL	low density lipoprotein
Lp(a)	lipoprotein (a)
MHC	major-histocompatibility-complex
OR	odds ratio
PAF	platelet activation factor
PASI	psoriasis area severity index
PGA	physician's (psoriasis) global assessment
PL	phospholipids
PPP	palmo-plantar pustulosis psoriasis
PSORS1-10	psoriasis susceptibility 1-10
RF	rheumatoid factors
SCB	Statistics Sweden
SMR	standardized mortality ratios
SPC	Stockholm psoriasis cohort
TG	triglycerides
TgA	IgA anti-transglutaminase
VLDL	very low density lipoprotein

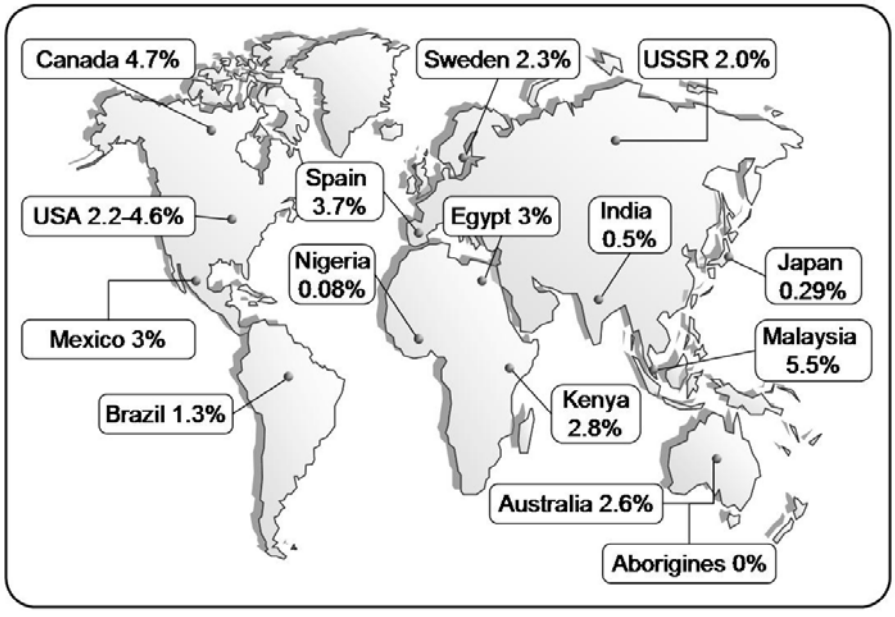
PSORIASIS

Psoriasis is a common, immune-mediated, multifactorial disease characterized by phenotypic diversity and genetic heterogeneity. The condition was first described by Celsus (25 BC-AD), a Roman scholar who referred to psoriasis as "*impeto*". However, Hippocrates (460-375 BC) probably had known psoriasis earlier. The biblical term "*Tsaraat*" represents a range of skin conditions including eczema, leprosy and psoriasis.[1,2] In fact, it wasn't until the 1700s that psoriasis was differentiated from other skin diseases. The disorder was recognized as a specific and separate clinical entity in 1808 by the English dermatologist Robert Willan (1757–1812)[3] who called it "*lepra*" derived from the Greek words "*loops*" (the epidermis) and "*lepo*" (the scale). Finally in 1841, the condition was given the name "*psoriasis*" by Viennese dermatologist Ferdinand von Hebra, who also was the first one to describe the picture of psoriasis we recognize today.[4] The word was derived from the Greek word "psora" meaning "*to itch*".

EPIDEMIOLOGY

Psoriasis is distributed worldwide but its prevalence varies among different geographical areas and ethnic groups.[5] Low prevalence has been reported among Japanese, Eskimos, Aboriginal Australians, West Africans and Indians from South America, whereas the prevalence in Europe including the Nordic countries, the UK and North American is high.[5] Caucasians are generally more frequently affected than other ethnic groups.[6] The reason for these variations is unclear but it is likely that both genetic and environmental factors play a role.

The Prevalence variation of psoriasis in the world



Psoriasis can manifest at any age, from infancy to old age and it has an equal distribution in both sexes.[7]

Several studies have shown a bimodal curve for the age of onset, with the mean age of onset for the first peek ranging from 15–20 years old, and the second peak occurring at 55–60 years of age.[8]

ENVIRONMENTAL RISK FACTORS

Although the etiology of psoriasis is unclear, studies indicate that an interaction of multiple genetic components and environmental factors are important in the disease pathogenesis[9,10] Several different environmental factors are recognized as triggering and exacerbating psoriasis, among which infections, especially those caused by streptococci[11-15], stressful life events[16,17], alcohol consumption[18-22], smoking[22-25], diet[25,26], medications[27-29] and trauma to the skin[30] have been reported.

Beta-hemolytic streptococci

Several studies suggest that current or prior infections caused by M-protein$^+$ β-hemolytic streptococci trigger guttate psoriasis,[13,16,17,31-34] and are associated with the plaque phenotype.[15,35-40]

Streptococcal M protein, which is a major antigenic determinant of the Lancefield groups A, C and G streptococci[41], shares epitopes with keratins and as a consequence may induce immune responses in the skin.[42,43]

The ability of *Streptococcus pyogenes* to trigger psoriasis seems to be serotype non-specific.[44]

Stressful life events

Despite the lack of firm evidence, clinical observations and epidemiological studies suggest that psychologically stressful life events can be implicated as a potential trigger for the onset and exacerbation of psoriasis.[16,17,45,46]

Several questionnaire-based investigations on the effect of stress on psoriasis have suggested that stress could act as a precipitating factor in the onset and/or exacerbation of the disease,[47-49] whereas one study has found only limited support for such a link.[50]

Alcohol consumption

Over the past decade a possible association between alcohol consumption and psoriasis has been discussed and several large epidemiological studies have been performed. The accumulated data points to a link between alcohol consumption and psoriasis. It appears that high consumption of alcohol may trigger[20], exacerbate[51] and influence the severity[18,19]and the course of psoriasis.[52]

The most profound association seems to exist between alcohol consumption and the severity of psoriasis and among males.[18,19,53-55]

Furthermore, large population-based surveys from Scandinavia have also shown that psoriatics as a group have higher alcohol consumption[19,54,56], an increased prevalence of alcoholism[57], and excess mortality related to alcohol compared with that of controls.[21,58]

A variety of mechanisms explaining the interaction between ethanol and psoriasis has been proposed by several *in vitro* studies including increased secretion of pro-inflammatory cytokines[59], increased lymphocytes proliferation[60], induced immune depression[61], and increased cAMP-dependent proliferation of epidermal cells.[62] In addition, an association between alcohol and HLA-DQA1*0201 allele has been shown in patients with psoriasis.[63]

Cigarette smoking

The most solid and striking link between cigarette smoking and psoriasis has been recognized in palmo-plantar pustulosis psoriasis (PPP).[64] Although psoriasis vulgaris and PPP initially were considered as closely related, recent data imply that the two conditions should be considered as distinct disorders.[65]

Still, several studies have linked current and prior smoking habits to the onset of psoriasis vulgaris, even though the association is not as strong as in patients with PPP.[20,25,66]

Furthermore, cigarette smoking has been shown to correlate with increased disease severity[21,67], and increased mortality in causes of death related to smoking in patients with psoriasis.[21,58,68]

Several studies have proposed different mechanisms that could link nicotine to psoriasis, including the enhancement of pro-inflammatory cytokines[69], and altered morphology and functionality of leukocytes.[70,71]

Diet

Psoriasis is less frequent among certain ethnic groups such as Japanese, Eskimos and West Africans. The prevalence differences are probably partly due to genetic variations. However, environmental factors, such as dietary habits, have been suggested as another contributing factor. High dietary intakes of essential fatty acids, omega-3 and omega-6 have been suggested to be protective against psoriasis.[72,73]

Furthermore, increased BMI that may reflect over-nutrition has recently been suggested as triggering psoriasis[25], while low caloric intake and a vegetarian diet have been shown to improve chronic inflammatory disorders like psoriasis.[74]

Medications

Certain pharmacological agents have been associated with the precipitation and exacerbation of psoriasis, namely lithium, beta adrenergic antagonists, anti-malarials, and non-steroidal anti-inflammatory drugs (NSAID).[28]

Trauma to the skin

Psoriasis lesions may appear as a consequence of injury to the uninvolved skin in psoriatic patients. The phenomenon is called Koebnerization and it was first described by the German dermatologist, Heinrich Köbner, in 1877.[75]

The skin response to the injury is not a specific feature for psoriasis, but it is well documented in other dermatosis such as lichen planus and sarcoidosis.[76]

GENETICS

Although the inheritance pattern of psoriasis is still unclear, several genetic and epidemiological studies have provided forceful evidence of a genetic predisposition for the disease. The risk of developing psoriasis is higher among first degree relatives of probands with psoriasis.[77] Further evidence of a genetic predisposition for psoriasis is provided by twin studies, showing 35-67% concordance for monozygotic twins versus 12-18% for dizygotic twins.[10,78]

To date, no specific psoriasis gene has been identified. However, several loci for genetic susceptibility to the disease (PSORS1-10) have been reported. The most important susceptibility locus is considered to be the PSORS1 locus in the major-histocompatibility-complex (MHC) region at 6p21.3. PSORS1 is estimated to account for 30-50% of the genetic predisposition for psoriasis.[79]

The strongest association of any known gene within the MHC region is with the HLA-Cw6 allele.[80] HLA-Cw6^{+} individuals have a 10–20-fold increased risk of developing psoriasis.[81] The allele is more prevalent among patients with guttate phenotype[82] and is associated with early onset of the disease.[83]

However, since not all psoriatics are HLA-Cw*0602^{+} and only approximately 10% of HLA-Cw*0602^{+} individuals develop psoriasis, it is still disputed whether this allele actually represents the predisposing psoriasis gene or merely that is a marker in the linkage disequilibrium with the true disease gene.[84] Further efforts to identify the long-sought gene/genes involving in the pathogenesis of psoriasis continue.

PATHOGENESIS

Although the underlying cellular changes in psoriasis are described, the pathogenesis of the disease remains elusive.

Psoriatic lesions are characterized by an increased proliferation of keratinocytes that remain immature. Other cellular changes include an increased infiltration of leukocytes (inflammation) and a poorly adherent stratum corneum which results in the characteristic scale or flakes of the lesions.[85]

Psoriasis vulgaris has been conceptualized as a T-lymphocyte mediated autoimmune disease, where T-helper-1 cytokines are considered as the conceivable forces behind the cellular changes.[85,86]

CLINIC

Psoriasis is a clinical diagnosis. The disease is characterized by erythematous and indurate plaques which usually are covered by thick silvery white scales. Although the clinical course of psoriasis is highly variable between individuals, the lesions are typically recurrent. To date, no curative treatment exists.[87]

The most frequent clinical type of psoriasis is plaque psoriasis, which commonly appears on the flexure areas: elbows and knees, but lesions on the scalp, umbilicus, and intertriginous area of the skin also may occur. The second most common clinical form is the guttate phenotype which is strongly associated with preceding or concurrent streptococcal infection.[13,16,17] The lesions of guttate psoriasis erupt explosively and are disseminated over large areas on the trunk and extremities, usually 1-2 weeks after an episode of streptococcal throat infection.

Guttate psoriasis has a more acute clinical course and may dissolve spontaneously. However it may eventually progress into plaque phenotype.[88]

Erythrodermic psoriasis is the most extensive clinical phenotype with more than 90 percent of the skin surface being involved. Pustular psoriasis is either localized to the palms and soles (PPP) or generalized. As in erythrodermic psoriasis, the latter phenotype can be life-threatening.

Although psoriasis usually affects the skin, nail and joint involvement are common.

CLINICAL ASSESSMENT

Clinical symptoms of psoriasis can vary from mild to severe and may have an impact on the patient's quality of life and interfere with social relationships.[47,49,89-92]

Different instruments for measuring the clinical severity of psoriasis have been developed.[93] The Psoriasis Area and Severity Index (PASI) which is based on the area involvement and the rate of desquamation, induration and erythema of lesions, is the most frequently used assessment tool. The PASI score is designed to reflect the severity of inflammation and proliferation of keratinocytes in psoriasis lesions. The score is calculated using a formula originally presented by Fredriksson and Pettersson[94], and it can vary from 0 to 72, with higher scores indicating the most severe cases of psoriasis.[95]

After the PASI, the most often used instrument to measure psoriasis severity is the Psoriasis Global Assessment (PGA). The PGA (sometimes called Physician's Global Assessment) is a single estimate of the patient's overall severity of disease.

Although the two methods are highly concordant, the PGA evaluates disease severity in a more intuitive way than does the PASI.[96]

PSORIATIC ARTHRITIS

An association of arthritis with psoriasis was first observed by Alibert in 1818.[97] However, psoriasis arthritis was described as a unique inflammatory arthritis occurring in the presence of psoriasis skin disease by Wright[98] and Baker[99] in the early sixties. Finally in 1964, the disease was included as a distinct clinical entity in the classification of rheumatic diseases by the American College of Rheumatology for the first time.[100]

The original diagnostic criteria of Moll and Wright[101] are the simplest and the most frequently used in current clinical studies, and include:

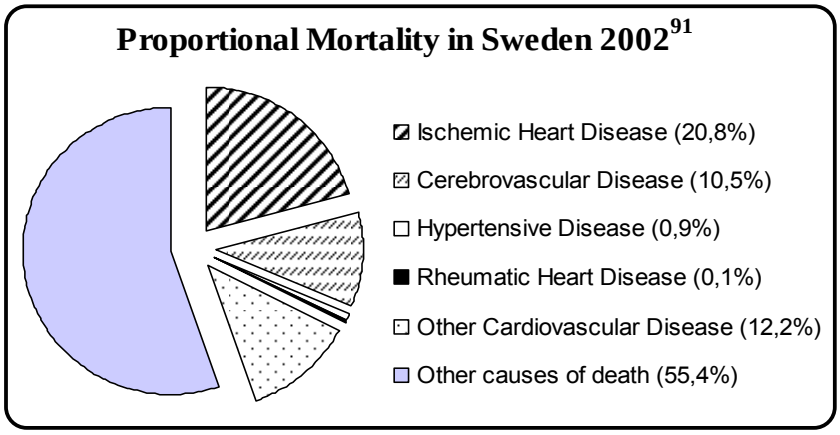
- The presence of peripheral arthritis and/or sacroiliitis or spondylitis
- The presence of psoriasis skin disease
- The (usual) absence of serological tests for rheumatoid factor.

Using these diagnostic criteria, Moll and Wright described five subgroups of psoriatic arthritis: only arthritis in distal interphalangeal joints, asymmetrical mono-oligoarthritis, symmetrical polyarthritis, spondylitis and arthritis mutilans.

The exact prevalence of psoriatic arthritis is unknown, but estimates vary from 0.3% to 1% of the general population, while among individuals with psoriasis, it is estimated to be 10-30%.[102-104]

CARDIOVASCULAR DISEASE

Since 1920s, cardiovascular diseases (CVD) have been the leading cause of death in Sweden.[105] Although cardiovascular mortality has been declining during the past 15 years, CVD still accounted for 44.6% of all causes of death in Sweden in 2002.[106]



Several environmental risk factors have been associated with the development of CVD. The established risk factors include lifestyle choices such as physical inactivity[107,108], cigarette smoking[109,110] and increased BMI[111], but other modifiable factors, like hypertension[110,112], Type II diabetes[113] and high serum cholesterol concentration[110,114] have also been identified as major contributors.

CARDIOVASCULAR DISEASE IN PSORIASIS

The link between psoriasis and cardiovascular disease has been reported by several studies.[21,115,116] Although the pathogenesis of increased cardiovascular events in patients with psoriasis remains to be established, there are several possible biological factors which may explain such a link. Firstly, psoriasis appears to be associated with traditional risk factors for CVD, including increased BMI, hypertension, hyperlipidemia, Type II diabetes and cigarette smoking.[21,47,57,116] Secondly, recent evidence strongly suggests that chronic inflammation, a characteristic feature of psoriasis, *per se* may play a role in the initiation and progression of dyslipidemia[117] and atherosclerosis.[118,119] Elevated levels of high-sensitive-C reactive protein (hs-CRP), a nonspecific marker of inflammation, is one of the emerging risk factors for CVD and the accumulated data has shown that increased hs-CRP levels can predict long-term risk for cardiovascular events.[120-122]

Finally, there is evidence that established treatments for psoriasis such as retinoids[123,124] and ciclosporin[125] may induce hyperlipidemia which can promote future CVD.

Nearly all of the energy required by the body is provided by the oxidation of carbohydrates and lipids. Whereas carbohydrates provide a readily available source of energy, lipids function primarily as an energy reserve. The major lipids in human plasma are cholesterol (C), cholesteryl esters (CE), triglycerides (TG) and phospholipids (PL). Functionally, lipids serve also as components of cell membranes and precursors of steroid hormones and bile acids.

Due to their poor solubility in the blood stream, C, TG and other lipids are transported in the core of spherical macromolecular complexes called lipoproteins. The term "lipoprotein" refers to this unique, soluble complex of lipids and specific proteins (apolipoproteins).[126,127]

All lipoprotein particles have a common structure of a neutral lipid core surrounded by a surface monolayer of phospholipids, free cholesterol and apolipoproteins. (Figure 1)[126,127]

The Structure of lipoproteins

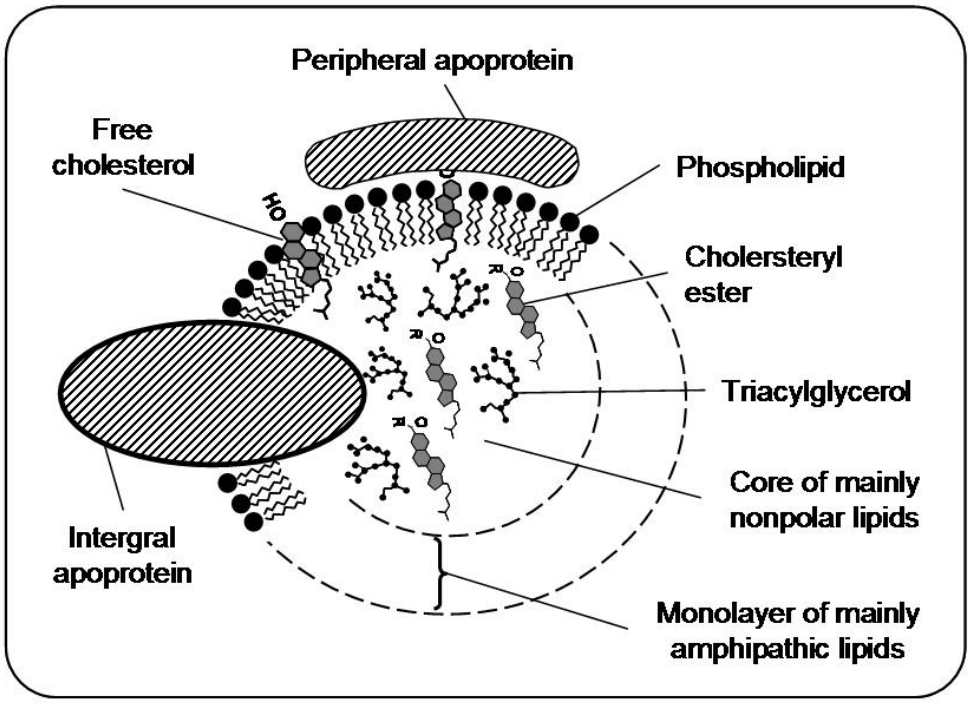


Figure 1 The core of lipoproteins, containing CE and TG, is non-polar and hydrophobic, while the outer layer, containing free cholesterol, PL, and specific apolipoproteins, is polarized which permit the lipoprotein particles to be transported in the circulation.

The apolipoproteins (apo) are important for the structural stability of the lipoprotein particles and serve a number of functions, including regulation of lipoprotein metabolism by acting as cofactors for enzymatic reactions and ligands for selective catabolism.[128]

The content of apolipoproteins and lipids (C, TG and PL) in lipoproteins varies. The higher the ratio of apolipoprotein to lipid content, the higher the density. Consequently, several lipoproteins can be identified according to their

density, lipid composition, and the apolipoproteins on the surface of the particle.[126,127] (Table 1)

The main five classifications of lipoproteins

Increasing density ↓

	Density (g/mL)	Dominated lipid component	Apolipoprotein
CM	<0.95	Exogenous (d*ietary*) Triglycerides (88%)	A, B48, C, E
VLDL	0.95-1.006	Endogenous Triglycerides (55%)	B100, C, E
IDL	1.006-1.019	Triglycerides (30%) Cholesteryl esters (35%)	B100, C, E
LDL	1.019-1.063	Cholesterol (10%) Cholesteryl esters (48%)	B100
HDL	1.063-1.21	Phospholipids (46%) Cholesteryl esters (15%)	AI, AII, C, D, E

Table 1 CM: Chylomicrons, VLDL: Very low density lipoproteins, IDL: intermediate density lipoprotein, LDL: Low density lipoproteins, HDL: High density lipoprotein

Chylomicrons (CM)

Chylomicrons are the largest and most lipid-rich lipoproteins, containing principally dietary TG absorbed by intestinal epithelia. CM are secreted by the intestine, and are abundant in plasma in the postprandial state.

Once transported to tissue, the TG contained in CM are hydrolyzed. The chylomicron remnants are then taken up by the liver via receptor-mediated endocytosis.[128]

Very low density lipoproteins (VLDL)

VLDL particles are secreted and used by the liver to export endogenously synthesized lipids such as C and TG to peripheral tissue. The VLDL particle contains several types of apolipoproteins, but the assembly and secretion of VLDL has long been known to be dependent on apolipoprotein B-100 (apoB-100).[129]

VLDL particles are heterogeneous and vary in size and composition. Thus, different sub-fractions of VLDL can be defined according to their density, diameter and flotation. (Table 2)

Normolipidemic human plasma contains, at least, two VLDL sub-fractions: large, floatable $VLDL_1$-particles and small, dense $VLDL_2$-particles.[130] $VLDL_1$ and $VLDL_2$ fractions have different metabolic outcomes. $VLDL_1$ particles are the major subclass of endogenous TG-rich lipoproteins and seem to be the major determinant of the plasma TG concentration in normolipidemic subjects.[131] They also are converted to a larger extent to remnants that are removed from plasma before undergoing conversion to LDL, while $VLDL_2$-particles are rapidly and efficiently converted to LDL.[132]

An increased number of VLDL particles in plasma is strongly associated with CVD, independently of traditional risk factors.[133] A variety of mechanisms link VLDL to atherosclerosis and CVD; hypertriglyceridemia secondary to VLDL elevation is associated with both procoagulant and prothrombotic factors in the blood[134] and affects the adhesiveness of platelets.[135]

Lipoproteins' sub-fractions

Sub-fractions	Density Peak (gm/ml)	PR (%)	CE (%)	UC (%)	TG (%)	PL (%)
$VLDL_1$	<1.006	11	8	6	58	17
$VLDL_2$	1.006–1.010	18	24	9	29	22
LDL-I	1.019–1.023	18	43	9	7	22
LDL-II	1.023–1.028	19	45	10	4	23
LDL-III	1.034–1.041	22	46	8	3	21
LDL-IV	1.044–1.051	26	42	7	5	19

Table 2 PR: protein; TG: triglycerides; CE: cholesteryl ester; PL: phospholipids; UC: unesterified cholesterol.

Intermediate density lipoprotein (IDL)

IDL particles are derived from triglyceride depletion of VLDL and can be taken up by the liver for reprocessing, or upon further TG depletion, become LDL.

Low density lipoprotein (LDL)

LDL particles are a metabolic product of VLDL metabolism and they are the principal carrier of dietary and endogenous C and CE in human plasma. Like VLDL and ILD particles, LDL belongs to the category of apoB-rich lipoproteins.

An elevated plasma concentration of LDL cholesterol has been recognized as an important risk factor for CVD for decades and multiple studies have consistently demonstrated the therapeutic value of lowering LDL plasma concentrations as a preventive measure against CVD.[136]

Similar to VLDL particles, sub-fractions of LDL have been identified on the basis of a number of characteristics, including particle buoyant density, size, charge, and lipid and apolipoprotein content. The LDL sub fractions also differ in their metabolic behavior and pathologic roles in the development of CVD.[137]

It is worth to mentioning that lipoprotein (a) (Lp(a)) has a similar structure to LDL. However, it contains an additional protein, apo(a). Lp(a) has a thrombotic effect and high levels of Lp(a) in the general population have been linked to CVD.[138]

High density lipoproteins (HDL)

HDL particles, which are the smallest lipoproteins with the highest density range, are protein-rich molecules produced in the liver and intestines. HDL particles have several beneficial properties, among which the most important one is their involvement in *reverse cholesterol transport* by serving as a scavenger to free cholesterol from tissue and transport it to the liver.

Compelling evidence suggests that elevated levels of HDL are protective against CVD. The plasma levels of HDL are, to a large extent, determined by apolipoprotein A-I, the major apolipoprotein component of HDL. However, HDL cholesterol consists of heterogeneous group of particles with different apolipoprotein compositions.[139] HDL sub-fractions are commonly separated by density to either HDL_2 and HDL_3 sub-fractions, or by apolipoprotein content to

apoAI and apoAI/apoAII particles containing either apoAI without apoAII or both apoAI and apoAII, respectively.[140] There is also a minor subpopulation of HDL that contain apoAII but no apoAI (AII HDL).[141]

The HDL sub-fractions seem to differ in their capacity to confer protection, with the large HDL_2 sub-fraction appearing to be more important than the small HDL_3 sub-fraction, and apoAI HDL being more metabolically activate.[142]

Furthermore, other factors may modulate the plasma levels of HDL and thus may influence the predisposition of an individual for developing CVD. Accumulated evidence indicates that oxidative modification of HDL can occur *in vivo*[143],and modified HDL particles have been detected in atherosclerotic plaques.[144] The modification of HDL not only attenuates its beneficial properties, such as the stimulation of cholesterol efflux from foam cells, endothelium-dependent vasoreactivity and anti-oxidative activity, but also generates a pro-atherogenic species that inhibits nitric oxide synthesis in endothelial cells.[145] A potential mechanism for the generation of pro-atherogenic, dysfunctional forms of HDL *in vivo* was recently presented.[145,146] An oxidation of HDL and apoAI was shown *in vivo*, which may result in a selective inhibition of *reverse cholesterol transport* from macrophages.[145,147]

LIPIDS AS PREDICTORS OF CARDIOVASCULAR DISEASE

Although the level of C, TG, VLDL, LDL and Lp(a) each *per se* has a positive association with CVD morbidity and mortality, the total C/HDL ratio, LDL/HDL ratio, the apoB/apoA-I ratio and the C/TG ratio in VLDL and LDL particles are employed as established risk factors in predicting the risk of CVD.

In summary, the risk of CVD may be more accurately predicted by looking at the assembly of lipids, and the composition and the metabolic function of the lipoproteins rather than the solely the level of each variable.[148,149]

LIPIDS IN PSORIASIS

Briefly, multiple studies have consistently shown an aberrant lipoprotein profile associated with psoriasis. A summary of selected studies on lipid profile in psoriasis over the last 15 years is presented in table 3. The studies, however, are not consistent, and they involve highly heterogeneous study populations and/or have not taken the duration of psoriasis or previous treatments into account.

Lipid profile in patients with psoriasis

Author	Study size	C	HLD	LDL	VLDL	TG	Lp(a)	ApoA	Apo B
Vahlquist[150]	20		↓	↑	↑				
Ferretti[151]	15	↑	↑						
Seishima[152]	38	ND	ND			↑		↓	↑
Uyanik[153]	72	ND	ND	ND		↑	↑	ND	↑
Rocha-Pereira[154]	48	↑	↓	↑	↑	↑	↑		↑
Pietrzak[155]	41		↓			↑			
Piskin[156]	100	↑	ND	↑	ND	ND			
Vanizor Kural[157]	35	↑		↑		↑			

Table 3 ND: No differences between patients with psoriasis and controls.

AIMS OF THIS THESIS

The present thesis is part of a larger epidemiological and genetic research project with a focus on psoriasis. Our long-term goal is to understand the clinical and genetic heterogeneity of psoriasis and to explore disease pathology in target organs in parallel with environmental disease determinants and associated risk factors. However, the aims of the studies in the present thesis are as follows:

- To establish a detailed baseline clinical characterization of adult psoriasis at disease onset.

- To investigate the prevalence of streptococcal infections in guttate and plaque phenotypes as a function of HLACw*0602 status at the onset of psoriasis.

- To assess the risk of cardiovascular death among inpatients and outpatients with psoriasis.

- To investigate the plasma lipid, lipoprotein and apolipoprotein profile in patients at the onset of psoriasis and compare it with that of matched controls.

MATERIAL AND METHODS

The studies of the present thesis have been approved by the Regional Committee of Ethics and written, informed consent has been given by all individuals (patients and healthy controls). The studies were performed according to the Declaration of Helsinki Principles.

THE STOCKHOLM PSORIASIS COHORT (I, II & IV)

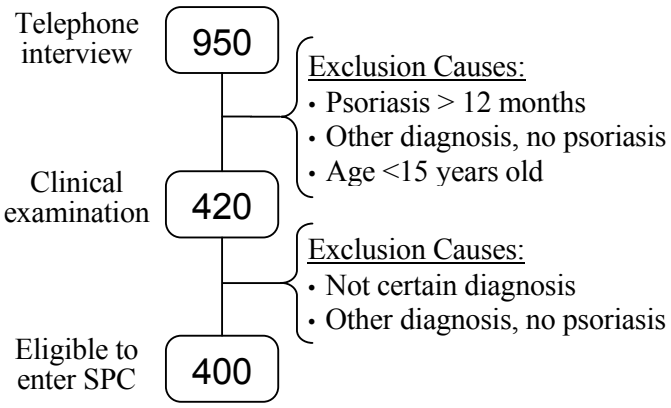
The Stockholm Psoriasis Cohort (SPC) was initiated in 2001 and recruitment of patients is still ongoing. Today, the cohort comprises more than 600 individuals with recent onset (<12 months) of psoriasis.

In the present thesis, the subjects in studies I, II and IV were the first 400 eligible patients who were examined consecutively at the department of Dermatology, Karolinska University Hospital, Stockholm, Sweden, between 2001 and 2003.

Individuals above 15 years of age with onset of psoriasis on non-hairy skin in the past 12 months were eligible to enter the SPC. The patients originated mainly from Sweden and most were recruited from the Stockholm area through advertisements in two different free daily newspapers, campaigns on the website and in the magazine of the Swedish Psoriasis Association, referrals from private dermatologists, other dermatology clinics, general practitioners, school nurses, sexual health centers, and youth clinics.

In total, 950 individuals either responded or were referred. Prior to clinical examination, a telephone interview was conducted by the examining physician *(Lotus Mallbris)* or an experienced nurse *(Susanne Bergquist)* trained in psoriasis. Exclusion criteria were a description and disease history compatible with PPP or eczema and/or other dermatological diagnosis without psoriasis and/or the first psoriasis lesion occurring more than 12 months prior to the interview.

In total, 420 individuals were examined clinically, of which 400 were eligible to enter the SPC. Only subjects with a clinically convincing diagnosis of psoriasis were included and individuals with a previous diagnosis or a history of skin lesions compatible with psoriasis were excluded.



Diagnosis was established according to established clinical criteria[158] by the same dermatologist *(*Lotus *Mallbris)*. All individuals with any joint symptoms were examined by an experienced rheumatologist *(Per Larsson).*

At the time of initial examination, patients were classified according to the pattern and severity of psoriasis lesions on their skin, the presence or absence of nail involvement, and psoriasis arthropathy.

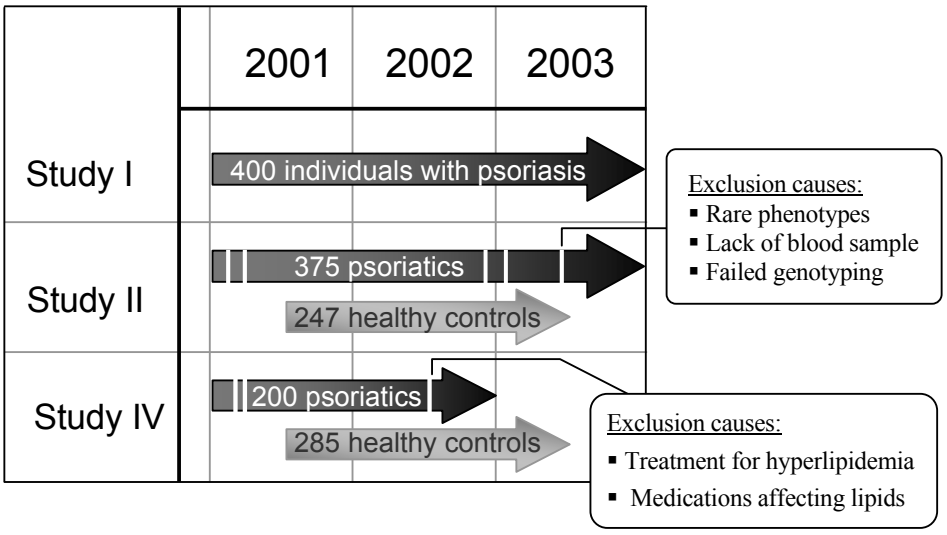
Participation

Participation involved attending a clinical examination that included a throat swab for streptococcal infection and measurement of blood pressure, completing a questionnaire concerning co-morbidity and environmental conditions, and providing blood samples for DNA extraction and laboratory analyses.

In the first study (I), all patients (n=400) were included, while patients who had rare phenotypes other than plaque or guttate psoriasis or lacked a blood sample, or where genotyping failed (n=25), were excluded in the second study (II). Hence, in total, data from 375 patients was analyzed in the second paper.

Furthermore, the first 200 patients without treatment for hyperlipidemia and other medication affecting lipid metabolism were included in addition in the fourth study (IV). Additional venous blood samples for the determination of lipoproteins were obtained from these individuals.

Psoriatic patients included in study I, II and IV were all derived from the SPC

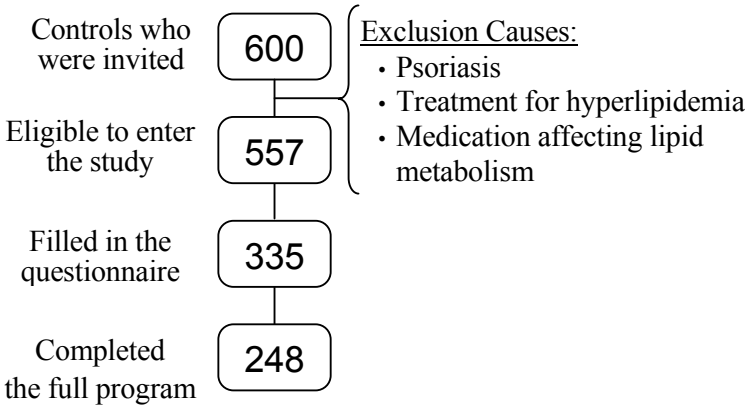


Control individuals

During the same period, between 2001 and 2003, healthy controls were randomly chosen from the Swedish Registry of Population so that they matched patients for place of residence, age and sex. Three controls were selected per case. If all three contacted controls declined participation, a new control was randomly selected and invited to participate. Initially, all control individuals (n=600) who matched patients included in paper IV (n=200) were contacted by mail and invited to volunteer for participation.

Participation involved completing the same questionnaire as for the patients, and attending an optional clinical examination, including providing a throat swab and blood samples at the same seasonal time as when the blood sample of the matching case was obtained and analyzed.

Controls with a previous diagnosis of psoriasis (n=26), treatment for hyperlipidemia (n=8), and other medication affecting lipid metabolism (n=9) were excluded. Thus, a total of 557 persons were eligible as controls, of whom 248 volunteered for the complete program, and an additional 87 individuals only completed the questionnaire.



Consequently, the participation rate of controls who completed the full program and were analyzed in study IV was low (44.5 percent). Considering the low compliance of the controls, an additional 37 control subjects, among non-responders, who met the inclusion criteria, were randomized and contacted by phone to be invited to participate. Data from these subjects was used for assessing the potential selection bias among non-responders.

GENOTYPING (II)

A total number of 375 patients with psoriasis and 248 healthy controls were genotyped. The genotyping was performed by allele-specific PCR amplification of the HLA-Cw*0602 under the conditions described by Bunce et al.[159]

LIPIDS, LIPOPROTEINS & APOLIPOPROTEINS (IV)

Fasting plasma concentrations of C and TG in VLDL, LDL, and HDL were determined by a combination of preparative ultracentrifugation, precipitation of apo B containing lipoproteins, and lipid analyses.[160] Measurements of apolipoprotein A-1 (apo A1) and apolipoprotein B (apo B) were performed using kits made by SYNCHRON LX® 20 systems (Beckman, Inc. Fullerton, CA, USA). Serum Lp(a) was determined by the IMMAGE® Immuno-chemistry System, (Beckman, Inc. Fullerton, CA, USA).

THE SWEDISH REGISTRY OF POPULATION (II, III & IV)

Since January 1, 1947, all inhabitants of Sweden have been assigned a 10-digit national registration number[161], which is a unique personal identifier and is used in most public administration including population-based registers and hospital archives. In Sweden, the system of national registration numbers has provided a unique opportunity to identify medical records and unambiguously link information from different sources.

The Swedish Population Register contains computerized official Swedish census data since 1960. All residents in Sweden alive at the end of each year are included, and the registry provides information on their current name, residential address in Sweden and national registration number. Since 1969, the Register also contains information on dates of emigration.

DEFINITIONS (I, II, IV)

Guttate psoriasis was defined as acute onset of scattered, small coin-like lesions.

Severity A PASI score below 3 was defined as mild, between 3 and 15 as moderate, and above 15 as severe disease.

Life crisis was defined as a distinct severe event profoundly affecting life occurring up to 2 months prior to disease onset, and in the absence of streptococcal pharyngitis. Life crisis included divorce, severe/life threatening diseases affecting the patient or close family members, deaths within the close family, serious financial difficulties, being dismissed from work, and harassment at school.

Infection was defined as acute symptoms requiring antibiotics or antiviral treatment (one case) occurring up to 10 days before the onset of psoriasis.

Increased BMI was defined as a BMI between 25 and 30 kilogram per m^2 and obesity as a BMI above 30 kilogram per m^2.[162]

SWEDISH NATIONAL INPATIENT REGISTRY (III)

Health care in Sweden is mainly funded by taxes and private heath care providers have been rare. Hence, in general, the Swedish National Health Service has been population-based.

Since 1964, the Swedish National Board of Health and Welfare has compiled data on individual hospital discharges in the Swedish National Inpatient Registry, which, for each discharge, contains the date of admission and discharge, main and contributing discharge diagnosis, surgical procedures, department and hospital, together with the individual's national registration number. Diagnoses are coded according to the seventh to the ninth Revision of International classification of Diseases (ICD 7-9).

Since 1987, the Swedish National Inpatient Registry has nationwide coverage, although the registration has been complete per county from the start. In 1969, the

register covered 60% of the Swedish population, in 1978 this percentage was 75%, and by the end of 1983 it was 85%.[163]

In study III, we used the Swedish Inpatient Registry to identify patients hospitalized for psoriasis as the main diagnosis at dermatological wards in Sweden during the period of January 1964 to December 1995.

MEMBERS OF THE SWEDISH PSORIASIS ASSOCIATION (III)

In study III, we used the members of the Swedish psoriasis association in 1987 to identify a cohort which represents outpatients. In total 19,757 members were identified. Subjects with incomplete personal identification data or technical problems with computerizing their data were excluded, while members who had a history of hospitalization were not excluded. Date of entry into the cohort was set to January 1, 1987, the year the register was established.

Members of the Swedish psoriasis association represent a cross-section with a wide range of disease severity, but with most having either mild disease or disease that is controlled by outpatient treatment. An estimated 5% are supporting members without a diagnosis of psoriasis and are included in the outpatient cohort.[164]

THE SWEDISH CAUSE OF DEATH REGISTRY (III)

Swedish statistics on causes of deaths are among the oldest worldwide, and they go back to 1749 when a nationwide report system was first introduced in Sweden. Using the Swedish Cause of Death registry, a full report on statistics on causes of death has annually been published by Statistics Sweden (SCB) or the National Swedish Board of Health and Welfare.

The Swedish Cause of Death Registry provides information on date and age at death and underlying main and contributory causes of death for every deceased Swedish resident irrespective whether the death occurs in Sweden or abroad.

Individuals are recorded with their national registration number and diseases are coded according to the International Classification of Diseases (ICD-8 to10).

The cause of death, including underlying and contributing causes, is generally determined from the medical death certificates which are obligatory for physicians to complete within a week after death. The current completeness of registration is estimated to exceed 99%.[165]

STATISTICS (STUDY I, II, III & IV)

All analyses were performed using PROC FREQ, PROC GENMOD and PHREG in the Statistical Analysis System (SAS®) package.[166] Statistical significance was set at $p<0.05$.

For comparisons between groups in studies I and II, the *Fisher's exact test* were performed.

Furthermore, in study II the prevalence of streptococcal throat infection and HLA-Cw*0602 and gene-environmental associations among the groups were estimated by odds ratios. The heterogeneity of the odds ratios for the groups was tested by an interaction term in a *logistic regression model* and *multiple logistic regression* was used to evaluate the independence of confounding factors.

In study III we estimated the relative risk by calculating *standardized mortality ratios* (SMRs) as a measurement of the ratio of the observed cardiovascular mortality rate in patients with psoriasis against the predicted (expected) mortality rate among general population. Trend tests were performed by *Poisson regression*. All reported p-values for trends were two-tailed. Comparisons between the cohorts were performed by *Cox' regression*.

In study IV, continuous variable were logarithmically transformed. *Linear regression* modeling for comparisons between patients and controls was performed. Furthermore, in order to display the difference in distribution among cases and controls, a *logistic regression* for the two lipid endpoints (HDL cholesterol and VLDL cholesterol-to-triglyceride ratio) which showed a highly significant difference between the groups, was performed. Individuals were categorized according to quartiles among controls and odds ratios were calculated.

Analysis of non-responders (IV)

Considering the low compliance of controls, an additional 37 control subjects among non-responders who met the inclusion criteria were recruited. Data from these subjects was used for assessing the potential selection bias due to non-response among controls. The analyses demonstrated no substantial differences in the main results.

RESULTS

A summary of the main results from each study is presented below. A more detailed description and additional information with illustrations are presented in the manuscript section (study I-IV).

Characterization of patients at onset of psoriasis (I)

To establish a material for further epidemiologic and genetic studies of psoriasis, the initial clinical characterization of 400 patients with onset of psoriasis was described. In total, 74 individuals had guttate psoriasis, while 326 individuals primarily had plaque phenotype. Guttate phenotype was associated with younger age and recent infection in 84% of patients, where acute streptococcal pharyngitis was verified in 63%. The predominant factor associated with the onset of plaque psoriasis was a recent distinct life crisis (46%).

A positive family history for psoriasis was approximately the same in both groups. Psoriasis arthropathy was diagnosed in 5% of guttate and 15% of non-guttate patients, with enthesopathy being the dominant symptom among guttate patients.

Cardiovascular disease, in particular hypertension, was mostly found among older patients with plaque psoriasis. Increased body mass index (BMI) was observed in 30% and obesity in 13% of all the individuals with psoriasis.

Precipitating environmental factors, family history and co-morbidity at the onset of psoriasis

	Guttate (n=74)		Non-guttate (n=326)		Total (n=400)	
	n	%	n	%	n	%
Precipitating factors						
Unknown	3	4	124	38	127	32
Only Life crisis[1]	9	12	151	46	160	40
Only Infections[2]	43	58	30	9	73	18
Infection + life crisis	19	26	20	6	39	10
Streptococcal throat infections	47	63	24	7	71	18
Family history of psoriasis						
First-degree relative/s	23	31	111	34	134	34
Psoriatic arthritis	4	5	52	16	56	14
Cardiovascular co-morbidity						
Myocardial infarction or angina pectoris	2	3	11	3	13	3
Hypertension	2	3	50	15	52	13

1 Severe event profoundly affecting life with 2 months prior to psoriasis onset, without ongoing infections.
2 Without life crisis

The study confirmed the strong link between the onset of guttate psoriasis phenotype and streptococcal throat infection, whereas the onset of plaque psoriasis was highly associated with a preceding distinct stressful life event.

Streptococcal infections and HLA-Cw*0602 status at the onset of psoriasis (II)

As expected, the frequency of streptococcal throat infections among healthy controls was much lower (2%), which in addition was only found among HLA-Cw*0602 negative individuals, indicating that there is no increased risk of streptococcal throat infection in association with HLA-Cw*0602 positivity in the general population.

The relationship between streptococcal throat infection and HLA-Cw*0602 status in individuals with onset of guttate and plaque psoriasis and in closely matched healthy controls was studied. In total 375 patients (guttate n=68, plaque n=708) who were clinically characterized in study I were genotyped.

As expected, HLA-Cw*0602 was more prevalent among guttate patients and, in general terms, among young patients. However, the results showed the novel perspective that, regardless of phenotype, the prevalence of prior/current streptococcal throat infection was twice as high among HLA-Cw*0602^{+} patients at the onset of psoriasis compared to HLA-Cw*0602^{-} patients (OR=3.6 C.I.=1.8-7.2, p<0.001). The interaction was not affected by delay between the first lesion and testing for streptococci, age of onset, sex or other environmental factors.

Prevalence of streptococcal infection at the onset of psoriasis phenotypes and in the healthy controls in respect to HLACw*0602 status

	Guttate (n=68)		Plaque (n=307)		Controls (n=247)	
HLA-Cw*0602 /Strep.[1]	n	**%**	n	**%**	n	%
- /+	7	**39**	10	**5**	5	2
+/+	37	**74**	11	**13**	0	0

[1] Streptococcal throat infections were verified by culture of throat-swabs

Cardiovascular mortality among individuals with psoriasis (III)

By calculating standardized mortality ratios, we assessed the risk of cardiovascular mortality among patients hospitalized for psoriasis compared with the risk among the general population. In total, 8991 inpatients with psoriasis were included in the study. Furthermore, to represent an outpatient cohort, 19,757 members of the Swedish Psoriasis Association were selected to be followed up for cardiovascular mortality.

Overall, 1529 deaths caused by cardiovascular events were observed in psoriasis inpatients compared to the expected 1007. Thus the overall relative risk among inpatients admitted at least once was increased by 50% (SMR 1.52; 95% CI: 1.44–1.60). The relative risk increased with increasing number of hospital admissions (p for trend <0.001) and among those admitted at a relatively young age (p for trend <0.001; SMR 2.62, 95% CI: 1.91–3.49, for patients aged 20 to 39 years at first admission). There were no differences between sexes.

Among outpatients with psoriasis, no increased cardiovascular mortality was found, compared with the general population (standardized mortality ratio, SMR 0.94; 95% confidence interval, CI: 0.89–0.99). Thus, it seems that a diagnosis of psoriasis *per se* does not appear to increase the risk of cardiovascular mortality. However, severe psoriasis, in this study measured as repeated admissions, and early age at first admission, was associated with an increased relative risk of cardiovascular death.

As mentioned in the thesis summary, it is known that psoriasis is associated with traditional risk factors, and we cannot exclude that these factors, to some extent, have inflated the links found in this study.

Dyslipidemia at psoriasis onset (IV)

Psoriasis patients manifested significant dyslipoproteinemia. The lipid composition of VLDL and HDL lipoprotein differed significantly in the patients compared with the controls. The patients had higher cholesterol concentrations in their VLDL (19% (95% CI: 10%-29%)) and HDL (14% (95% CI: 4%-26%)) particles. The differences were not affected by adjustment for confounding factors, such as age, sex, smoking, physical exercise, BMI, alcohol consumption and systolic blood pressure.

Although there were relative differences in both VLDL and HDL C/TG ratio were almost identical, the two lipid profiles were completely uncorrelated (r=-0.001), indicating that the observed differences have no tendency to occur in the same patients, and therefore are unlikely to have the same underlying causes.

Furthermore, patients had a significantly higher hs-CRP concentration, which positively correlated with the total plasma cholesterol concentration. However, adjusting for hs-CRP in complementary analyses did not affect the main results.

The study supports the notion that dyslipoproteinemia in psoriasis may be genetically determined rather than acquired.

GENERAL DISCUSSION

Internal and external validity

To reduce problems of generalization in studies I, II and IV, patients were recruited through multiple channels, including self-referral. However, since ethical permission to include children in the SPC was not obtained at the time, only individuals who were 15 years or older were included in the study. Consequently, our data cannot automatically be generalized to psoriasis with an earlier onset, younger than 15 years of age, where other genetic and environmental factors may play a role.

Furthermore, it is likely that patients with a high degree of concern and with a more acute onset of disease, especially when associated with an infection, might be more prone to seek health care than patients with a more insidious onset. Therefore the prevalence of guttate psoriasis in this study may be overestimated. However, other Scandinavian studies have reported as high as 30-40% prevalence of guttate psoriasis among the younger population.[167]

We had a female dominance (approaching 1.3:1) which yet again may reflect a sex-related preference in seeking health care[163], whereas previous reports have observed either an equal sex distribution or a male predominance among patients with psoriasis.

Likewise, prior knowledge about psoriasis and the presence of psoriasis in the family, and campaigns on the website and in the magazine of the Swedish Psoriasis Association may influence the inclination to seek medical advice at an early stage and render individuals who are familiar with psoriasis more willing to participate. This may explain why we recorded a higher familial occurrence of psoriasis among patients with late onset compared with previous studies.[168,169] However, the frequency of HLA-Cw6^{+} among patients included in the studies was lower than previously reported in a Swedish psoriasis population (SPC: HLD-Cw6^{+} 36% vs. other reported: 67%).[83] Then again, HLD-Cw6 is reported to be more prevalent among patients with early onset of the disease[168] and in the SPC we have not included individuals younger than 15 years old.

Another issue is if our findings are different for those individuals who have participated and those who have been theoretically eligible to enter the studies. Although this selection bias concerns both participation of the patients and the controls, it is more noticeable with regard to the low participation rate among the controls in study IV. However, we observed nearly the same lipid profile in a subgroup of 37 non-responders, indicating that a hypothetical selection bias of controls did not necessarily influence our results. Moreover, other characteristics of the subgroup of non-responders were comparable regarding BMI, cigarette smoking, blood pressure and physical exercise.

Cardiovascular mortality

In study III, we conducted a historical cohort study to assess cardiovascular mortality among psoriasis patients. By using the Swedish Inpatient Registry and the Swedish Cause of death registry, we were able to select a study population of a

great size with follow-up for several decades. Exposure was defined as a discharge diagnosis of psoriasis from a dermatological ward in Sweden and the outcome was cardiovascular death. Exposure and outcome data derived from these registries is of high quality, thus minimizing non-differential misclassifications and optimizing precision. Despite these advantages, there remains a concern as to whether the increased relative risk of cardiovascular death shown in the study reflects a true link among psoriatics in general.

Firstly, psoriasis is known to be associated with several lifestyle factors such as smoking, obesity, and diabetes that *per se* may increase the risk of cardiovascular morbidity. Secondly, it appears that these co-morbidity and lifestyle factors influence the severity of psoriasis diseases and consequently increase the chances of being admitted.

Although we cannot exclude that such factors have inflated the links to some extent, we have tried to minimize the confounding potential of these factors by choosing a narrow and specific definition of the exposed population, and excluded those with a prior history of cardiovascular disease. Moreover, the increasing risk with increasing duration of follow-up, as well as the lack of difference between males and females, strongly argues against substantial confounding.

In addition, dyslipoproteinemia constitutes an established risk factor for cardiovascular events and we believe that the results obtained in study IV lends further credence to the theory that there may be a real biological link between psoriasis and metabolic disturbance leading to cardiovascular morbidity.

Future perspectives

The sample sizes of the Stockholm psoriasis cohort, including the biological material obtained (biopsies, plasma, serum and blood), is still growing. The large number of patients included in SPC will allow us to study the clinical and genetic heterogeneity of psoriasis and to explore the disease pathology in target organs in parallel with environmental disease determinants and associated risk factors.

The first structural follow-up, involving clinical and laboratory examination of the patients is ongoing. The longitudinal follow-up of the patients will provide robust information about the clinical course of psoriasis and response to treatment for distinct genotypes and phenotypes.

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