

THE CARDIOMETABOLIC ASPECTS OF PSORIASIS

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the Witwatersrand, in fulfilment of the requirements for the degree**

of

Doctor of Philosophy

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DECLARATION

I, Nasrin Goolam Mahyooddeen declare that this thesis is my own work. It is being submitted for the degree of Doctor of Philosophy in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

.....

6th day of September 2019

DEDICATION

To my husband, Zakir

and

my children, Yahya and Tasmiya

انت سعادتِي

You are my happiness

PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS PROJECT

Publications

1. Goolam Mahyooddeen, N., Crowther, N.J., Tikly, M. 2018. Double trouble: psoriasis and cardiometabolic disorders. *Cardiovasc J Afr*, 29, 189-194.
2. Goolam Mahyooddeen, N., Crowther N.J., Snyman, T., Pillay, L., Tikly, M. 2018. High burden of the metabolic syndrome and its component disorders in South Africans with psoriasis. *Int J Dermatol*, 58, 557-562.

Conference presentations

1. The prevalence of the metabolic syndrome and its components in South Africans with psoriasis. *51st Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) Congress*, Cape Town, South Africa. April 2016 (poster presentation)
2. The cardiometabolic profile of patients with psoriasis and psoriatic arthritis- a case-control study in South Africans. *25th South African Rheumatism and Arthritis Association (SARAA) Congress*, Johannesburg, South Africa. February 2017 (oral presentation)
3. The cardiometabolic profile of patients with psoriasis- a case-control study. *52nd SEMDSA Congress*, Johannesburg, South Africa. May 2017 (oral presentation)

4. Prevalence and determinants of type 2 diabetes in psoriatic patients in South Africa. *18th International Congress of Endocrinology*, Cape Town, South Africa. December 2018 (oral presentation)
5. Non-alcoholic fatty liver disease in psoriasis and psoriatic arthritis. *26th SARAA Congress*, Durban, South Africa. March 2019 (oral presentation)

ABSTRACT

Background:

Psoriasis is a chronic, immune-mediated inflammatory disease in which cardiometabolic diseases (CMDs) are increasingly recognised as major comorbidities, often resulting in premature death. The aim of this research was firstly to determine the burden of CMDs and non-alcoholic fatty liver disease (NAFLD) in South Africans with psoriasis and then to investigate the interplay between visceral fat, metabolic biomarkers, adipokines and pro-inflammatory cytokines in psoriasis.

Methods and Participants:

A cross-sectional study of 103 patients with psoriasis and 98 control participants, matched for body mass index, ethnicity and gender was undertaken. The severity of cutaneous psoriasis was assessed using the Psoriasis Area and Severity Index (PASI) score. Demographic, clinical, anthropometric and biochemical data was obtained. Consenting participants (n=149) also underwent limited non-contrast abdominal CT scans to assess for visceral, subcutaneous and intra-hepatic fat. Patients were defined as having the metabolic syndrome by the Harmonised guidelines. NAFLD was defined radiologically based on a liver-to-spleen attenuation ratio (LAR) of less than one.

Results:

There was a high prevalence of CMDs, specifically MetS, type 2 diabetes (T2D) and hypertension in psoriasis patients compared to matched controls (52.4% vs. 33.7%, $p=0.007$; 25.2% vs. 4.1%, $p<0.0001$; 70.9% vs. 49.0%, $p=0.001$ respectively). Multiple logistic regression analysis showed that severe psoriasis was an independent risk factor for MetS (odds ratio [95% CIs]: 4.42 [1.72, 11.4]; $p=0.002$), hypertension (2.48 [0.97, 6.32]; $p=0.05$) and T2D (11.3 [3.07, 41.3]; $p=0.0002$).

In addition, we demonstrated that psoriasis patients had a higher visceral fat volume than control participants matched for body mass index (BMI); that visceral fat was an independent predictor of psoriasis (odds ratio [95% CI]: 1.56 [1.15, 2.11], $p<0.005$) and that its effect was mediated by the pro-inflammatory cytokine interleukin 6 (IL-6). Furthermore, psoriasis was an independent risk factor for T2D (7.94 [2.64, 23.9], $p<0.01$).

Although we found no difference in NAFLD overall between patients and controls, participants with NAFLD had a significantly higher prevalence of CMDs compared to those without NAFLD. The NAFLD prevalence was highest in patients with PsA receiving methotrexate (50.0% vs. 16.4% in participants without PsA not using methotrexate, $p<0.05$). Therapy with methotrexate in PsA, as well as insulin resistance and hypertriglyceridaemia, were independent predictors of NAFLD (odds ratio

[95% CI], odds ratio: 2.77 (1.31, 5.87), $p < 0.05$; 1.98 (1.44, 2.72), $p < 0.0001$; 1.63 (2.55, 2.52), $p < 0.05$, respectively)

Conclusions:

There is a high burden of CMDs, in this population with psoriasis, particularly in patients with severe psoriasis. Visceral fat and its mediators play a role in psoriasis-associated CMD. Patients with PsA receiving methotrexate are vulnerable to NAFLD. The present study highlights the need for CMD prevention and screening programmes in psoriasis patients and the need for further mechanistic studies into the aetiology of CMDs in psoriasis.

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“There are no shortcuts to any place worth going.”

Beverly Sills

These words could not be any more apt than for the journey known as the “PhD”. This thesis, like so many others, is the result of the hard work and dedication of several amazing people.

I wish to sincerely thank my supervisors Professors Mohammed Tikly and Nigel Crowther and Dr. Lushen Pillay who each brought unique strengths to this project. Professors Tikly and Crowther took a great deal of time and effort to share their wealth of experience and knowledge with passion, patience and a sense of humour that certainly eased the gradient of the very steep learning curve that a PhD candidate faces.

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ABBREVIATIONS

25(OH)D	25-Hydroxy vitamin D
ALP	Alkaline phosphatase
ALT	Alanine amino transferase
AST	Aspartate amino transferase
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
CKD	Chronic kidney disease
CMD	Cardiometabolic disease
CRP	C-reactive protein
CT	Computed tomography
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DC	Dendritic cell
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
GGT	Gamma glutamyl transferase
GLP 1	Glucagon-like-peptide 1
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HOMA	Homeostasis model assessment
HR	Hazards ratio

hsCRP	High-sensitivity C-reactive protein
HU	Hounsfield unit
IL	Interleukin
IQR	Interquartile range
LDL	Low-density lipoprotein
Lp(a)	Apolipoprotein A
LAR	Liver-to-spleen attenuation ratio
MACE	Major adverse cardiovascular event
MHC	Major histocompatibility complex
MetS	Metabolic syndrome
NAFLD	Non-alcoholic fatty liver disease
OR	Odds ratio
PASI	Psoriasis area and severity index
PsA	Psoriatic arthritis
PsC	Cutaneous psoriasis
ROI	Region of interest
SBP	Systolic blood pressure
SD	Standard deviation
SES	Socio-economic status
T2D	Type 2 diabetes
TNF	Tumour necrosis factor
VIF	Variance inflation factor
WAT	White adipose tissue
WC	Waist circumference

PREFACE

There is a high burden of cardiometabolic disease (CMD) in sub-Saharan Africa. Although studies have demonstrated an association between psoriasis and CMDs, there is a paucity of data on CMD in psoriasis in this region. Thus, there is very little known about the anthropometric characteristics of psoriasis patients or the prevalence of CMDs in this population. Moreover, there is a paucity of data on potential mechanisms whereby psoriasis may lead to increased CMD risk.

The hypothesis of this study was that increased adiposity results in an increased inflammatory environment which in turn increases the risk and severity of psoriasis and CMD. With this in mind, a cross-sectional case-control study of adult South Africans with psoriasis, including those with associated inflammatory arthritis referred to as psoriatic arthritis (PsA), was undertaken. In the first instance, the study focussed on the prevalence of CMDs and their association with psoriasis and visceral adiposity. Abdominal fat and non-alcoholic fatty liver disease (NAFLD) were measured by computed tomography.

This thesis is presented in a format recommended by the University of the Witwatersrand. As such, it is divided as follows:

- Chapters 1 and 2 cover the introduction and literature review, and the methods, respectively. These are written in the traditional monograph format.
- Chapters 3 to 5 are the specific studies undertaken in the course of the PhD research work. These chapters are presented in research publication format. Chapter 3 has been published in a peer-reviewed journal and Chapter 4 is currently under review.
- Chapter 6 summarises and contextualises the main findings of the research and includes study limitations and recommendations for future work.

STUDENT CONTRIBUTIONS

I was involved in all stages of the research work including conceptualisation of the project. The original hypothesis was refined in collaboration with all my supervisors. I was solely responsible for obtaining ethics approval, patient recruitment, data collection and phlebotomy. I then processed and stored all blood samples at the National Health Laboratory Services (NHLS) Research Laboratory.

Laboratory assays were conducted by laboratory technicians at the NHLS routine laboratory and overseen by Ms. Tracy Snyman. The enzyme-linked immune-sorbent assays (ELISA) were conducted by Dr. Marketa Toman. The procedure of the laboratory assays was taught to me by the NHLS scientists and I conducted limited batches of assays under their supervision. I observed the process of CT scanning for all study participants. CT scans were reported on by a specialist radiologist, Dr. Sheetal Daya. I recorded and collated all data, and performed all statistical analyses under the supervision of Professor Nigel Crowther.

CHAPTER 1 INTRODUCTION AND LITERATURE REVIEW

1.1 What is psoriasis?

Psoriasis is a complex, chronic, immune-mediated inflammatory skin disorder characterised by well-demarcated, erythematous, pruritic plaques with overlying micaceous scales (Nestle *et al.*, 2009). The word '*psoriasis*' is derived from the Greek word '*psora*', meaning 'itch' and literally means 'itching condition' (Smith *et al.*, 2006). It encompasses a broad spectrum of disease which may vary in severity from isolated plaques to involvement of almost the whole body surface area. It is associated with both extra-cutaneous manifestations and psycho-social disability and has been recognised by the World Health Organisation as a major global health challenge (Boehncke *et al.*, 2015). Psoriasis is associated with an impaired psychological quality of life which exceeds that observed in several chronic conditions including malignancy and heart failure (Rapp *et al.*, 1999).

1.2 History of psoriasis

Although it is believed that psoriasis has been prevalent since ancient times, vague and discrepant terminology in early manuscripts has resulted in great difficulty in clearly characterising the origins of the disease, which may have been confused with leprosy. The oldest, and most accurate, description of psoriasis is credited to the Roman, Cornelius Celsus (25 B.C. to 30 A.D.) (Benedek, 2013). He described a '*species of impetigo*

having various figured scales [that] fall from the surface of the skin.' A detailed report of a patient with psoriasis was described by Jasālīq, a Persian physician, in the 8th century A.D (Shafii *et al.*, 1979). In 1808, Robert Willan, a British dermatologist, is thought to have been the first Western physician to have accurately described psoriasis, in his discourse '*On Cutaneous Disease*', differentiating it from leprosy. Thomas Bateman later described the association between psoriasis and arthritis in 1813 (Nestle *et al.*, 2009).

Various treatments have historically been used for psoriasis. Most ancient physicians recognised that cutaneous lesions required topical therapy, with skin disorders often being treated with herbs and resins. Pine tar had been reported as a topical therapy used by Hippocrates. Tar ointment was used topically as treatment for psoriasis in the latter 1800s, but coal tar ointment was only introduced as topical therapy for psoriasis in 1925 (Farber, 1992). Other topical therapies for psoriasis included anthralin, chrysorabin and ammoniated mercury. One of the earliest recognised systemic therapies for psoriasis was arsenic, including a lavender-tinged tincture known as Fowler's solution (Farber, 1992). Despite their potential toxicity, arsenic-based compounds remained in use until the mid-20th century at which time corticosteroids and methotrexate were introduced.

Reports of comorbidities with psoriasis date as far back as 1897 to a German report documenting the association between diabetes and psoriasis (Takeshita *et al.*, 2017). In the 20th century, Reed *et al.* described a high prevalence of coronary artery disease at post-mortem examination in patients with psoriasis and PsA (Reed *et al.*, 1961). This was followed by a paper by McDonald and Calabresi which showed an increased prevalence of occlusive vascular disease in psoriasis patients (McDonald *et al.*, 1978). In a retrospective record review comparing 323 psoriasis, and 325 non-psoriatic dermatology patients, they reported an increased prevalence of myocardial infarction (MI), stroke, thrombophlebitis and pulmonary embolism in psoriasis patients (McDonald *et al.*, 1978).

1.3 Epidemiology

There is wide global variation in the prevalence of psoriasis, partly because accurate epidemiological data are difficult to obtain. Other factors influencing the variation in the prevalence of psoriasis include age, geography, ethnicity as well as differences in design of epidemiological studies. Patients may present at any age, but a bimodal peak in presentation has been described with the mean age of onset ranging between 16 and 22 years and 57 and 60 years for the first and second presentation respectively (Henseler *et al.*, 1985). The prevalence of psoriasis is similar in men and women (Griffiths *et al.*, 2007).

Psoriasis has an estimated prevalence in Europe of 2% (Boehncke *et al.*, 2015). A 2013 systematic review estimated the global prevalence in adults to be between 0.91% and 8.5% with the highest prevalence of psoriasis reported in Norway (Parisi *et al.*, 2013). Psoriasis is estimated to affect 125 million people worldwide. (Takeshita *et al.*, 2017). In one study, the prevalence of psoriasis is lower in African-Americans compared to Caucasians by 52% (Gelfand *et al.*, 2005).

There is a paucity of epidemiological data on psoriasis from Africa, especially sub-Saharan Africa. A Tanzanian study showed a prevalence of 0.1% (Gibbs, 1996), while in Cote d'Ivoire the prevalence was 0.75% (Kassi *et al.*, 2013). Overall, psoriasis is considered to be less common in Africans than Caucasians (Leder *et al.*, 1997).

There is a limited number of South African psoriasis studies. In a survey of dermatological outpatients in public sector hospitals in Johannesburg, the frequency of psoriasis was 2.9% with Indian patients having the highest frequency (9.6%) (Hartshorne, 2003). In keeping with other studies from Africa, psoriasis was less common in black African patients with a prevalence ranging from 0.65% (Dlova *et al.*, 2015) to 2.1% (Hartshorne, 2003). A cross-sectional study from Kwazulu-Natal demonstrated that clinical parameters alone were insufficient to assess overall disease severity in psoriasis (Hariram *et al.*, 2011). More recently, the clinical,

biochemical and radiological characteristics of psoriatic arthritis (PsA) of a South African cohort was described (Maharaj *et al.*, 2016). This study found that almost 60% of patients with PsA had a polyarticular presentation similar to rheumatoid arthritis (RA) and noted an absence of black patients with PsA (Maharaj *et al.*, 2016).

1.4 Pathology and pathogenesis

The interplay between genetic factors and environmental triggers results in the classic psoriatic plaque, characterised histologically by epidermal hyperplasia, vascular hyper-proliferation, and chronic inflammation (Krueger *et al.*, 2005) (Fig 1.1). Common triggers for the disease are local skin trauma (Koebner phenomenon), infections such as *Streptococcus pyogenes* and the human immunodeficiency virus (HIV) (Schon *et al.*, 2005). Psychological stress, high body mass index (BMI) and smoking are also considered risk factors for psoriasis (Naldi, 2004). Family and twin studies have shown a strong genetic basis for psoriasis with approximately a third of patients having a family history of psoriasis (Chandran, 2010). Genome-wide analysis studies have identified at least nine chromosomal loci (*PSORS1* through *PSORS9*) that are associated with psoriasis. *PSORS1*, located within the major histocompatibility complex (MHC) on chromosome 6p21, accounts for between 35% and 50% of the heritability of psoriasis (Trembath *et al.*, 1997). This area contains 3 major genes of interest: *HLA-Cw6* which encodes a class I MHC protein, *CCHR1* which encodes the x-helical rid protein 1 and *CDSN* which encodes

corneodesmosin. The latter 2 are over-expressed in the epidermis of patients with psoriasis (Allen *et al.*, 1999). The causative gene at this locus has been elusive because of significant linkage disequilibrium in psoriasis (Nestle *et al.*, 2009).

A complex cross-talk between keratinocytes and dendritic cells (DCs) in the skin, and T-lymphocytes, mediated by a variety of cytokines, results in keratinocyte hyperplasia, a pathological hallmark of psoriasis (Nestle *et al.*, 2009). The Th17 immune response is considered to be a central driving mechanism in the pathogenesis of the psoriatic plaque (Eberle *et al.*, 2016). Initially, keratinocytes recruit DCs to produce IL-23 and IL-12, which in turn activate mostly T helper (Th) 1 and Th17 cells, resulting in further up-regulation of cytokine secretion especially IL-17, interferon- γ (IFN γ), tumour necrosis factor (TNF) and IL-22 (Kim *et al.*, 2015). These cytokines amplify psoriatic inflammation and keratinocyte hyperplasia (Schon *et al.*, 2005).

Infiltration of the skin by cells of the Th17 lineage is a pivotal factor in the development of the psoriatic plaque (Fig 1.2). Moreover, pro-angiogenic factors produced by keratinocytes such as vascular endothelial growth factor drive abnormal vascular proliferation within the psoriatic plaque (Nestle *et al.*, 2009). The chronic course of the disease may be attributed to the re-activation of memory Th17 cells (Eberle *et al.*, 2016).

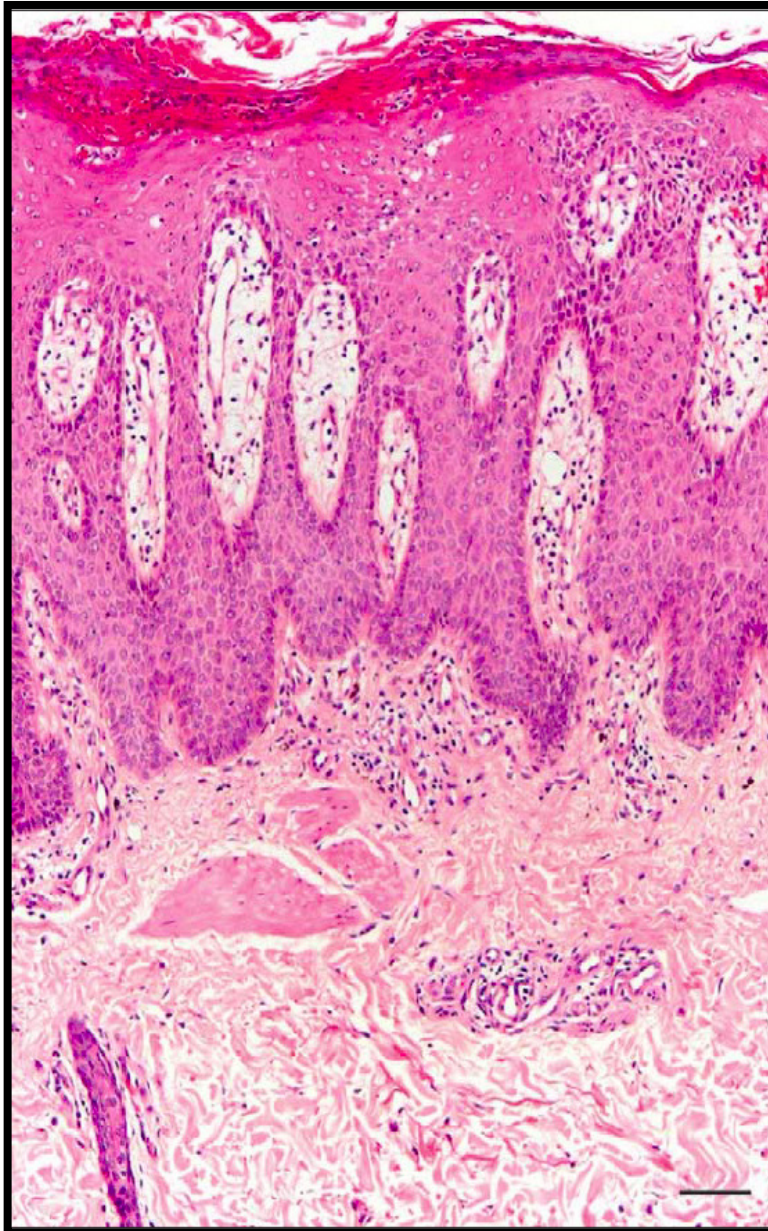


Figure 1.1 Histology of psoriasis

From *Lancet*, Griffiths *et al*, Pathogenesis and clinical features of psoriasis, 370., 263-271. Copyright © (2007) Reprinted with permission.

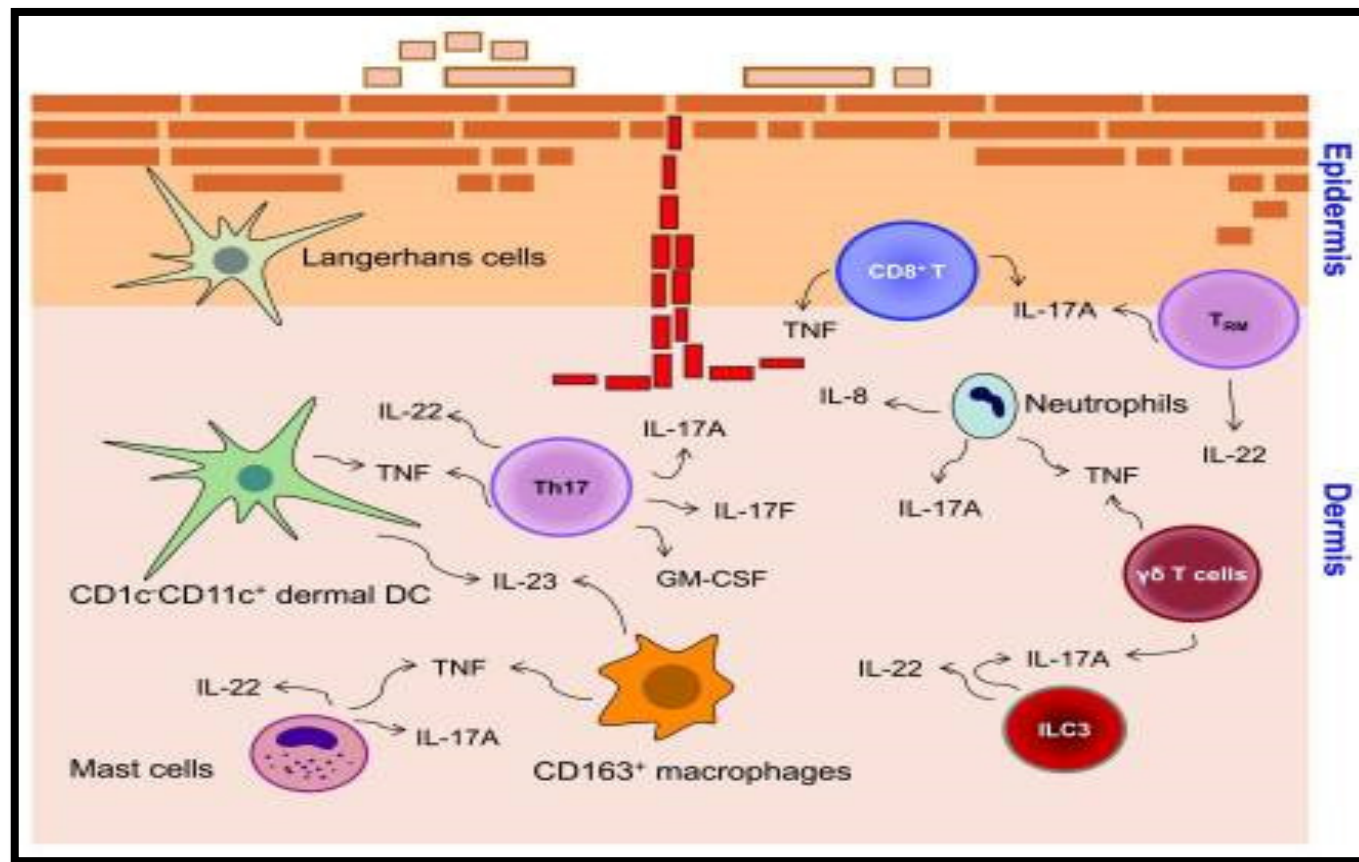


Figure 1.2 Pathogenesis of psoriasis

From *F100Res*, Eberle *et al*, Recent advances in understanding psoriasis, 5., 770. 2016) Open access.

1.5 Clinical features and sub-types of psoriasis

Psoriasis vulgaris, which accounts for 85-90% of cases, is the commonest sub-type (Nestle *et al.*, 2009). Psoriatic plaques are typically characterised by a well-demarcated erythematous base with overlying adherent silvery scales (Fig 1.3). These lesions usually occur on the extensor surfaces of the limbs, the scalp and on the trunk. Five other sub-types are recognised: guttate, erythrodermic, inverse, generalised pustular psoriasis and palmoplantar pustulosis psoriasis (Boehncke *et al.*, 2015).

Guttate psoriasis (from the Latin '*gutta*' which means 'droplet') occurs acutely in children and adolescents usually following a streptococcal infection. Although a self-limiting condition, its long-term prognosis is not known (Langley *et al.*, 2005). Erythrodermic psoriasis is a potentially life-threatening condition involving the whole body surface area. It may be complicated by high-output cardiac failure, hypothermia, and metabolic changes (Griffiths *et al.*, 2007) (Fig 1.4). The lesions of inverse psoriasis classically involve the flexures and, unlike other psoriasis sub-types, do not have overlying scales (Fig 1.5) (Langley *et al.*, 2005). Pustular psoriasis is a rare sub-type of psoriasis characterised by an eruption of monomorphic pustules associated with pyrexia (Griffiths *et al.*, 2007). Palmoplantar pustulosis may occur in association with psoriasis vulgaris. However, based on genetic studies, it is believed to be a distinct clinical entity (Langley *et al.*, 2005).



Figure 1.3 Psoriasis vulgaris

From *N Eng J Med* Schon *et al*, Psoriasis, 352., 1899-1912. Copyright © (2005) Massachusetts Medical Society. Reprinted with permission



Figure 1.4 Erythrodermic psoriasis



Figure 1.5 Flexural psoriasis

From *N Eng J Med*, Schon *et al*, Psoriasis, 352., 1899-1912. Copyright © (2005) Massachusetts Medical Society. Reprinted with permission.

1.6 Extra-cutaneous features associated with psoriasis

Up to 25% of patients with psoriasis may have an associated inflammatory arthritis commonly referred to as PsA (Griffiths *et al.*, 2007). The peripheral arthritis is typically sero-negative for rheumatoid factor and it is often associated with enthesitis and dactylitis. (Griffiths *et al.*, 2007, Ritchlin *et al.*, 2017). There are 4 variants of peripheral arthritis. The commonest are the oligo-articular (which is usually asymmetrical) and polyarticular (which may mimic rheumatoid arthritis) variants. Arthritis mutilans is a rare variant often resulting from inadequate treatment. It is characterised by joint deformities, specifically shortening and telescoping of the digits (Gladman *et al.*, 2005) (Fig 1.6). Finally, axial arthritis or spondyloarthritis can occur in isolation or in combination with one of the variants of peripheral arthritis (Ritchlin *et al.*, 2017).

Nail involvement may be seen in all sub-types of psoriasis including with PsA. The nail dystrophic changes may include pitting of the nails, onycholysis and onychodystrophy (Schon *et al.*, 2005, Langley *et al.*, 2005). Furthermore, patients with psoriasis may present with ocular manifestations which range from blepharitis and conjunctivitis to anterior uveitis (Rehal *et al.*, 2011).

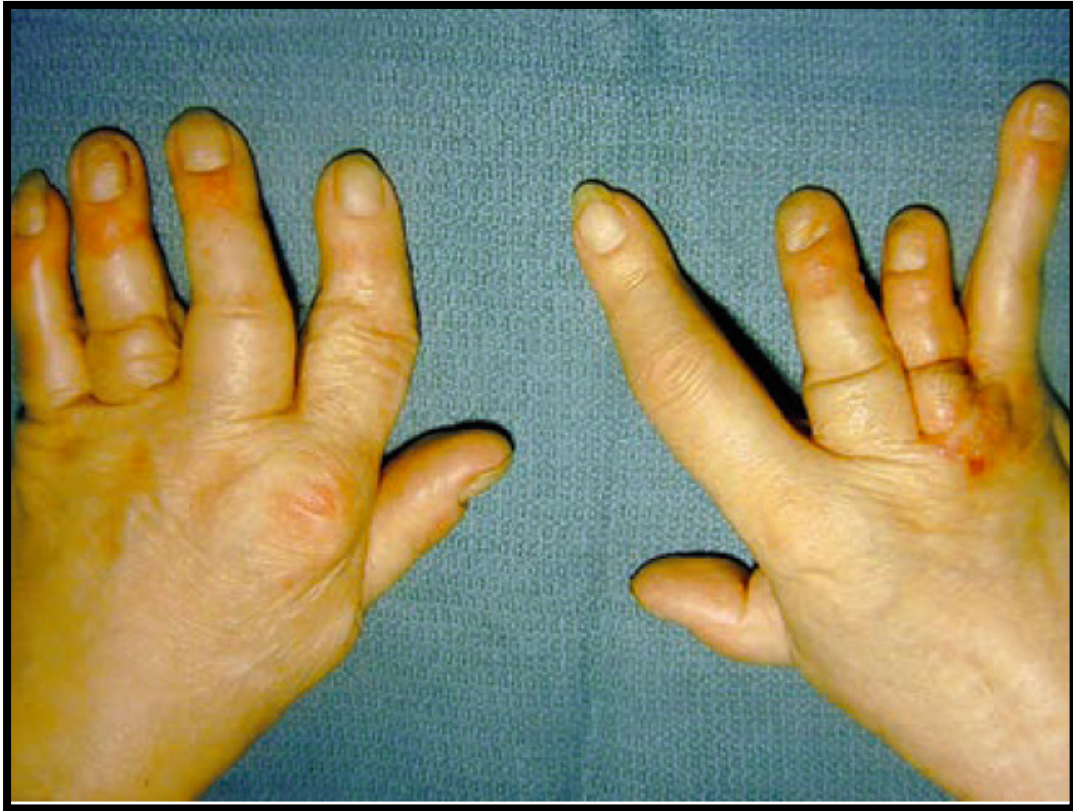


Figure 1.6 Arthritis mutilans

From *N Eng J Med*, Ritchlin et al, *Psoriatic arthritis*, 376., 957-970. Copyright© (2017) Massachusetts Medical Society. Reprinted with permission

1.7 Comorbidities associated with psoriasis

Psoriasis is increasingly recognised as a systemic disease, not only because of its association with PsA (Boehncke *et al.*, 2015), but also because serum inflammatory biomarkers are raised in psoriasis patients (Sergeant *et al.*, 2008). In addition to PsA, several other comorbidities are also associated more frequently with psoriasis than other dermatologic diseases (Henseler *et al.*, 1995). These include inflammatory bowel disease (Ni *et al.*, 2014), malignancies (Boehncke *et al.*, 2015), depression (Dommasch *et al.*, 2015), metabolic syndrome (MetS) and its components (Gisondi *et al.*, 2007, Langan *et al.*, 2012) and non-alcoholic fatty liver disease (NAFLD) (Mantovani *et al.*, 2016) (Table 1.1).

Furthermore, cardiovascular complications such as MI (Gelfand *et al.*, 2006), stroke (Gelfand *et al.*, 2009) and abdominal aortic aneurysms (Khalid *et al.*, 2016) are also more prevalent in psoriasis patients. These associations may be related to several factors including the presence of pro-inflammatory mediators in psoriasis, lifestyle-related risk factors (e.g. alcohol use and smoking) as well as treatment-related variables.

In the Nurses' Health Study, the incident risk of developing Crohn's disease was higher in women with psoriasis or PsA (relative risk (RR) (95% CI) 3.76 (1.82 7.74)) (Li *et al.*, 2013). This may be related to the fact that the susceptibility loci for the *PSORS1* gene of psoriasis and for both

ulcerative colitis and Crohn's disease lie within the 6p21 locus (Wolf *et al.*, 2008). Studies of psoriasis and malignancy have yielded inconsistent results (Ni *et al.*, 2014, Takeshita *et al.*, 2017), partly because the risk of cancer that may be attributed to psoriasis itself is unclear. However, psoriasis patients have a 41% increased risk of mortality related to cancer (Abuabara *et al.*, 2010) and lymphoma, in particular cutaneous T-cell lymphoma, has been consistently associated with psoriasis (Chiesa Fuxench *et al.*, 2016).

The best recognised association between psoriasis and infection is the development of guttate psoriasis following streptococcal pharyngitis phenomenon that is related to molecular mimicry (Takeshita *et al.*, 2017). Although the risk of infection related directly to psoriasis is not well understood, infection is the second most common cause of excess mortality in patients receiving therapy for severe psoriasis (Abuabara *et al.*, 2010). A cohort study from the Netherlands showed that psoriasis was independently associated with serious infection (hazard ratio (95% CI) 1.54 (1.44-1.65)) (Wakkee *et al.*, 2011). Unfortunately, the study was unable to correct for confounders such as smoking and alcohol abuse. Moderate to severe psoriasis has been shown to be a risk factor for chronic kidney disease (CKD) (HR (95% CI) 1.93 (1.79 – 2.08)) after adjustment for traditional risk factors (Wan *et al.*, 2013).

Psoriasis has a significant impact on a patient's health-related quality of life, (Rapp *et al.*, 1999) with physical and emotional impairments predisposing patients to psychiatric disorders including major depression, anxiety disorders and suicidal ideation (Takeshita *et al.*, 2017). The visibility of the psoriatic plaques has been suggested to cause negative psychosocial effects, high levels of psychological stress and mood disorders in psoriasis patients (Gupta *et al.*, 1995, Dommasch *et al.*, 2015). Conversely, stress has also been shown to precipitate and exacerbate psoriatic plaques. In a meta-analysis of almost 100 cross-sectional studies, psoriasis patients were found to be more likely to experience depression than controls (pooled OR (95% CI) 1.57 (1.40-1.76)) (Dowlatshahi *et al.*, 2014). It has been suggested that pro-inflammatory cytokines in psoriasis such as IL-1, TNF and interferon (IFN) gamma may act as neuromodulators and hence mediate mood disorders (Ni *et al.*, 2014).

Disease concomitance in psoriasis contributes significantly to the morbidity and mortality experienced by patients. Thus, patients with severe psoriasis had four year shorter life expectancy than healthy controls, which was due mainly to their increased cardiometabolic risk (Gelfand *et al.*, 2007).

Table 1.1 Comorbidities associated with psoriasis

Psoriatic arthritis (Griffiths <i>et al.</i> , 2007)
Inflammatory bowel disease (Ni <i>et al.</i> , 2014) Crohn's disease Ulcerative colitis
Parkinson's disease (Sheu <i>et al.</i> , 2013)
Psychiatric disease Major depression (Dommasch <i>et al.</i> , 2015) Alcohol abuse (Lindegard, 1986) Anxiety (Ni <i>et al.</i> , 2014)
Malignancy (Boehncke <i>et al.</i> , 2015) Lymphoma i.e. cutaneous T-cell lymphoma (Takeshita <i>et al.</i> , 2017)
Infection (Takeshita <i>et al.</i> , 2017, Abuabara <i>et al.</i> , 2010)
Chronic kidney disease (Wan <i>et al.</i> , 2013)
Cardiometabolic diseases Obesity (Armstrong <i>et al.</i> , 2012) Metabolic syndrome (Gisondi <i>et al.</i> , 2007, Langan <i>et al.</i> , 2012) Type 2 diabetes mellitus (Henseler <i>et al.</i> , 1995) Hypertension (Henseler <i>et al.</i> , 1995) Dyslipidaemia (Mallbris <i>et al.</i> , 2006) Myocardial infarction (Gelfand <i>et al.</i> , 2006) Stroke (Ahlehoff <i>et al.</i> , 2012, Gelfand <i>et al.</i> , 2009) Abdominal aortic aneurysms (Khalid <i>et al.</i> , 2016) Non-alcoholic fatty liver disease (Mantovani <i>et al.</i> , 2016) Hyperuricaemia and gout (Gisondi <i>et al.</i> , 2014)
Emerging disorders (Takeshita <i>et al.</i> , 2017) Chronic obstructive pulmonary disease Peptic ulcer disease Obstructive sleep apnoea syndrome Sexual dysfunction

1.8 Psoriasis and cardiometabolic disorders

There is now a large body of evidence linking chronic inflammation to accelerated atherosclerosis (Libby *et al.*, 2009). Rheumatoid arthritis was the first chronic inflammatory condition to be associated with an increased risk of premature cardiovascular death, by as much as 50% (Choy *et al.*, 2014). The traditional Framingham risk factors such as type 2 diabetes mellitus (T2D), hypertension, and smoking have been shown to only partly account for the increased cardiometabolic risk in RA (Boyer *et al.*, 2011). Mechanistically, the pro-inflammatory state of RA leads to cytokine-mediated accelerated atherosclerosis (Ku *et al.*, 2009, Sattar *et al.*, 2005). The epidemiological evidence supporting the notion that psoriasis is associated with a similar increased CMD risk is less well-established. The precise pathobiology driving atherosclerosis in psoriasis is complex and not fully elucidated. One hypothesis is that the chronic inflammatory state of psoriasis triggers a 'psoriatic march', proposed by Boehncke, which suggests a direct link between psoriasis, the pro-inflammatory condition and cardiovascular disease (CVD) (Fig 1.7) (Boehncke *et al.*, 2011).

Although not formally proven, the concept contextualises cardio-vascular comorbidity in psoriasis, purporting that the pro-inflammatory milieu in psoriasis leads to insulin resistance and subsequent endothelial cell dysfunction. This in turn causes accelerated atherosclerosis ultimately resulting in myocardial infarction (MI), stroke or other CVDs (Boehncke *et al.*, 2011). The hypothesis also considers additional factors which may

influence progression to CVD such as the effects of obesity and systemic therapy, as well as the effect of insulin resistance and epidermal homeostasis (Boehncke *et al.*, 2011).

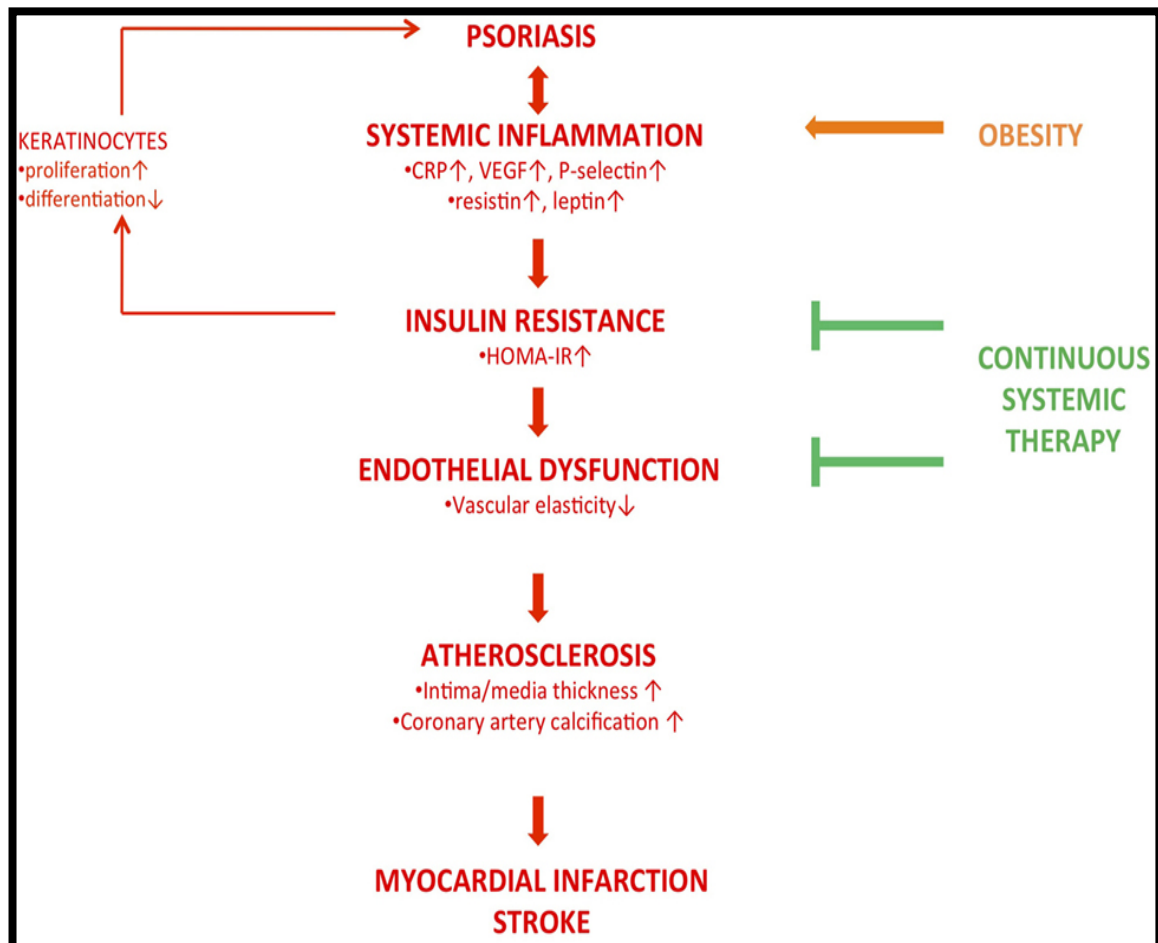


Figure 1.7 The psoriatic march

From *Exp Dermatol*, Boehncke *et al*, The 'psoriatic march' a concept of how severe psoriasis may drive cardiovascular morbidity, 20., 303-307. Copyright © (2017) Massachusetts Medical Society. Reprinted with permission.

1.9 Epidemiology of cardiometabolic disease in psoriasis

The association between CMD and psoriasis was recognised first in the late 19th century and expanded in the 20th century, as described earlier. Several recent registry-based studies, mainly from the United Kingdom (UK) and Denmark have supported the initial observations (Tables 1.2 and 1.3). In a prospective study of 130 000 psoriasis patients and more than 500 000 control participants in the UK General Practice Research Database (UKGPRD), psoriasis was found to be a risk factor for myocardial infarction (MI), with hazard ratios (HR) of 1.54 (95% CI: 1.24-1.91) and 7.08 (3.06-16.36) in mild and severe cutaneous psoriasis, respectively (Gelfand *et al.*, 2006). The increased risk remained even after controlling for major cardiovascular risk factors such as age, sex, smoking, T2D, hypertension, prior MI, dyslipidaemia and BMI.

In the Danish study of more than 36 000 psoriasis patients, psoriasis was associated with an increased risk of adverse cardiovascular events and all-cause mortality (Ahlehoff *et al.*, 2011). Younger patients and those with severe cutaneous disease appeared to have the greatest risk, a finding that was similar to that of the UKGPRD cohort. Two meta-analyses, comprising 14 cohorts of patients from Europe and the United States have shown that the risk for CVD is greatest in patients with severe psoriasis (Samarasekera *et al.*, 2013, Armstrong *et al.*, 2013c). A major limitation of many studies included in the meta-analyses was the lack of adjustment for traditional cardiovascular risk factors.

Some smaller studies have failed to show the association between psoriasis and CVD. A prospective study of 1 380 psoriasis patients, followed-up for 10 years, showed no increase in cardiovascular mortality (standard mortality ratio: 0.83, 90% CI 0.7-1.0) (Stern *et al.*, 1988). In another study comparing over 15 000 patients and over 27 000 controls, psoriasis was found to be an equivocal risk factor for admission for ischaemic heart disease (IHD), after controlling for age and sex (HR 1.10, 95% CI: 0.99-1.23) (Wakkee *et al.*, 2010). Moreover, age- and sex-matched survival analysis revealed no difference in the risk of acute MI. A recent Dutch study of 262 ambulatory psoriasis patients, over 55 years of age, showed no increase in CV morbidity and mortality (Dowlatsahi *et al.*, 2013a). The strength of this study was that CV events were identified using clinical data and specialized investigations, including CT scans, electro-, and echocardiography to minimise classification bias (all previous studies had used diagnostic codes). However, the limitations of this study were the small sample size, older age of the cohort (mean=64 years), and that most patients had mild cutaneous psoriasis. Overall, the balance of evidence suggests that psoriasis, especially severe cutaneous disease, is associated with an increased risk of CVD.

Other metabolic disorders shown to occur more frequently in psoriasis are metabolic syndrome (MetS) and its components, hyperuricaemia, and NAFLD. In a UK study, MetS was more prevalent in psoriasis patients compared to the general population, more so in patients with severe than

with mild cutaneous disease (odds ratio for mild psoriasis: 1.22, 95% CI: 1.11-1.35; severe psoriasis: 1.98, 95% CI: 1.62-2.43) (Langan *et al.*, 2012). A smaller number of studies have assessed the risk of incident psoriasis in relation to either MetS or its components. In a large, prospective, population-based study of 34 996 Norwegian participants with 13 years of follow up (the North Trøndelag Health (HUNT) Study) psoriasis was associated with an increased relative risk of MetS (1.66 (1.30, 2.14)) (Snekvik *et al.*, 2018). Furthermore, systematic reviews suggest that individual components of MetS (T2D, dysglycaemia, obesity, and hypertension) occur more frequently in psoriasis patients (Armstrong *et al.*, 2013b, Armstrong *et al.*, 2012, Armstrong *et al.*, 2011). (Table 1.4).

The association between T2D and psoriasis is well-described in the literature with studies showing both an increased incidence and prevalence of T2D in patients with psoriasis. In a nested case-control analysis the UKGPRD found an increased incidence of T2D in comparison to non-psoriatic participants with an adjusted OR of 2.56 (95%CI 1.11, 5.92) (Brauchli *et al.*, 2008) with the risk increasing with both psoriasis disease duration and severity. A Taiwanese nationwide study also showed an increased incidence of T2D in psoriasis compared to control participants (10.5 and 18.2 per 1 000 person years for mild and severe psoriasis respectively vs. 5.39 per 1 000 person-years in controls) (Lee *et al.*, 2014). Retrospective reviews of patients with psoriasis have also

demonstrated an increased risk for T2D in this group (Xiao *et al.*, 2009, Kimball *et al.*, 2008b).

Similar trends have been noted for obesity (Setty *et al.*, 2007, Neimann *et al.*, 2006) and hypertension (Qureshi *et al.*, 2009, Kaye *et al.*, 2008). Most studies also noted a risk gradient with these comorbidities being most strongly associated with severe compared to mild psoriasis.

A meta-analysis of 16 observational studies found that psoriasis patients were more likely to be obese (pooled odds ratio=1.66, 95% CI: 1.17-1.82) (Armstrong *et al.*, 2012). A combined mean BMI of 30.6 kg/m² has been observed in a review of clinical trials where biologics have been tested for the treatment of moderate to severe cutaneous psoriasis (Sterry *et al.*, 2007). Studies have also shown that psoriasis is associated with abdominal obesity, which is a proxy measure of visceral adipose tissue, and is a well-recognised risk factor for T2D, hypertension, coronary artery disease and decreased life expectancy (Janssen *et al.*, 2002). Thus, the prospective Nurses' Health Study II identified 809 incident cases of psoriasis and observed that it was more common in participants with an increased waist circumference, a surrogate marker for abdominal visceral fat (Setty *et al.*, 2007). The HUNT study demonstrated that the relative risk for MetS was attenuated from 1.66 (1.30, 2.14) to 1.33 (0.97, 1.81) after correcting for waist circumference and BMI implying that adiposity is a

driver of the association between psoriasis and MetS (Snekvik *et al.*, 2018). In a cross-sectional case-control study, participants with psoriasis were shown to have higher levels of visceral fat measured by computed tomography (CT) compared to controls (Balci *et al.*, 2010). The role of visceral fat in chronic inflammation is discussed below.

Studies have shown that patients with psoriasis have a proatherogenic lipid profile, including an increased prevalence of hypertriglyceridaemia (Langan *et al.*, 2012, Gisondi *et al.*, 2007, Mallbris *et al.*, 2006), raised total cholesterol (TC), low-density lipoprotein (LDL) cholesterol and lipoprotein(a) (Lp(a)), as well as lowered high-density lipoprotein (HDL) cholesterol (Mallbris *et al.*, 2006, Pietrzak *et al.*, 2010, Ma *et al.*, 2013). A minority of studies have shown no significant relationship of psoriasis with dyslipidaemia (Ma *et al.*, 2013). Asymptomatic hyperuricaemia is more common in psoriasis, even after correcting for confounders (age, sex, and features of MetS) (Gisondi *et al.*, 2014). Likewise, the risk of gout is increased in psoriasis and PsA (HR (95% Ci) 1.71, (1.36-2.15)) (Merola *et al.*, 2015).

1.9.1 Psoriasis and non-alcoholic fatty liver disease

Recent studies have shown a relationship between psoriasis and NAFLD (Abedini *et al.*, 2015, Candia *et al.*, 2015, Gisondi *et al.*, 2016, van der Voort *et al.*, 2014, van der Voort *et al.*, 2016, Madanagobalane *et al.*,

2012a), the latter being commonly associated with obesity and insulin resistance (Benedict *et al.*, 2017). A meta-analysis has further shown that NAFLD is more common in participants with moderate-to-severe compared to mild psoriasis, and in patients with psoriatic arthritis (PsA) (Candia *et al.*, 2015).

Non-alcoholic fatty liver disease encompasses a spectrum of disease beginning with steatosis and progressing to steatohepatitis, cirrhosis and hepatocellular carcinoma (Benedict *et al.*, 2017). The major risk factors for NAFLD include age (>50 years), obesity, T2D, insulin resistance and certain gene variants, particularly the *PNPLA3* genotype (Byrne *et al.*, 2015).

Racial and ethnic differences in the prevalence of NAFLD have also been described, with a lower prevalence documented in African-Americans compared to Caucasians (Nguyen *et al.*, 2008). Although liver biopsy is considered the gold-standard for the diagnosis of NAFLD (Pappachan *et al.*, 2017), it has the potential for procedure-related complications. Less invasive diagnostic modalities such as ultrasonography, CT scanning and magnetic resonance imaging (MRI) are used more readily in clinical practice (Dyson *et al.*, 2014).

Ultrasonography is an inexpensive, accessible imaging technique. Its key disadvantage is that accuracy of the result is operator-dependent and can be further influenced by patient-related factors such as adiposity and the presence of overlying bowel gas (Strauss *et al.*, 2007, Kinner *et al.*, 2016). Non-contrast (i.e. unenhanced) CT scanning allows for quantitative imaging and therefore greater standardisation of results (Kinner *et al.*, 2016). Magnetic resonance imaging has the potential to offer improvements on either of the former two modalities. A meta-analysis of 46 studies has shown MRI to have a sensitivity (% (95% CI)) of 97.4 (83.5-99.6) compared to CT scanning which has a sensitivity of 72.0 (59.7-81.7). (Bohte *et al.*, 2011). However, its costs are often prohibitive in the clinical setting. Transient elastography is an ultra-sound-based technique that is used to measure “liver stiffness” and detect liver fibrosis (Wong *et al.*, 2010). Although its diagnostic sensitivity may vary depending on the level of liver fibrosis, it has a sensitivity of at least 90% for significant fibrosis (Hashemi *et al.*, 2016).

Recent studies from the developing world have also shown an increased prevalence of NAFLD in participants with psoriasis compared to the general population. Thus, a study in India reported a higher prevalence of NAFLD in psoriasis (17.4%) compared to control (7.9%) participants (Madanagobalane *et al.*, 2012a) and similarly in a study from Iran (65.6% vs. 35%) (Abedini *et al.*, 2015). Older studies have also shown a high

prevalence of liver toxicity in psoriasis patients using methotrexate (Dahl *et al.*, 1971) (see 1.11.2). However, more recent studies question whether these abnormalities may have been cases of NAFLD (Lindsay *et al.*, 2009). The aetiology of NAFLD in psoriasis is not known, however, chronic sub-clinical inflammation related to visceral adiposity has been proposed as a potential mechanism explaining the link between these two diseases (Mantovani *et al.*, 2016).

Table 1.2 Longitudinal Studies arising from the UK General Practice Research Database showing cardiometabolic disease outcomes in patients with mild and severe psoriasis

Study	Psoriasis Patients	Control Participants	Variables in Multivariate Models	Main Outcomes	HR [95% CI] Mild Psoriasis	HR [95% CI] Severe Psoriasis
1 (Gelfand <i>et al.</i>, 2006)	Mild: 127139 Severe: 3837	556995	Age, gender, HT, DM, BMI, previous MI, cholesterol, smoking	Psoriasis may confer an independent risk of MI	1.54 [1.24-1.91]	7.08 [3.06-16.36]
2 (Gelfand <i>et al.</i>, 2007)	Mild: 133568 Severe: 3951	Mild: 560358 Severe: 15075	Age, sex	Severe but not mild psoriasis is associated with an increased risk of death	1.0 [0.97-1.02]	1.4 [1.3-1.6]
3 (Gelfand <i>et al.</i>, 2009)	Mild: 129143 Severe: 3603	Mild: 496666 Severe: 14330	Age, gender, HT, DM, cholesterol, smoking, cerebrovascular disease	Both mild and severe psoriasis were independent risk factors for stroke	1.06 [1.0-1.1]	1.43 [1.1-1.9]
4 (Mehta <i>et al.</i>, 2010)	Severe: 3603	14330	Age, gender, smoking, DM, HT, hyperlipidaemia	Severe psoriasis was an independent risk factor for cardiovascular mortality	-	1.57 [1.26-1.96]
5 (Abuabara <i>et al.</i>, 2010)	Severe: 3603	14330	Age, gender	Patients with severe psoriasis were at increased risk for death from CVD	-	1.57 [1.26-1.96]

HT, hypertension; DM, diabetes mellitus; BMI, body mass index; MI, myocardial infarction; HR, hazard ratio

Table 1.3 Longitudinal studies showing cardiovascular disease outcomes arising from the Danish Nationwide Cohort

Study	Sample Size	Control Group Size	Variables in Multivariate Models	Main Outcomes	RR [95%CI] Mild psoriasis	RR [95%CI] Severe psoriasis
1 (Ahlehoff et al., 2011)	Mild: 34371 Severe: 2621	4 003 265	Age, sex, comorbidities, medication	Cardiovascular mortality increased in patients with psoriasis	1.14 [1.06-1.22]	1.57 [1.27-1.94]
2 (Ahlehoff et al., 2011)	Mild: 34371 Severe: 2621	4 003 265	Age, sex, comorbidities, medication	MI increased in patients with psoriasis	1.22 [1.12-1.33]	1.45 [1.10-1.90]
3 (Ahlehoff et al., 2012)	Mild: 36765 Severe: 2793	4 478 926	Age, sex, comorbidities, medication	Psoriasis associated with an increased risk of ischemic stroke	1.25 [1.17-1.64]	1.65 [1.33-2.05]

MI, myocardial infarction; RR, risk ratio

Table 1.4 Systematic reviews showing association of type 2 diabetes, hypertension and obesity with psoriasis

Condition	No. of Studies	<u>Odds Ratio (95% CI)</u>		
		Overall	Mild psoriasis	Severe psoriasis
Type 2 diabetes (Armstrong <i>et al.</i> , 2013b)	27	1.59 (1.38-1.83)	1.53 (1.16-2.04)	1.97 (1.48-2.62)
Hypertension (Armstrong <i>et al.</i> , 2011)	24	1.58 (1.42-1.76)	1.30 (1.15-1.47)	1.49 (1.20-1.86)
Obesity (Armstrong <i>et al.</i> , 2012)	16	1.66 (1.49-1.89)	1.46 (1.17-1.82)	2.23 (1.63-2.05)

1.10 Pathophysiological basis linking psoriasis with cardio-metabolic disease

1.10.1 Inflammation: The common denominator?

There is now overwhelming evidence that chronic sub-clinical systemic inflammation accelerates atherosclerosis (Libby *et al.*, 2009) including histological studies demonstrating the presence of inflammation in atherosclerotic lesions (Paoletti *et al.*, 2004). Both innate and adaptive immunity are known to play a role in this process (Libby *et al.*, 2009). This has been well-documented in T2D (Ray *et al.*, 2009), as well as in RA (Ku

et al., 2009) and systemic lupus erythematosus (Roman *et al.*, 2003). In addition, RA has been shown to be associated with an increased risk of premature cardiovascular death (Choy *et al.*, 2014) and this association is partly linked to obesity (Lago *et al.*, 2011). Further evidence linking inflammation to atherosclerosis is that C-reactive protein (CRP), a well-recognised biomarker of inflammation is also associated with atherothrombotic disease, as well as the MetS and its components (Ridker, 2003). As psoriasis is a systemic disease, the prevailing pro-inflammatory milieu is considered to contribute to the increased CMD risk (Davidovici *et al.*, 2010).

A meta-analysis of 78 studies found significantly elevated levels of pro-inflammatory cytokines in psoriasis patients compared to controls (Dowlathshahi *et al.*, 2013b). Patients with psoriasis have high levels of inflammatory markers, with CRP, IL-6 and TNF serum concentrations being significantly higher compared to controls (Kaur *et al.*, 2017). Elevations in high-sensitivity CRP (hsCRP) are associated with subclinical atherosclerosis (Ridker, 2003). It is considered a useful clinical tool to identify patient populations at high vascular risk (Ridker, 2003) and has been shown to be elevated in patients with psoriasis as compared to non-psoriatic controls (Takahashi *et al.*, 2010). Similarly both IL-6 (Coimbra *et al.*, 2010) and TNF (Gerdes *et al.*, 2011) have also been shown to be significantly elevated in patients with psoriasis. Both TNF and IL-6 are pro-inflammatory cytokines and are over-expressed in psoriatic plaques as

well as in obesity. Tumour necrosis factor is strongly implicated in insulin resistance (Davidovici *et al.*, 2010). The mechanism whereby IL-6 contributes to the pathogenesis of psoriasis is not fully understood, however it has been proposed that it may cause increased mitogenesis at the site of psoriatic skin lesions (Castells-Rodellas *et al.*, 1992).

1.10.2 Visceral fat and adipokines

Obesity, as discussed previously, is prevalent in participants with psoriasis. In addition to the psoriatic plaque itself, adipose tissue is a further source of inflammation. White adipose tissue (WAT), which is the primary component of visceral fat is composed of adipocytes and other immunologically active cells such as macrophages (Ahima *et al.*, 2000).

Hence, it is not merely an inert storage depot, but rather a metabolically and immunologically active tissue. Adipocytes secrete various adipokines which are predominantly pro-inflammatory, e.g. leptin, visfatin, and resistin. However, they also secrete adiponectin which improves insulin sensitivity and has anti-inflammatory properties (Ronti *et al.*, 2006). A meta-analysis of observational studies in psoriasis has shown that leptin levels are elevated and adiponectin levels decreased in patients with psoriasis compared to the control populations (Kyriakou *et al.*, 2017).

Other pro-inflammatory factors that are produced by WAT include TNF, IL-1, IL-6 and plasminogen activator inhibitor type 1 (PAI-1), all of which have been shown to directly or indirectly affect endothelial cell function and insulin sensitivity (Hivert *et al.*, 2008) (Table 5). Adipokine dysregulation and the resulting inflammatory state is a central mechanism whereby visceral fat may mediate the development of various CMDs (Ahima *et al.*, 2000). A study has shown that patients with psoriasis have greater levels of visceral fat compared to healthy controls matched for age and sex (Balci *et al.*, 2010).

Table 1.5 Adipokines in psoriasis

Adipokine	Key Physiological Functions	Levels in Psoriasis
Leptin (Johnston <i>et al.</i> , 2008)	Primary function: controlling appetite via hypothalamic modulation of food intake. Plays a role in acute and chronic inflammation including up-regulating the production of inflammatory cytokines.	Increased
Adiponectin (Davidovici <i>et al.</i> , 2010)	Anti-inflammatory cytokine that correlates negatively with body mass index	Decreased
Resistin (Johnston <i>et al.</i> , 2008)	Pro-inflammatory cytokine with a link to insulin resistance	Increased
Visfatin (Gerdes <i>et al.</i> , 2011)	Pro-inflammatory cytokine that up-regulates other mediators e.g. TNF, IL-1 β , IL-6	Increased
Tumour necrosis factor (Mossner <i>et al.</i> , 2009)	Pro-inflammatory cytokine which blocks insulin signaling	Increased
Interleukin-6 (Zalewska <i>et al.</i> , 2006)	Inflammatory mediator with pro- and anti-inflammatory effects	Increased
Interleukin-17 (Lockshin <i>et al.</i> , 2018)	Pro-inflammatory cytokine	Increased
Plasminogen activator inhibitor type I (Nordt <i>et al.</i> , 1999)	Plays a role in vascular endothelial dysfunction due to accumulation of fibrin	Increased

1.10.3 Possible genetic links

Epidemiological studies suggest a common genetic link between psoriasis, T2D and obesity. In a 2016 cross-sectional, population-based twin study in 33 588 Danish participants a significant association between psoriasis, T2D and obesity was observed (Lonnberg *et al.*, 2016). Analysing data from twins discordant for psoriasis and including both monozygotic and dizygotic twin pairs, the study observed evidence for a shared genetic aetiology of obesity and psoriasis.

Moreover, there is evidence indicating that the strongest predictor of major adverse cardiovascular events (MACE) in patients with psoriasis is a family history of CVD (Egeberg *et al.*, 2016). In a study of more than 25 000, mainly young, Danes with mild psoriasis, and over 4000 patients with severe disease, approximately two-thirds of patients in each group had a family history of CVD. The adjusted incidence rate ratios of MACE (with 95% CI) in patients with a family history of cardiovascular events were 1.28 (1.12-1.46) in those with mild psoriasis, and 1.62 (1.14-2.30) in participants with severe psoriasis. There was no increased risk for MACE in psoriasis patients without a family history of CVD.

1.10.4 Conventional cardiovascular risk factors

Patients with psoriasis have a higher burden of classic CV risk factors compared to the general population (Gisondi *et al.*, 2010, Prey *et al.*,

2010). In particular, and as discussed previously, there are higher prevalences of T2D, dyslipidaemia, hypertension and obesity, in participants with psoriasis. Furthermore, it is known that patients with psoriasis have a higher prevalence of smoking than those who do not have psoriasis (Armstrong *et al.*, 2014b). Smoking has also been linked to a higher risk of psoriasis. Thus, in a meta-analysis of 25 studies the odds ratio for psoriasis was 1.78 (95% CI 1.53-2.06) in smokers compared to non-smokers (Armstrong *et al.*, 2014b).

Smoking may increase the risk of psoriasis by increasing oxidative stress, and nicotine induces the production of pro-inflammatory cytokines including IL-12, TNF and IL-2 (Naldi, 2016). Furthermore, smoking may also negatively affect the course of psoriasis. Smoking more than 20 cigarettes per day was associated with a two-fold increased risk of severe psoriasis as opposed to those who smoked 10 or less cigarettes per day (Fortes *et al.*, 2005). Analyses for men and women demonstrated this effect was greater for women (OR, 1.8; 95% CI, 1.2-2.6, for a 400-U (which corresponds to 20 cigarettes a day for 20 years) increase in cigarette-years) than for men (OR, 1.2; 95% CI, 0.9-1.6, for a 700-U (which corresponds to 20 cigarettes a day for 35 years) increase in cigarette-years) (Fortes *et al.*, 2005).

1.10.5 Other factors

Psoriasis therapy

Attempts to explain the association between psoriasis and CMD is complicated by the use of conventional anti-psoriatic therapies. Drugs such as acitretin, and cyclosporine as well as corticosteroids, which are used to treat both severe cutaneous psoriasis and PsA, potentially increase the risk of CMDs (Pietrzak *et al.*, 2013). These agents may precipitate weight gain and unmask hypertension, T2D, and dyslipidaemia (Boehncke *et al.*, 2015, Carretero *et al.*, 2013). Furthermore non-steroidal anti-inflammatory drugs, used in the treatment of PsA increase the risk of hypertension and CVD (McGettigan *et al.*, 2006). Methotrexate, a dihydrofolate reductase inhibitor, which is used at low doses to treat psoriasis, has anti-inflammatory properties. Similarly, biologic therapies including anti-TNF therapies are not associated with increased CMD risk and some studies have shown them to be protective (Sattar *et al.*, 2007).

Socioeconomic status, level of education and psoriasis

Psoriasis is known to be associated with lower socio-economic status (SES) and lower education levels. In a French cross-sectional study of 903 patients both lower SES and lower education were associated with severity of psoriasis (Mahe *et al.*, 2017). A recent analysis of patients enrolled in the Psoriasis Longitudinal Assessment and Registry (PSOLAR) showed a strong association between poor psoriasis control and lower

education (Kimball *et al.*, 2018). It is significant that measures of SES and education level have been shown to increase CVD risk (Schultz *et al.*, 2018).

1.11 Medical management of psoriasis

The treatment of psoriasis depends on the sub-type, site and surface area involved. Treatment modalities vary from the use of topical therapies to systemic immunosuppressive agents and most recently include biologic agents. Drug interactions and systemic adverse events often limit the use of anti-psoriatic drugs and require that patients be closely monitored.

1.11.1 Topical therapy

Topical therapies for psoriasis include: moderate to potent glucocorticoid preparations, vitamin D analogues (calcipotriene), coal tar preparations, retinoids such as tazarotene and tacrolimus (Raboobee *et al.*, 2010).

These agents are generally prescribed alone for patients with mild or limited cutaneous disease and as adjunctive therapy for patients receiving systemic therapy (Menter *et al.*, 2009a). Ultraviolet A spectrum light in combination with either topical or oral psoralens (known as PUVA) is an extremely effective treatment strategy. However, the major concerns around its long-term use are related to melanoma and squamous cell carcinoma risk (Naldi *et al.*, 2005b, Archier *et al.*, 2012).

1.11.2 Systemic therapy

Systemic therapy is indicated for severe cutaneous psoriasis, PsA or in those patients who, despite having limited disease, have debilitating symptoms (Menter *et al.*, 2009b). Oral glucocorticoids are not considered a part of the therapeutic armamentarium owing to their risk of precipitating generalised pustular psoriasis when discontinued (Brenner *et al.*, 2009).

Traditional effective systemic anti-psoriatic therapies include:

methotrexate, acitretin, and cyclosporine. Recent attention has focussed on the use of biologic agents for the management of psoriasis which may be classified as either T-cell targeted therapies (alefacept, efalizumab) or cytokine modulators. The latter include TNF inhibitors e.g. adalimumab, etanercept and infliximab, IL-12/23 monoclonal antibody i.e. ustekinumab or IL-17A inhibitors such as secukinumab and ixekizumab and brodalumab (Ronholt *et al.*, 2017). Biologic agents are indicated for severe disease refractory to oral immunosuppressive agents.

Methotrexate

Methotrexate, a competitive inhibitor of dihydrofolate reductase, is the oldest systemic anti-psoriatic therapy and remains both commonly used and highly effective (Lebwohl *et al.*, 2005). However, it is not an innocuous agent and its chronic use is associated with several adverse effects including myelosuppression, pulmonary fibrosis and hepatotoxicity (Lebwohl *et al.*, 2005, Menter *et al.*, 2009b).

Hepatotoxicity is of particular concern in patients with psoriasis as it has been shown to be more frequent in such patients, particularly in PsA (Helliwell *et al.*, 2008). The precise reasons for this are not known. Histologically methotrexate-associated liver toxicity may mimic or overlap with non-alcoholic steatohepatitis. Psoriasis patients who were overweight or who had T2D were more likely to develop hepatic fibrosis on methotrexate therapy (Rosenberg *et al.*, 2007). However, a study has also reported that methotrexate therapy may exacerbate steatohepatitis in patients with risk factors for NAFLD, but may also cause liver injury related to a high cumulative dose (Langman *et al.*, 2001).

Acitretin

Acitretin is a systemic retinoid commonly associated with muco-cutaneous side-effects such as brittle nails, cheilitis, sticky skin and palmoplantar desquamation (Lebwohl *et al.*, 2005). It is also known to be teratogenic and is associated with derangements of liver function in a small proportion of patients. Its use is also associated with dyslipidaemia, specifically hypertriglyceridaemia (Yamauchi *et al.*, 2003).

Other therapies

Cyclosporin A, a calcineurin inhibitor, is considered to be a highly effective, if not the most effective, oral drug to treat psoriasis (Lebwohl *et al.*, 2005). However, its significant systemic adverse effect profile,

including hypertension, electrolyte abnormalities, renal and hepatic impairment, may preclude its long-term use. (Faerber *et al.*, 2001). Close monitoring is recommended if it is used for longer durations (Shupack *et al.*, 1997).

Several drugs have been used “off-label” to treat psoriasis when traditional therapies have been unsuccessful. These include: hydroxyurea, azathioprine, sulfasalazine and 6-thioguanine (Menter *et al.*, 2009b).

Biologic Therapies

The term biologic therapy usually refers to a sub-set of large molecules that are designed to offer targeted therapy for a particular condition and usually includes monoclonal antibodies as well as receptor fusion proteins (Ronholt *et al.*, 2017). They are highly effective in most cases of moderate to severe psoriasis and PsA. While they have proved safe and useful in short-term studies, their long-term outcomes have not yet been fully explored. At present, they are largely used as second-line therapy, not least of all because of their high cost (Boehncke *et al.*, 2015). Aside from their efficacy in PsA, there remain questions relating to the utility of biologic agents in addressing comorbidities associated with psoriasis.

1.12 Strategies to reduce cardiovascular risk in psoriasis

Psoriasis management guidelines in the first world highlight the importance of addressing cardiometabolic risk factors. However, there is a need for further research to address whether systemic therapy for psoriasis may potentially ameliorate CVD risk (Menter *et al.*, 2011, Johnsson *et al.*, 2012).

1.12.1 General Measures

Several expert groups recommend clinical and biochemical screening of psoriasis patients for early detection and management of comorbidities such as hypertension, dysglycaemia and lipid abnormalities (Kimball *et al.*, 2008a). The cessation of smoking, which is common in psoriasis (Neimann *et al.*, 2006, Naldi *et al.*, 2005a) is critical to management in this group of patients (Johnsson *et al.*, 2012).

Weight reduction not only reduces cardiovascular risk, but has also been shown to attenuate the severity of psoriasis. A randomised control study investigating the impact of hypocaloric dietary intervention and physical activity over 20 weeks, in 303 overweight/obese patients with moderate to severe plaque psoriasis, demonstrated a 48% reduction in psoriasis area and severity index score in the intervention arm, compared to only 25.5% in the information-only arm ($p=0.02$) (Naldi *et al.*, 2014). The weight loss target of $\geq 5\%$ was achieved in 29.8% of the intervention arm compared

with 14.5% in the information-only arm ($p=0.001$). There are also anecdotal case reports of improvement in psoriasis following bariatric surgery (de Menezes Ettinger *et al.*, 2006, Hossler *et al.*, 2011).

1.12.2 Drug therapy

Anti-inflammatory agents used in the treatment of psoriasis

Given the earlier discussion on chronic systemic inflammation as a risk factor for CMD, there is emerging evidence that controlling inflammation reduces the risk of CMD. There are several lines of clinical and biochemical evidence suggesting that methotrexate, a drug widely used for the treatment of moderate-severe cutaneous psoriasis and PsA, has anti-inflammatory and cardio-protective properties. Thus, methotrexate was found to provide a substantial survival benefit mainly by reducing cardiovascular mortality in RA (Choi *et al.*, 2002). The cardio-protective effect of methotrexate is mediated by increased adenosine levels that bind to adenosine A2 receptors on macrophages and block foam cell formation (Cronstein, 2010, Reiss *et al.*, 2008).

In psoriasis, methotrexate and biologics like the TNF inhibitors have been shown to lower the risk for CVD (Ahlehoff *et al.*, 2013). Use of these agents in a Danish study has shown lower incidence of annual rates of death, MI and stroke than patients on other therapies with incidence (95% CI) rates of 6.0 (2.7-13.4) and 17.3 (12.3-24.3) for biologics and

methotrexate, respectively, compared to 44.5 (34.6-57.0) for other therapies.

Data from a small prospective study and retrospective analyses suggest that systemic anti-inflammatory therapies (such as methotrexate or TNF inhibitors) in participants with psoriasis or PsA may have the potential to ameliorate cardiovascular disease (Armstrong *et al.*, 2014a, Ahlehoff *et al.*, 2013). While these have generated considerable interest, no conclusive data from randomized clinical trials is available to date. The advent of biologic therapies for psoriasis in recent years has raised the question as to whether these agents may offer potential cardiovascular benefit. A meta-analysis of 22 randomised controlled trials of IL-12/23 antibodies and anti-TNF agents showed there was no significant difference, in comparison to placebo, for adverse cardiovascular events with these agents (Ryan *et al.*, 2011).

Conversely treatment with anti-diabetic drugs, pioglitazone (Malhotra *et al.*, 2012) and glucagon-like-peptide 1 (GLP 1) agonists (Ahern *et al.*, 2013) have been shown to improve psoriasis. Pioglitazone is a well-known insulin-sensitising agent, hence its efficacy may support the role of insulin resistance in the pathogenesis of psoriasis. The GLP 1 agonists are thought to be effective as a result of their extra-pancreatic effects, particularly their anti-inflammatory action (Drucker *et al.*, 2011). However,

they may also exert indirect effects as their use is also associated with weight loss.

1.13 Summary and research gaps

A growing body of evidence now supports the association between CMDs and psoriasis. The risk for CMDs appears to be greatest with moderate-to-severe psoriasis and PsA. Based on the literature review it is apparent that there are no published data to date on the burden of CMDs in patients with psoriasis in sub-Saharan Africa. This is especially relevant since the burden of non-communicable diseases in this region is increasing and rivals infectious disease as the major cause of morbidity and mortality in adults (Dalal *et al.*, 2011, Mayosi *et al.*, 2009).

Secondly, there is a fairly large body of evidence relating to the complex interactions between body adiposity, chronic inflammation and the psoriatic plaque which leads to increased CVD risk (Davidovici *et al.*, 2010). Apart from genetic factors that might be common to both psoriasis, obesity and CMDs, there remain many gaps in our understanding of the precise mechanisms and mediators of these interactions. Finally, there is a general paucity of data on NAFLD in sub-Saharan Africa and particularly, the interaction of obesity and NAFLD in this region.

1.14 Hypothesis and aims

The overarching hypothesis of this research work is that increased adiposity results in an increased inflammatory environment which increases the risk and severity of psoriasis and CMD (Fig 1.8).

Specifically, an increase in visceral fat, contributes to the inflammatory milieu via the secretion of pro-inflammatory adipokines. This increases the risk and severity of psoriasis. Furthermore, pro-inflammatory mediators secreted by the psoriatic plaque itself augments the prevailing inflammatory burden.

With this in mind, the overall aim of this study was to determine whether psoriasis is associated with a higher risk for CMDs (T2D, hypertension, dyslipidaemia and NAFLD) and whether visceral fat and associated adipokines mediate these associations. The specific objectives are described below:

1. To describe and compare characteristics of patients with mild or severe psoriasis patients with matched controls. The following characteristics of all cases were evaluated and compared with controls:
 - a. Anthropometric measurements
 - b. CMD prevalence
 - c. Biochemical parameters

2. To measure by CT scanning, abdominal fat in all consenting cases and controls and to assess the association of visceral fat with risk for CMDs and psoriasis, and whether any of these associations are mediated by adipokines
3. To assess liver function and the prevalence of NAFLD in cases and controls and determine the risk factors for NAFLD

The objectives were met by conducting a cross-sectional case-control study in adult psoriasis and PsA patients. Demographic, clinical, biochemical and imaging features were documented to assess the prevalence of CMD's and determine the association with psoriasis and visceral adiposity.

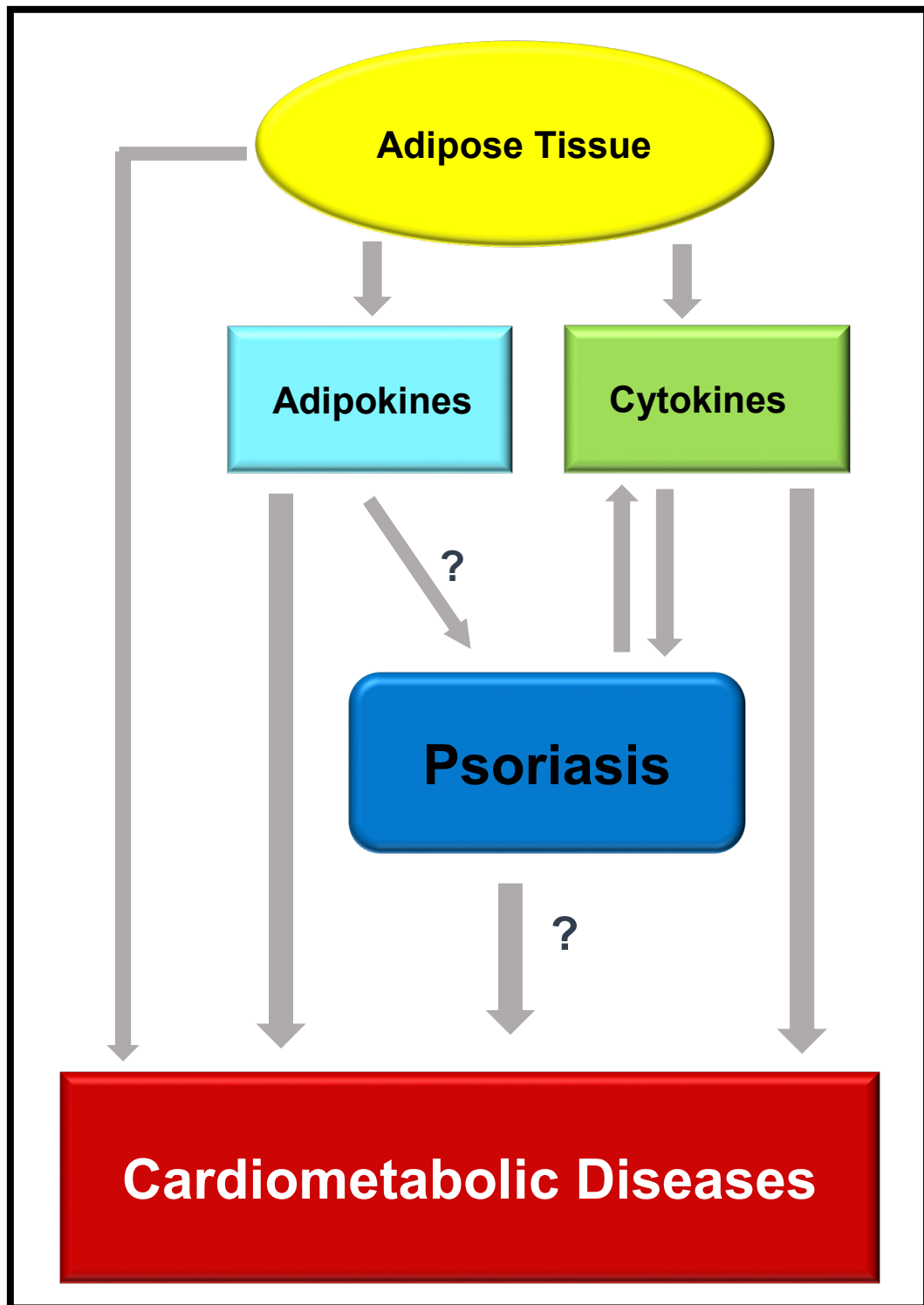


Figure 1.8 Relationship between adipose tissue and cardiometabolic diseases in psoriasis

CHAPTER 2 METHODS

2.1 Study population

2.1.1 Site Selection

Patients were recruited from the Dermatology and Rheumatology clinics of the University of the Witwatersrand Academic Hospital Complex i.e., Charlotte Maxeke Academic Hospital, Chris Hani Baragwanath Academic Hospital and Helen Joseph Hospital in Johannesburg, South Africa. The diagnosis of psoriasis and/or PsA was made by a dermatologist and/or rheumatologist. Consecutive, consenting patients were recruited into the study as per the sample size calculation (see below).

2.1.2 Sample Size

A sample size calculation was performed based on the use of multivariable logistic regression analysis, which was the principle statistical method used in this study. We assumed a minimum effect size (r^2) of 0.15, with 80% power at the 5% significance level and a maximum of 11 predictor variables per regression model. This gave a final sample size of 122 participants.

The total sample size was 201 participants which included 103 patients and 98 controls that were recruited into the study from January 2015 to September 2016. Complete data, including CT measures, was collected

on 149 participants (69 patients and 80 controls). Complete blood data was available for 188 out of the 201 study participants (91 patients and 97 controls) due to insufficient serum volumes. Fifty two additional participants were recruited and data collected but this excluded CT measures due to either failure to consent or infrastructural constraints. An analysis comparing those participants who underwent CT scanning versus those not included in CT studies showed no significant differences in the characteristics of the 2 groups (data shown in Appendix 3, Table A1).

It should be noted that sub-group analyses were also performed in this study, particularly comparing the psoriasis and control groups. Within these analyses the sample size for the psoriasis and control groups varied between 69 to 103 cases, and 80 to 98 controls. These sample sizes were deemed to be sufficient based on data from other studies (Vachatova *et al.*, 2016, Balci *et al.*, 2010) and the experience of the investigators. A sample size calculation was performed for the analysis of NAFLD prevalence between psoriasis cases and controls, and this is described in Chapter 5. Sub-group analyses performed across 3 or more groups e.g. controls, mild and severe psoriasis cases were possibly underpowered, and must be considered as one of the limitations of the current study.

2.1.3 Participant Selection

Inclusion criteria:

Patients 18 years or older who have been diagnosed clinically with psoriasis or PsA.

Exclusion criteria:

Patients less than 18 years of age, human immunodeficiency virus seropositivity, pregnancy or inflammatory arthritis due to another cause e.g. rheumatoid arthritis, ankylosing spondylitis.

Exclusion criteria for CT scan:

Participants who did not consent were excluded from CT scanning.

Control participants

Control participants were individuals without any known chronic immune-mediated inflammatory disorder and were matched for area of residence, gender, ethnicity and BMI. These individuals were recruited from the patients' residential area i.e. the patient was requested to bring in an unrelated individual e.g. friend, neighbour, spouse that had not been diagnosed with psoriasis.

2.2 Data collection

Clinical data were documented by a combination of a clinical records review, socio-economic status (SES) questionnaire, clinical examination and laboratory investigations. Demographic details included age, gender, ethnicity (black African, Asian-Indian, Caucasian, mixed ancestry) based on self-reporting by the study participant and level of education. The

medical history encompassed a history of smoking, alcohol intake and comorbidities, and therapy for psoriasis. The latter included four types of anti-psoriatic therapy, namely, topical therapy, oral methotrexate, oral acitretin and other immunosuppressive agents.

The clinical parameters that were documented were anthropometric measures of weight, height, waist circumference, hip circumference, blood pressure, type of psoriasis and presence of PsA. The severity of cutaneous involvement was assessed by the Psoriasis Area and Severity Index (PASI) score. The PASI score is a composite measure of psoriasis severity in which lesions are quantitatively assessed based on the presence of scaling, erythema and induration. A final score is derived after weighting for the severity of the lesion and the body surface area involved (Appendix 4) (Puzenat *et al.*, 2010). Socio-economic status was quantified based on the participants' response to a validated South African questionnaire (Griffiths *et al.*, 2008) (Appendix 5). Briefly, the questionnaire defines SES according to an individual's access to a defined list of 12 household items i.e. television, radio, computer, electricity, microwave, motor vehicle, satellite, fridge, washing machine, DVD player, telephone and cellular phone. Participants with a score greater than 10 were classified as having high SES. The educational status of participants was classified as whether or not they had completed high school.

2.2.1 Anthropometric and blood pressure measurements

Weight in kilograms (kg) was measured in participants with light clothing, without shoes. It was used together with height to the nearest centimetre (cm) to calculate the BMI (kg/m²). The waist circumference was measured using a soft tape measure at the midpoint of the upper border of the iliac crest and the lower border of the last rib. The hip circumference was taken as the measurement around the widest portion of the buttocks. Visceral and subcutaneous fat was quantified based on a non-contrast CT scan at the level of L4 (see below). The BP was measured with the participant seated. A minimum of 2 readings was taken 10 minutes apart and the mean of 2 readings was recorded.

2.2.2 Blood analyte measurements

We performed venous sampling after an overnight fast. Plasma glucose, serum lipids (total cholesterol, triglycerides and high density lipoprotein (HDL) cholesterol), liver enzymes (gamma glutamyl transferase (GGT), alkaline phosphatase (ALP), aspartate amino transferase (AST) and alanine amino transferase (ALT), urea and creatinine were measured using enzymatic methods on the ADVIA 1800 chemistry autoanalyser (Siemens Healthcare Diagnostics, Tarrytown, NY, USA). Low density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula (Friedewald *et al.*, 1972). Measurement of high-sensitivity C-reactive protein (hsCRP) and apolipoprotein A (Lp(a)) were performed by immunoturbidimetric methods and 25-hydroxy vitamin D levels (25[OH]D)

was measured using a chemiluminescence method on the ARCHITECT system (Abbott, Illinois, USA). Enzyme-linked immunosorbent assay (ELISA) kits were used to measure TNF (Quantikine R&D systems, Abingdon, UK), leptin (Biovendor Research and Diagnostic Products, Czech Republic, EU), adiponectin (Quantikine R&D systems, Abingdon, UK), and IL-6 (Quantikine R&D systems, Abingdon, UK).

2.2.3 Abdominal fat measurements

Multidetector CT scan (Brilliance 16, Philips, Netherlands) using the intervention pre-biopsy protocol was used to obtain non-contrast axial images at the level of the L4/L5 intervertebral disc space. The imaging was done within one month of the clinical assessment and time of blood sampling. This consisted of 16 x 3mm contiguous slices at 3mm increments (KVp 120, mAs 250, FOV 350mm, matrix 512 x 512). The images were transferred to an Apple work station and assessed using the open source image analysis software Osirix (Osirix Foundation, Geneva, Switzerland) (Rosset *et al.*, 2004). Using multiplanar reformatting, 7 slices were selected from immediately below the L4 pedicle to the level of the L4/L5 disc (Shuster *et al.*, 2012).

This stack of slices was saved as a separate volume-of-interest, for measurement of intra- and extra-abdominal fat. A closed polygon drawing tool was used to demarcate visceral adipose tissue and abdominal

subcutaneous adipose tissue. The subcutaneous adipose tissue region was bound by parietal peritoneum or fascia transversalis, and excluded the vertebral column as well as the paraspinal muscle. The subcutaneous adipose tissue was defined as fat superficial to the parietal peritoneum and included paraspinal and abdominal musculature.

In order to measure intra-peritoneal fat, all extra-peritoneal pixels were set to zero to prevent bleeding of pixels from the extra-peritoneal compartment. The segmentation tool was used to seed the fat of the entire volume-of-interest, excluding bowel, bone, muscle and major vessels to produce the intra-peritoneal fat volume. Similarly, to obtain the extra-peritoneal fat volume, the intra-peritoneal pixels were set to zero, and the segmentation tool was utilized to seed the extra-peritoneal fat, excluding bone and muscle. The region-of-interest (ROI) volume function was used to calculate the volume of both intra- and extra-peritoneal fat.

2.2.4 Assessment of non-alcoholic fatty liver disease

Hepatic fat was measured by selecting three ROIs through the mid-level of the liver and spleen. Liver and spleen attenuation, measured in Hounsfield units (HU), was determined by calculating the mean (HU) of the ROI in each organ. These values were then used to calculate the liver-to-spleen attenuation ratio (LAR) (Davidson *et al.*, 2006). Participants with a history of excessive ethanol use were excluded from CT scanning. The presence

of NAFLD was defined based on a LAR of less than one (Davidson *et al.*, 2006) i.e. the lower the LAR, the greater the hepatic fat content.

2.2.5 Diagnosis of cardiometabolic diseases

Metabolic syndrome was defined according to 2009 Harmonised guidelines (Alberti *et al.*, 2009). In patients without a history of T2D and hypertension, the diagnosis of T2D was based on a fasting plasma glucose > 7 mmol/L (2015). Impaired fasting glucose and hypertension were defined as per the Harmonised guidelines (Alberti *et al.*, 2009), as was MetS. In order to diagnose MetS three or more of the following five abnormalities need to be present: (i) increased abdominal circumference (cut-off points used: black, white, and coloured males: ≥ 94 cm; Indian males: ≥ 90 cm, all females ≥ 80 cm); (ii) elevated BP: systolic > 130 mmHg and/or diastolic > 85 mmHg and/or on anti-hypertensive treatment; (iii) raised fasting plasma glucose > 5.6 mmol/L and/or on anti-diabetic treatment; (iv) elevated fasting triglycerides ≥ 1.7 mmol/L and/or on treatment for high triglycerides; (v) reduced HDL cholesterol ≤ 1.0 mmol/L in males and ≤ 1.3 mmol/L in females.

Estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modified Diet in Renal Disease equation (Levey *et al.*, 2006), based on a previous large population-based cohort study of chronic kidney disease in psoriasis (Wan *et al.*, 2013). The Framingham general

cardiovascular risk profile was used to quantify cardiovascular risk in all eligible patients with available data (D'Agostino *et al.*, 2008) (Appendix 6).

2.2.6 Assessment of cardiovascular risk

The Framingham 10-year risk of general CVD score (D'Agostino *et al.*, 2008) was used to calculate CVD risk in all patients (Appendix 6). This is a multivariable, gender-specific risk assessment tool that is used to predict the risk of all CVD based on evaluation of the Framingham study participants. The following variables are taken into account when calculating the Framingham risk score: age, total and HDL cholesterol levels, systolic blood pressure, smoking and T2D status. (Each variable is scored based on a pre-defined score sheet. The final score determines CVD risk (%)) (D'Agostino *et al.*, 2008).

2.3 Data analysis

Data were recorded and entered into a Microsoft Excel spreadsheet. Participants were anonymised by allocating each a unique study number which was used to identify clinical records CT scans and laboratory specimens.

2.3.1 Statistical methods

All analyses were performed using Statistica version 13.2 (StatSoft, Tulsa, OK, USA). The demographic and clinical characteristics of the patients were presented using means $\pm$ standard deviations (SD) or medians and interquartile ranges (IQR) for continuous variables with normal or skewed distribution, respectively, and as proportions (%) for categorical variables. Data that was not normally distributed was log transformed to normality before being analysed using parametric statistical tests. Categorical variables were compared across groups using the χ^2 test. Continuous variables were compared between groups using Students unpaired t test or ANOVA and, where appropriate ANCOVA was used with adjustment for age and waist circumference (see Chapter 3).

2.3.2 Multivariable logistic regression models

Relationship of mild and severe psoriasis with the metabolic syndrome

Logistic regression analysis was used to assess whether the relationships of mild and severe psoriasis with MetS, T2D, hypertension, high triglycerides and low HDL were affected after adjusting for possible confounders i.e. age, BMI, hsCRP, smoking, education and SES (see Chapter 3).

Predictors of psoriasis and cardiometabolic disorders

In Chapter 4 risk factors for psoriasis were isolated by performing univariate logistic regression analyses of study variables with psoriasis. All variables with $p < 0.20$ in the univariate models were included as independent variables into a single multivariable logistic regression model with psoriasis as the dependent (outcome) variable. Backward, stepwise removal of non-significant variables was performed until all variables in the model were significantly ($p < 0.05$) related to psoriasis.

Multivariable logistic regression analysis, performed using the same process as for psoriasis, was used to isolate the predictors for the following cardiometabolic disorders: MetS, T2D, hypertension, hypertriglyceridaemia, hypercholesterolaemia, high LDL and low HDL. Multi-collinearity was assessed in all models using the variance inflation factor (VIF) and independent variables with a $VIF > 5.0$ were excluded from the model (see Chapter 4).

Particular note was taken of the multivariable models in which visceral fat and/or psoriasis were included as independent variables in the initial model. In those models, where either of these variables did not continue through to the final model, forward regression analysis was performed to determine which variable was responsible for attenuating their effect on the particular outcome variable. The variables chosen for addition to the

forward regression model were any of those included in the initial multivariable model and particularly those that continued through to the final model. Variables were also chosen based on scientific plausibility (see Chapter 4).

Predictors of hepatic dysfunction

In Chapter 5 a multivariable logistic regression model was performed for NAFLD, This regression model was developed using the same methods as described above and multi-collinearity was identified as previously described (see Chapter 5).

2.4 Ethics

The study was approved by the University of the Witwatersrand Human Research Ethics Committee (HREC) on 28 April 2014 (Clearance certificate number: M1403100) (Appendix 7).

CHAPTER 3 HIGH BURDEN OF THE METABOLIC SYNDROME AND ITS COMPONENT DISORDERS IN SOUTH AFRICANS WITH PSORIASIS

3.1 Introduction

Psoriasis is a complex, chronic immune-mediated inflammatory skin disorder that has a global prevalence ranging between 0.91-8.5% (Parisi *et al.*, 2013). A wide range of comorbidities associated with psoriasis have been identified, including inflammatory arthritis (referred to as psoriatic arthritis (PsA)) (Griffiths *et al.*, 2007), Crohn's disease (Griffiths *et al.*, 2007), malignancies (Griffiths *et al.*, 2007) and chronic kidney disease (CKD) (Wan *et al.*, 2013). Furthermore, several studies in mainly Caucasian populations have shown an increased prevalence of metabolic syndrome (MetS) (Singh *et al.*, 2017) and its component disorders, i.e., obesity (Armstrong *et al.*, 2012), hypertension (Armstrong *et al.*, 2013a), type 2 diabetes mellitus (T2D) (Armstrong *et al.*, 2013b) and dyslipidaemia (Ma *et al.*, 2013), in psoriasis. These cardiometabolic diseases (CMDs) are particularly prevalent in patients with severe psoriasis (Armstrong *et al.*, 2012, Armstrong *et al.*, 2013a, Armstrong *et al.*, 2013b, Ma *et al.*, 2013, Singh *et al.*, 2017). Previous studies have also shown lower vitamin D levels in psoriasis patients compared to controls (Hambly *et al.*, 2017).

There is increasing evidence that there is a link between chronic inflammation and CMDs, including atherosclerosis (Hotamisligil, 2006). Chronic subclinical systemic inflammation accelerates atherosclerosis and

histological studies demonstrate the presence of inflammation in atherosclerotic lesions (Libby *et al.*, 2009). Further evidence linking inflammation to atherosclerosis is the observation that C-reactive protein (CRP), a well-recognised biomarker of inflammation, is also associated with atherothrombotic disease (Ridker, 2003). Inflammation has also been linked to the development of rheumatoid arthritis (RA) (Choy *et al.*, 2014), T2D (Hotamisligil, 2006), and MetS and its component disorders (Hotamisligil, 2006). It has therefore been hypothesised that the high prevalence of CMDs in psoriasis may arise from the high inflammatory milieu (Boehncke *et al.*, 2011, Davidovici *et al.*, 2010).

In the absence of any published data on CMD comorbidities in sub-Saharan Africa, the primary aim of this study was to determine the burden of MetS, and its component diseases, in a predominantly non-Caucasian cohort of South African psoriasis patients. The secondary aims were to determine the relation of MetS with disease severity and the association of hsCRP, as a marker of inflammation, serum vitamin D levels, estimated glomerular filtration rate (eGFR) and socio-demographic factors with psoriasis.

3.2 Methods

The methods used in this chapter have been described in detail in Chapter 2. These included a clinical records review, clinical examination (including

anthropometry, measurement of blood pressure and assessment of disease severity) and assessment of SES and educational status. Plasma glucose, urea, creatinine, serum lipids (total cholesterol, HDL cholesterol, triglycerides), hsCRP, Lp(a) and 25-hydroxy vitamin D (25[OH]D) levels were measured in overnight venous blood samples. The eGFR and LDL cholesterol were calculated as previously described.

3.2.1 Statistical methods

Standard statistical methods were used to analyse and present data as described in Chapter 2. Logistic regression analysis was used to assess whether the relationships of mild and severe psoriasis with MetS, T2D, hypertension, high triglycerides and low HDL cholesterol were affected after adjusting for possible confounders. All analyses were performed using Statistica version 13.2 (StatSoft, Tulsa, OK, USA).

3.3 Results

3.3.1 Demographic, clinical and cardiometabolic characteristics

The demographic, clinical and biochemical characteristics of the 103 patients and 98 control participants are shown in Tables 3.1 and 3.2. Most of the patients were of either Indian (42.1%) or mixed ancestry (31.8%) and only 11.7% were Caucasian and 14.6% black African patients. The mean $\pm$ SD disease duration for psoriasis was 18.9 ± 13.3 years and median (IQR) PASI score was 4.80 (2.40, 11.7). Sixty-one (59.2%)

patients were deemed to have severe psoriasis and 28 (27.2%) had PsA.

There were no differences in age and gender between patients with severe and mild psoriasis ($p=0.85$ and $p=0.81$, respectively). The prevalence of smoking was significantly higher in psoriasis patients compared to the control group ($p<0.0005$). The psoriasis group was of lower SES than the control group, with respect to both ownership of household items and education (both comparisons, $p<0.0005$).

Table 3.1 Demographic, clinical characteristics of South Africans with psoriasis and control participants

Variable	Psoriasis	Controls	P value
<i>Female gender</i>	55 (53.4)	61 (62.2)	0.204
<i>Age (years)</i>	53.3 ± 14.5	47.9 ± 14.5	0.009
<i>Disease duration (years)</i>	18.9 ± 13.3	-	-
<i>PASI score</i>	4.80 (2.40, 11.7)	-	-
<i>Psoriatic arthritis</i>	28 (27.1)	-	-
<i>Smokers</i>	61 (59.2)	26 (26.5)	<0.0001
<i>Systemic therapy</i>	43 (41.7)	-	-
<i>High SES</i>	50 (48.5)	74 (75.5)	<0.0001
<i>Completed high school</i>	52 (50.5)	81 (82.7)	<0.0001
<i>BMI (kg/m²)</i>	31.6 ± 8.42	29.3 ± 6.67	0.058
<i>Obesity</i>	52 (50.5)	38 (38.8)	0.095
<i>Waist circumference (cm)</i>	101 ± 16.4	94.5 ± 15.2	0.004
<i>Hip circumference (cm)</i>	107 ± 14.7	103 ± 12.1	0.073
<i>Waist : hip ratio</i>	0.946 ± 0.09	0.916 ± 0.11	0.035
<i>Systolic BP (mmHg)</i>	141 ± 24.6	129 ± 17.2	0.0004
<i>Diastolic BP (mmHg)</i>	86.4 ± 12.8	81.5 ± 11.6	0.005

Data given as mean ± SD, median (interquartile range) or n (%); N= 103 and N=98, for cases and controls respectively.

SES, socio-economic status; BMI, body mass index; BP, blood pressure

Table 3.2 Biochemical characteristics of South Africans with psoriasis and control participants

Variable	Psoriasis	Controls	P value
<i>HbA1c (%)†</i>	6.20 (5.90, 6.90)	5.95 (5.55, 6.30)	<0.0001
<i>Glucose (mmol/L)§</i>	5.71 (4.70, 6.00)	5.20 (4.20, 5.60)	0.744
<i>Total cholesterol (mmol/L)§</i>	5.31 (4.45, 6.20)	5.31 (4.62, 6.29)	0.176
<i>HDL cholesterol (mmol/L)§</i>	1.21 (1.05, 1.56)	1.37 (1.10, 1.73)	0.054
<i>LDL cholesterol (mmol/L)§</i>	3.24 (2.55, 4.04)	3.38 (2.64, 4.13)	0.180
<i>Triglycerides (mmol/L)§</i>	1.60 (1.05, 2.01)	1.11 (0.83, 1.76)	0.047
<i>Lipoprotein (a) (mg/dL)§</i>	25.3 (9.40, 38.8)	21.4 (10.0, 38.8)	0.971
<i>hsCRP (ng/mL)§</i>	4.70 (2.00, 10.9)	2.00 (1.10, 4.80)	<0.0001
<i>Framingham risk score*</i>	19.1 (8.47, 32.5)	7.25 (3.65, 13.8)	<0.0001
<i>Vitamin D (ng/mL)§</i>	19.0 (12.6, 24.1)	18.1 (13.1, 24.3)	0.582
<i>Urea (mmol/L)§</i>	5.40 (4.20, 6.85)	5.40 (4.40, 6.00)	0.421
<i>Creatinine (µmol/L)§</i>	87.0 (71.0, 102)	79.0 (71.0, 94.0)	0.130
<i>Estimated GFR (ml/min/m²)§</i>	70.8 (63.8, 83.4)	74.9 (66.0, 91.8)	0.140

Data given as mean ± SD, median (interquartile range) or n (%); §N= 91 and N=97, for cases and controls respectively. *N=80 and N=79, for cases and controls respectively.

GFR, glomerular filtration rate

There was a high prevalence of obesity in both patients and controls (50.5% and 38.8% respectively). The psoriasis group had a significantly greater waist circumference (WC) ($p=0.004$), higher systolic and diastolic BP ($p=0.0002$ and $p=0.005$, respectively), triglyceride ($p=0.047$) and HbA1c levels ($p<0.0005$); and a trend towards lower HDL cholesterol levels ($p=0.054$). The difference in WC remained significant ($p=0.006$) after adjustment for gender and ethnicity. The difference in WC remained significant after adjustment for age ($p=0.023$) and differences in systolic BP and HbA1c levels remained statistically significant ($p=0.015$ and $p=0.013$, respectively) after adjusting for age and WC.

The median hsCRP in the psoriasis group was more than twice that of the control group ($p<0.0005$), the difference persisting after adjusting for age and WC ($p=0.002$). The Framingham CVD risk score was significantly higher in psoriasis patients than in controls ($p<0.0001$). No significant differences in cholesterol-related lipid levels, glucose and vitamin D levels, urea, creatinine and eGFR were observed.

3.3.2 Prevalence of metabolic syndrome and its components

The prevalence of MetS was significantly higher in the psoriasis group than the control group (52.4% vs. 33.7%; $p=0.007$), as were T2D (25.2% vs. 4.1%; $p<0.0005$) and hypertension (70.9% vs. 48.9%; $p=0.001$) (Fig 3.1). There were no significant differences in the prevalence of low HDL

cholesterol levels (28.2 vs. 21.4%; $p=0.27$) or hypertriglyceridaemia (26.2 vs. 19.4%; $p=0.25$) between the 2 groups.

Subgroup analysis showed the prevalence of MetS was significantly higher in the severe psoriasis sub-group (65.6%) compared to both the mild psoriasis sub-group and control group (33.3% and 33.7%, respectively, $p<0.0005$ for both) (Fig. 3.1). In the case of T2D, compared to a prevalence of 4.1% in the control group, the prevalence was increased in both the severe and mild psoriasis sub-groups (31.1%, $p<0.0005$ and 16.7%, $p=0.01$, respectively). Hypertension was more prevalent only in the severe psoriasis sub-group (73.8% vs. 49.0% in control group, $p=0.002$).

The prevalence of a low HDL cholesterol was higher in the severe psoriasis sub-group (36.1%) when compared to both the control group, (21.4%, $p=0.043$) and the mild psoriasis sub-group (16.7%, $p=0.025$). There were no significant differences across the three groups in the prevalence of hypertriglyceridaemia. There was no difference in the Framingham CVD risk score between patients with severe and mild disease (21.4 (8.05, 34.2) vs. 18.0 (8.66, 30.9), respectively, $p=0.61$). However, both groups had a significantly higher score compared to controls (7.25 (3.65, 13.8), $p<0.0001$ for both groups).

When we compared patients with PsA (n=28) to those with cutaneous psoriasis only (n=75), the former group had a higher prevalence of MetS (71.4% vs. 45.3%, $p=0.018$) and low HDL cholesterol levels (53.6% vs. 18.7%, $p=0.0004$). However, no significant differences were noted in the prevalence of T2D (32.1% vs. 22.7%, $p=0.33$), hypertension (78.6% vs. 68.0%, $p=0.28$) or high TG levels (32.1% vs. 24%, $p=0.52$) or in the Framingham CVD risk score (22.1 (8.05, 42.7) vs. 18.0 (8.66, 30.7), $p=0.52$) between those with PsA and those with cutaneous psoriasis, respectively.

Logistic regression analysis showed that, after adjusting for potential confounders (age, BMI, hsCRP, smoking, education and SES), severe, but not mild psoriasis, was associated with a higher risk of MetS ($p=0.002$), T2D ($p<0.0005$) and a trend towards an association with hypertension ($p=0.05$) (Table 3.3). Neither mild ($p=0.48$) or severe psoriasis ($p=0.32$) was associated with an increased risk of low HDL cholesterol nor an increased risk for high TG levels.

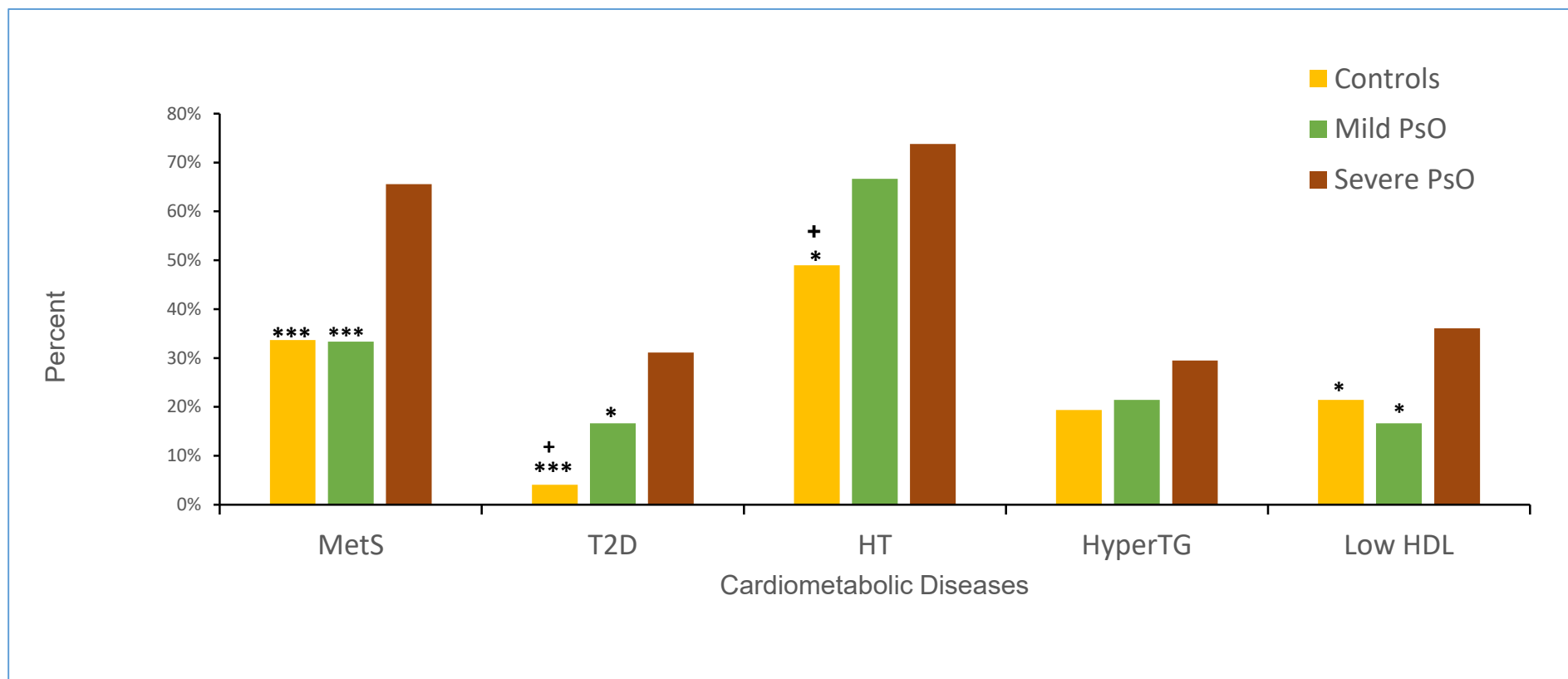


Figure 3.1 Prevalence of cardiometabolic diseases in South Africans with psoriasis

PsO, psoriasis; MetS, metabolic syndrome; T2D, type 2 diabetes; HT, hypertension; HyperTG, hypertriglyceridaemia; HDL, high density lipoprotein cholesterol

*p < 0.05, **p < 0.005, ***p < 0.0005 vs. severe PsO; +p < 0.05 vs. mild PsO

Table 3.3 Logistic regression models showing relationship of mild and severe psoriasis with cardiometabolic diseases

Psoriasis severity (unadjusted)	Metabolic syndrome OR (95% CI), p value	Type 2 diabetes OR (95% CI), p value	Hypertension OR (95% CI), p value	Low HDL OR (95% CI), p value
<i>Mild disease</i>	0.98 (0.46, 2.11), 0.97	4.70 (1.29, 17.2), 0.02	2.08 (0.97, 4.45), 0.06	0.73 (0.28, 1.90), 0.52
<i>Severe disease</i>	3.75 (1.90, 7.39), 0.0001	10.6 (3.38, 33.4), <0.0001	2.93 (1.46, 5.89), 0.002	2.07 (1.01, 4.23), 0.04
Psoriasis severity (adjusted)*				
<i>Mild disease</i>	0.49 (0.16, 1.49), 0.20	3.27 (0.72, 14.9), 0.12	1.39 (0.50, 3.85), 0.53	0.67 (0.22, 2.05), 0.48
<i>Severe disease</i>	4.42 (1.72, 11.4), 0.002	11.3 (3.07, 41.3), 0.0002	2.48 (0.97, 6.32), 0.05	1.57 (0.63, 3.90), 0.32

*Adjusted for age, body mass index, hsCRP, smoking, education and socio-economic status; p values relative to the reference group (non-psoriatic)

3.4 Discussion

In this case-control study of mainly indigent urban South Africans, we found a higher prevalence of MetS, hypertension and T2D in patients with psoriasis, even after adjusting for possible confounders. Moreover, we observed a risk-gradient for CMD, sometimes referred to as the 'psoriatic march' (Boehncke *et al.*, 2011) where the risk is greatest in severe psoriasis and less so in mild disease. The Framingham CVD risk score was also found to be higher in the psoriasis group.

A third of the control group fulfilled the criteria for MetS, compared to more than 50% in the psoriasis group of whom 70% had hypertension and 25% had T2D. The prevalence rates of MetS are substantially higher than reported in Western industrialised countries but similar to those in developing countries. The prevalence of MetS varies from 13.5% - 25.9% for the general population to 20.8% - 34.2% in psoriasis patients in the United States (Love *et al.*, 2011), United Kingdom (Langan *et al.*, 2012) and Italy (Gisondi *et al.*, 2007). In developing countries like India (Madanagobalane *et al.*, 2012b) and Tunisia (Mebazaa *et al.*, 2011) the prevalence is in the order of 30% for the general population and 40% - 44% in psoriasis patients.

That more than 50% of the patients and 38% of controls in the present study were obese is a reflection of the growing problem of obesity in South

Africa. In the South African National Health and Nutrition Examination Survey (of 7267 participants), the overall prevalence of obesity was 28.9% (Shisana *et al.*, 2014).

The risk gradient where the highest risk for CMD is associated with severe psoriasis is a phenomenon that has been elegantly demonstrated in several previous studies. The seminal study on psoriasis and CMD concluded that psoriasis conferred an independent risk for myocardial infarction with the risk being greatest in severe psoriasis (Gelfand *et al.*, 2006). Subsequent studies have demonstrated similar relationships in terms of CVD (Armstrong *et al.*, 2013c), T2D (Armstrong *et al.*, 2013b) and hypertension (Armstrong *et al.*, 2013a). Sub-group analysis in the present study showed the increased risk of MetS and hypertension was exclusively in the severe psoriasis sub-group. Of note, we observed a very strong association between T2D and severe psoriasis (OR [95% CIs]: 11.3 [3.07, 41.3]) which far exceeds the pooled risk documented in a previous meta-analysis (1.97 [1.48-2.62]) (Armstrong *et al.*, 2013b).

The serum lipid levels for the psoriasis and control groups were similar for total cholesterol, LDL and HDL cholesterol, Lp(a) and triglycerides after adjusting for confounders. A previous study has shown higher total cholesterol levels in psoriasis, but similar to our findings, did not

demonstrate any difference in LDL cholesterol or Lp(a) between the psoriasis patients and controls (Mallbris *et al.*, 2006).

The pathophysiological mechanism linking psoriasis and CMD is not entirely understood but there is some evidence in psoriasis, and in other chronic inflammatory disorders such as rheumatoid arthritis, that the cytokine-driven pro-inflammatory systemic state contributes to increased risk of atherosclerosis and CMD (Davidovici *et al.*, 2010). The significantly higher hsCRP levels in psoriasis in the present study are noteworthy in this respect.

Previous studies have observed a higher prevalence of CKD (Wan *et al.*, 2013) and lower vitamin D levels (Hambly *et al.*, 2017) in psoriasis, but this was not evident in the present study. However, as in other studies, we found associations between lower education (Mahe *et al.*, 2017) and smoking with psoriasis (Naldi *et al.*, 1992).

Although not the primary focus of the study, a disproportionately high number of patients were of Asian-Indian or mixed ancestry and relatively few black African patients. This is against a background of the majority of patients attending state-run services being black Africans. These findings mirror those of an earlier study performed at the same dermatology clinics

(Hartshorne, 2003) and may reflect ethnic differences in genetic risk for psoriasis.

Some of the limitations of the study are the cross-sectional design, the relatively small sample size and that patients had already been initiated on systemic therapy at the time of recruitment into the study. In addition, patients were recruited from public hospitals and these findings may therefore, not be generalisable to all South African patients.

In this study of mainly indigent non-Caucasian South Africans, the burden of MetS and its components was increased in psoriasis as was the Framingham CVD risk score. Moreover, the risk of these CMDs is greater in severe psoriasis, supporting the notion of a 'psoriatic march' and an aetiological link between the severity of chronic inflammation of psoriasis and burden of MetS. Public health initiatives for reducing obesity and smoking could have a positive effect on the severity of psoriasis.

This study showed a higher prevalence of CMDs in participants with psoriasis. The next chapter will determine possible aetiological pathways for psoriasis-related CMDs and for psoriasis using multivariable logistic regression analysis. The analyses will include the association of visceral fat with psoriasis and the potential roles of adipokines i.e. leptin, adiponectin, IL-6, and TNF in the pathogenesis of CMDs and psoriasis.

CHAPTER 4 THE RELATIONSHIP OF VISCERAL FAT AND ADIPOKINES WITH CARDIOMETABOLIC DISEASES IN PSORIASIS

4.1 Introduction

Psoriasis is an immune-mediated inflammatory disorder which is increasingly shown to be associated with cardiometabolic diseases (CMDs) (Gisondi *et al.*, 2010, Boehncke, 2012). Epidemiological evidence also supports the association of psoriasis with obesity. A meta-analysis of 16 observational studies has shown that patients with psoriasis are more likely to be obese (Armstrong *et al.*, 2012). In particular, psoriasis is associated with abdominal obesity (Gisondi *et al.*, 2007), a well-recognised risk factor for type 2 diabetes (T2D), hypertension, coronary artery disease and decreased life expectancy (Janssen *et al.*, 2002).

Studies have shown that patients with psoriasis have greater levels of visceral fat compared to healthy controls matched for age and sex (Balci *et al.*, 2010). White adipose tissue (WAT), which is the primary component of visceral fat, is composed of adipocytes and other immunologically active cells such as macrophages (Kershaw *et al.*, 2004). Adipocytes secrete adipokines which are mainly pro-inflammatory and include leptin, visfatin, and resistin. Adiponectin, on the other hand, improves insulin sensitivity and has anti-inflammatory properties (Kershaw *et al.*, 2004). Other pro-

inflammatory factors that are produced by white adipose tissue include tumour necrosis factor (TNF), interleukin (IL)-1, and IL-6, all of which have been shown to directly or indirectly affect endothelial cell function and insulin sensitivity (Hivert *et al.*, 2008, Kershaw *et al.*, 2004). A large body of evidence now suggests that chronic inflammation leads to accelerated atherosclerosis and other CMDs (Libby *et al.*, 2002, Libby *et al.*, 2009) and is a possible mechanism by which obesity may increase CVD risk.

Current evidence suggests that chronic inflammatory diseases such as rheumatoid arthritis are associated with an increased risk of premature cardiovascular death (Choy *et al.*, 2014) and that this association is partly linked to obesity (Lago *et al.*, 2011). Epidemiological evidence supporting the notion that psoriasis is associated with a similar increased CMD risk is less well-established and the precise pathobiology of this association is complex and incompletely understood. One hypothesis is that the chronic inflammatory state of psoriasis triggers a 'psoriatic march' where the pro-inflammatory milieu leads to insulin resistance and endothelial cell dysfunction, predisposing to CMDs (Boehncke *et al.*, 2011).

Patients with psoriasis have high levels of inflammatory markers, with CRP (Dowlathahi *et al.*, 2013b, Vachatova *et al.*, 2016), leptin (Kyriakou *et al.*, 2017, Vachatova *et al.*, 2016) and TNF serum concentrations being

significantly higher compared to controls, whilst adiponectin levels are lower (Kyriakou *et al.*, 2017, Vachatova *et al.*, 2016). While previous studies have separately shown an increased prevalence of CMDs (Gisondi *et al.*, 2010, Langan *et al.*, 2012), adipokine dysregulation (Dowlatshahi *et al.*, 2013b, Gerdes *et al.*, 2011) and increased visceral fat in psoriasis (Balci *et al.*, 2010), to date there have been no studies that have assessed these relationship in a single cohort. Therefore, the aim of the present study was to determine whether psoriasis is associated with increased visceral adiposity and inflammation and whether these 2 factors mediate the relationship between psoriasis and CMDs.

4.2 Methods

The specific details of participant recruitment, biochemical analyses and body fat imaging are explained in Chapter 2. The following demographic and clinical parameters were analysed: weight, height, waist circumference, blood pressure (BP), PASI score, anti-psoriatic therapy, socioeconomic status (SES), smoking status and education level. Subcutaneous and visceral fat volume were measured by abdominal CT scan. Venous blood samples were obtained after an overnight fast for plasma glucose and serum lipids (total cholesterol, triglycerides and HDL cholesterol), hsCRP, insulin, leptin, adiponectin and TNF. The LDL cholesterol was calculated as previously described.

4.2.1 Statistical Methods

Standard statistical methods were used to analyse and present data as described in detail in Chapter 2. Forward and backward multivariable logistic regression models were used to isolate the risk factors for psoriasis and the following cardiometabolic disorders: MetS, T2D, hypertension, hypertriglyceridaemia, hypercholesterolaemia, high LDL and low HDL cholesterol.

4.3 Results

4.3.1 Clinical, socio-demographic, biochemical and anthropometric characteristics of patients and controls

Tables 4.1 and 4.2 summarise the clinical, socio-demographic, biochemical and anthropometric characteristics of the patient and control groups. It should be noted that complete blood data was available for 188 out of the 201 study participants due to insufficient serum volumes.

As shown in the previous chapter the BMI was similar but the waist circumference was significantly higher in patients compared to controls. The psoriasis group had a significantly higher visceral fat volume compared to the control group ($p=0.007$), but no difference was observed with respect to subcutaneous fat volume. In addition, and as shown previously, psoriasis patients had a higher prevalence of MetS, T2D, hypertension and low HDL cholesterol levels than controls. In the previous

chapter it was shown that psoriasis patients had significantly higher hsCRP, whilst in the current analyses psoriasis patients had significantly higher IL-6 and lower adiponectin levels than controls ($p < 0.0001$ and $p = 0.004$ respectively). However, there were no differences between leptin and TNF levels between groups. Sub-group analysis showed no differences in prevalence of CMDs between anti-psoriatic treatment groups. (Data shown in Appendix 3, Table A2). However, the prevalence of T2D was significantly higher in both the methotrexate and topical therapy groups than the control group ($p < 0.0005$ for both) and the prevalence of MetS was significantly higher in the methotrexate group compared to the control group ($p < 0.005$). Anti-psoriatic therapies were later included in multivariable regression models but not found to be - significantly associated with T2D or MetS.

Table 4.1 Clinical, socio-demographic, and anthropometric characteristics of patients and controls

Variable	Psoriasis	Controls
Subject numbers	103	98
Female	55 (53.4)	61 (62.2)
Race		
Black	15 (14.5)	16 (19.3)
White	12 (11.7)	14 (14.3)
Indian	44 (42.7)	42 (42.9)
Mixed ethnicity	32 (31.1)	26 (26.6)
Age (years)	53.3 ± 14.5	47.9 ± 14.5 *
Duration of psoriasis (years)	18.9 ± 13.3	-
PASI score	8.79 ± 10.2	
Therapy	-	
Topical	60 (58.3)	
Methotrexate	25 (24.3)	-
Acitretin	13 (12.6)	
Other	5 (4.85)	
Smokers	43 (41.7)	16 (16.3) ***
High socioeconomic status	50 (48.5)	74 (75.5) ***
Completed high school	52 (50.5)	81 (82.7) ***
BMI (kg\m²)	30.1 (25.3, 36.1)	28.1 (25.0, 32.7)
Waist (cm)	101 ± 16.4	94.5 ± 15.2 **
Hip (cm)	104 (96,115)	102 (96,109)
Subcutaneous fat (cm³) §	439 (323, 648)	410 (268, 596)
Visceral fat (cm³) §	198 (133, 278)	153 (89.4, 218) *
Systolic BP (mmHg)	137 (127, 156)	128 (117,139) ***
Diastolic BP (mmHg)	86.4 ± 12.8	81.5 ± 11.6 *
Hypertension	73 (70.9)	48 (48.9) **

Data expressed as mean ± SD, median (interquartile range) or n (%)

§N= 69 and N=80, for cases and controls respectively;

*p < 0.05, **p < 0.005, ***p<0.0005 vs. controls

PASI, psoriasis area and severity index; BMI, body mass index; BP, blood pressure

Table 4.2 Biochemical characteristics of patients and controls

Variable	Psoriasis	Controls
<i>HbA1c (%)</i>[§]	6.20 (5.90, 6.90)	5.95 (5.55,6.30) ***
<i>HOMA index</i>[§]	2.57 (1.74, 4.39)	2.23 (1.56, 3.03) *
<i>Type 2 diabetes</i>	26 (25.2)	4 (4.1) ***
<i>Total cholesterol (mmol/L)</i>[§]	5.31 ± 1.24	5.57 ± 1.34
<i>High total cholesterol level</i>	68 (66.7)	65 (66.3)
<i>HDL cholesterol (mmol/L)</i>[§]	1.21 (1.05,1.56)	1.37 (1.10,1.73)
<i>Low HDL cholesterol level</i>	29 (28.1)	21 (21.4)
<i>LDL cholesterol (mmol/L)</i>[§]	3.21 ± 1.12	3.44 ± 1.21
<i>High LDL cholesterol level</i>	73 (83.0)	67 (70.1)*
<i>Triglycerides (mmol/L)</i>	1.60 (1.05, 2.01)	1.11 (0.83, 1.76) *
<i>Hypertriglyceridaemia</i>	27 (26.2)	19 (19.4)
<i>Metabolic syndrome</i>	54 (52.4)	33 (33.7) *
<i>hsCRP (ng/mL)</i>[§]	5.2 (2.00, 11.0)	2.10 (1.10, 4.90) ***
<i>Vitamin D (ng/mL)</i>[§]	19.0 (12.6, 24.1)	18 (13.1, 24.3)
<i>Leptin (ng/mL)</i>[§]	17.2 (8.40, 35.8)	19.0 (8.60, 32.3)
<i>Adiponectin (µg/mL)</i>[§]	5.05 (3.03, 7.46)	6.25 (4.35, 9.75) **
<i>TNF (pg/mL)</i>[§]	6.85 (4.80, 9.55)	6.30 (4.50, 8.30)
<i>IL-6 (pg/mL)</i>[§]	3.70 (1.90, 7.00)	1.70 (1.10, 3.20) ***

Data expressed as mean ± SD, median (interquartile range) or n (%)

[§]N= 91 and N=97, for cases and controls respectively;

*p < 0.05, **p < 0.005, ***p<0.0005 vs. controls

4.3.2 Association of psoriasis and visceral fat with cardiometabolic diseases

In the univariate logistic regression analysis, psoriasis was a significant risk factor for MetS ($p=0.008$), T2DM ($p=0.0002$) and hypertension ($p=0.002$) and marginally for high LDL-C ($p=0.05$) but not so for any of the other measures of dyslipidaemia (Table 4.3). Visceral fat was a significant risk factor for psoriasis ($p=0.004$), MetS ($p<0.0001$), T2D ($p=0.002$), hypertension ($p<0.0001$), hypertriglyceridaemia ($p=0.001$) and low HDL-C levels ($p=0.002$).

Multivariable logistic regression analysis (Table 4.4) showed that lower education level ($p=0.0001$), smoking ($p<0.0001$) and IL-6 ($p<0.0001$) were predictors of psoriasis (Table 4.4). Psoriasis was a significant predictor of T2D ($p=0.002$), as were age ($p=0.025$) and HOMA ($p<0.0001$). The predictors of MetS were low SES ($p=0.026$), HOMA ($p=0.002$), TNF ($p=0.008$) and visceral fat ($p=0.003$). The only variable associated with hypertension risk was visceral fat ($p<0.0001$). Low adiponectin levels, as well as age and hip circumference were associated with hypertriglyceridaemia ($p=0.011$, $p=0.041$ and $p=0.035$, respectively). The predictors of low HDL cholesterol levels were hip circumference ($p=0.009$), low adiponectin levels ($p=0.0008$) and TNF ($p=0.01$). The only predictor of high cholesterol levels was age ($p=0.003$). Age ($p<0.0001$) and Asian-Indian ethnicity ($p=0.008$) were associated with a higher risk of high LDL cholesterol.

Table 4.3 Univariate logistic regression models showing associations of psoriasis with risk of cardiometabolic diseases and visceral fat with risk of cardiometabolic diseases and psoriasis

<i>Categorical variable</i>	<i>Psoriasis</i>	<i>Visceral fat</i>
<i>Psoriasis</i>	-	1.56 (1.15, 2.11), 0.004
<i>Type 2 diabetes</i>	7.94 (2.64, 23.9), 0.0002	1.77 (1.24, 2.54), 0.002
<i>Metabolic syndrome</i>	2.18 (1.22, 3.85), 0.008	3.89 (2.38, 6.37), <0.0001
<i>Hypertension</i>	2.53 (1.41, 4.55), 0.002	2.65 (1.71, 4.12), <0.0001
<i>Hypertriglyceridaemia</i>	1.48 (0.76, 2.89), 0.25	1.67 (1.22, 2.28), 0.001
<i>Low HDL cholesterol</i>	1.44 (0.75, 2.75), 0.27	1.63 (1.19, 2.22), 0.002
<i>High total cholesterol</i>	1.35 (0.72, 2.55), 0.35	1.31 (0.94, 1.82), 0.11
<i>High LDL cholesterol</i>	2.03 (1.00, 4.15), 0.05	1.91 (1.25, 2.92), 0.003

Values expressed as OR (95% CI), p value

Table 4.4 Logistic regression models showing significant predictors of psoriasis and cardiometabolic diseases

Model number	Categorical variable	Independent variables	Odds ratio (95 % CI)	p-value
1	<i>Psoriasis</i>	Smoking	4.05 (2.01, 8.15)	<0.0001
		High school graduate	0.24 (0.11, 0.50)	0.0001
		Interleukin-6	1.18 (1.07, 1.31)	< 0.0001
2	<i>Type 2 diabetes</i>	Age	1.04 (1.01, 1.09)	0.025
		Psoriasis	8.01 (2.07, 31.0)	0.002
		HOMA	1.38 (1.16, 1.64)	<0.0001
3	<i>Metabolic syndrome</i>	Socio-economic status	0.34 (0.13, 0.89)	0.026
		HOMA	2.05 (1.31, 3.22)	0.002
		TNF	1.28 (1.07, 1.54)	0.008
		Visceral fat	2.28 (1.33,3.93)	0.003
4	<i>Hypertension</i>	Visceral fat	2.65 (1.71, 4.12)	0.00001
5	<i>Hypertri-glyceridaemia</i>	Age	1.03 (1.00,1.06)	0.041
		Hip circumference	1.31 (1.01, 1.68)	0.035
		Adiponectin	0.88 (0.79, 0.97)	0.011
6	<i>Low HDL cholesterol</i>	Hip circumference	1.03 (1.01,1.06)	0.009
		Adiponectin	0.82 (0.73,0.92)	0.0008
		TNF	1.16 (1.03,1.29)	0.010
7	<i>High total cholesterol</i>	Age	1.03 (1.01, 1.06)	0.003
8	<i>High LDL cholesterol</i>	Age	1.06 (1.03, 1.09)	0.00003
		Asian-Indian	2.98 (1.32, 6.72)	0.008

There were several univariate analyses in which either visceral fat or psoriasis were significantly associated with the outcome variable but did not remain significant in the multivariable model. These models were further analysed using forward regression analyses to determine which independent variable was responsible for attenuating the effect of psoriasis or visceral fat on the respective outcome variable. Thus, for psoriasis, visceral fat was significant in a univariate (Table 4.3) but not a multivariate model (Table 4.4). Forward regression analysis demonstrated that IL-6 rendered the relationship between visceral fat and psoriasis non-significant ($p=0.06$) (Table 4.5). Psoriasis was associated with MetS in a univariate ($p=0.008$) but not a multivariable regression model, and this was found to be due to visceral fat which weakened the relationship between psoriasis and MetS to non-significance ($p=0.325$).

Similarly, visceral fat was significantly associated with T2D in the univariate but not in the multivariate model, and forward regression analysis showed that HOMA attenuated the association between visceral fat and T2D to non-significance ($p=0.192$). The loss of the significant association of psoriasis with hypertension in the univariate model ($p=0.002$) was shown to be due to visceral fat, which renders the association non-significant ($p=0.23$) (Table 4.5). Visceral fat was a predictor of hypertriglyceridaemia ($p=0.001$), low HDL cholesterol ($p=0.002$) and high LDL cholesterol ($p=0.003$) levels in the univariate models, but did not remain significant in the multivariate models. These

relationships were attenuated to non-significance by age and adiponectin ($p=0.20$), TNF ($p=0.13$) and age ($p=0.16$), respectively, in the forward regression analyses (Table 4.5).

Table 4.5 Forward logistic regression models for determining variables that attenuate association of psoriasis with cardiometabolic diseases, and visceral fat with cardiometabolic diseases and psoriasis

<i>Categorical variable</i>	Model number	Independent variables	Odds ratio (95 % CI)	p-value
<i>Psoriasis</i>	1	<i>Visceral Fat</i>	1.56 (1.15, 2.11)	0.004
	2	<i>Visceral fat</i>	1.35 (0.99, 1.85)	0.06
		<i>Interleukin 6</i>	1.17 (1.03, 1.32)	0.013
<i>Type 2 diabetes</i>	1	<i>Visceral fat</i>	1.77 (1.24, 2.54)	0.002
	2	<i>Visceral fat</i>	1.33 (0.86, 2.06)	0.192
		<i>HOMA</i>	1.43 (1.12, 1.80)	0.003
<i>Metabolic syndrome</i>	1	<i>Psoriasis</i>	2.18 (1.22, 3.85)	0.008
	2	<i>Psoriasis</i>	1.48 (0.67, 3.24)	0.325
		<i>Visceral fat</i>	3.79 (3.21, 6.21)	<0.0001
<i>Hypertension</i>	1	<i>Psoriasis</i>	2.53 (1.41, 4.55)	0.002
	2	<i>Psoriasis</i>	1.58 (0.74, 3.37)	0.23
		<i>Visceral fat</i>	2.56 (1.64, 3.99)	<0.0001
<i>Hypertri-glyceridaemia</i>	1	<i>Visceral fat</i>	1.67 (1.22, 2.28)	0.001
	2	<i>Visceral fat</i>	1.28 (0.87, 1.86)	0.20
		<i>Adiponectin</i>	0.86 (0.76, 0.98)	0.02
		<i>Age</i>	1.03 (1.00, 1.07)	0.08
<i>Low HDL cholesterol</i>	1	<i>Visceral fat</i>	1.63 (1.19, 2.22)	0.002
	2	<i>Visceral fat</i>	1.29 (0.93, 1.79)	0.13
		<i>TNF</i>	1.24 (1.07, 1.44)	0.003
		<i>Adiponectin</i>	0.81 (0.70, 0.93)	0.003
<i>High LDL cholesterol</i>	1	<i>Visceral fat</i>	1.91 (1.25, 2.92)	0.003
	2	<i>Visceral fat</i>	1.38 (0.87, 2.17)	0.16
		<i>Age</i>	1.05 (1.02, 1.09)	0.001

4.6 Discussion

In this case-control study where clinical and metabolic parameters, body fat distribution and biomarkers of inflammation were measured simultaneously in a single cohort of patients with psoriasis, we found that visceral fat was an independent predictor of psoriasis and that the effect of visceral fat was mediated by the pro-inflammatory cytokine IL-6. A recent study has shown evidence to suggest a causal relationship between a high BMI and psoriasis risk (Budu-Aggrey *et al.*, 2019). A previous study has demonstrated that visceral fat, was increased in patients with psoriasis (Balci *et al.*, 2010), and circulating IL-6 levels have been found to be elevated in psoriasis in two previous studies (Gerdes *et al.*, 2011, Zalewska *et al.*, 2006). The mechanism by which IL-6 may contribute to the aetiology of psoriasis is not fully understood however it has been proposed that it may cause increased mitogenesis at the site of psoriatic skin lesions (Castells-Rodellas *et al.*, 1992).

Adipokine dysregulation and the resulting inflammatory state is a central mechanism whereby visceral fat may mediate the development of various CMDs (Ahima *et al.*, 2000). The current study supports this hypothesis by demonstrating that the association of visceral fat with high triglyceride is mediated through adiponectin, whilst the association with low HDL levels is mediated by both adiponectin and TNF. These relationships are supported by studies demonstrating that visceral fat correlates negatively with adiponectin (Kershaw *et al.*, 2004) but positively with TNF levels

(Ahima *et al.*, 2000, Kershaw *et al.*, 2004) and studies showing that adiponectin is associated with lower triglyceride but higher HDL levels (Lago *et al.*, 2009), whilst TNF is associated with lower HDL levels (Lago *et al.*, 2009). Visceral fat is also known to be associated with insulin resistance (Bergman *et al.*, 2006, Hivert *et al.*, 2008). This relationship was observed in the current study with visceral fat identified as a risk factor for T2D via its effects on insulin sensitivity. This possible aetiological pathway for T2D has been reported in previous studies (Donath *et al.*, 2011).

Psoriasis is associated with increased levels of CMDs (Gisondi *et al.*, 2010, Boehncke, 2012). The present study also demonstrates this and further shows that psoriasis is an independent risk factor for T2D, with none of the study variables acting as significant mediators. Previous studies have also demonstrated that T2D is more prevalent in psoriasis compared to control participants (Armstrong *et al.*, 2013b, Solomon *et al.*, 2010, Lee *et al.*, 2014).

Further studies are required to determine the factors that may mediate the relationship of psoriasis with T2D. Our results also show that the relationship of psoriasis with hypertension (Table 4.3) may be due to confounding by visceral fat (Fig. 4.1). Thus, in a multiple regression model for hypertension, psoriasis was not a significant risk factor for hypertension

(Table 4.4) and forward regression analyses demonstrated that this was due to attenuation of the association of psoriasis with hypertension by visceral fat (Table 4.5). These data can be interpreted either as showing that psoriasis causes visceral adiposity which in turn leads to higher blood pressure, or that the relationship between psoriasis and hypertension is due to confounding from visceral fat. The latter hypothesis is scientifically more plausible. A similar argument can be made for the relationship observed between psoriasis and MetS (Tables 4.3 to 4.5). These are important findings as they suggest that in studies demonstrating a relationship of psoriasis with hypertension or MetS, that this is not an aetiological association but is purely a result of confounding from visceral adiposity. It is interesting to note that in a recent meta-analysis of studies on the association of psoriasis with MetS (Singh *et al.*, 2017) or hypertension (Armstrong *et al.*, 2013a), none of the studies had adjusted for visceral adiposity.

Triglycerides, but none of the cholesterol-related lipid species, were higher in participants with psoriasis. Other studies have shown more atherogenic lipid profiles in those with psoriasis (Pietrzak *et al.*, 2010). However, in the present investigation, visceral fat was more strongly associated with lipid levels than was psoriasis, and these relationships were mediated through adiponectin and TNF. It is therefore possible that, in studies where psoriasis has been shown to be a risk factor for dyslipidaemia, this effect may be due to confounding due to visceral fat.

Smoking and a lower education level were both associated with a higher risk for psoriasis. A high prevalence of smoking in psoriasis patients has been observed previously (Kimball *et al.*, 2014) and in a meta-analysis the odds ratio for psoriasis was 1.78 (95% CI 1.53-2.06) in smokers compared to non-smokers (Armstrong *et al.*, 2014b). Smoking may increase the risk of psoriasis by increasing oxidative stress and via nicotine which induces the production of pro-inflammatory cytokines (Naldi, 2016). In a cross-sectional study of 903 patients performed in France, lower education was associated with psoriasis (Mahe *et al.*, 2017) and results from a large cohort study in the United States produced similar findings (Kimball *et al.*, 2014).

The main limitations of this study are its cross-sectional design and use of multivariable regression models, which only allow us to determine associations between variables and cannot be used to prove causative relationships. Furthermore, data obtained from multivariable regression models must be interpreted with caution and should be guided by scientific plausibility and supportive data from the literature. However, the study did have some important strengths. This study involved the measurement of a large number of highly relevant variables that for the first time allowed us to interrogate the relationships between psoriasis, visceral adiposity, adipokines and CMDs. This allowed us to develop possible mechanistic pathways for how psoriasis may lead to higher risk for CMDs, and to suggest aetiological pathways for psoriasis (Fig. 4.1). Such analyses will

allow future studies to take a more directed approach for determining the true aetiology of psoriasis-associated CMDs.

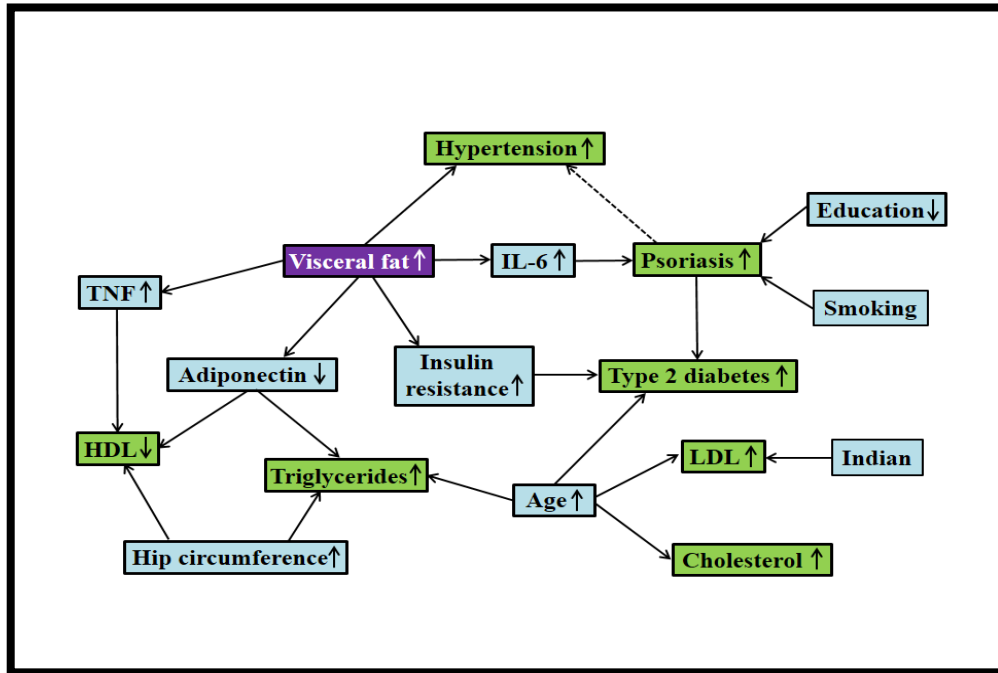


Figure 4.1 Theoretical linkage between study variables based on data from multivariable regression model

Legend

Visceral fat is shown to play a central role, being linked to psoriasis via IL-6 and to increased triglyceride and decreased HDL-C levels via adiponectin and TNF and to type 2 diabetes via insulin resistance. Psoriasis is a risk factor for type 2 diabetes but its relationship with high blood pressure (shown by broken arrow) may be due to confounding from visceral fat. High LDL-C and total cholesterol levels are linked to aging with Indian ethnicity also associated with higher LDL-C levels (outcome variables are shown in green blocks, input variables in blue blocks and visceral fat in purple).

In conclusion, this study demonstrates a possible role for visceral adiposity in the causation of psoriasis. It also shows that adipokines may be the mechanism through which visceral fat increases the risk for psoriasis and related CMDs. In addition, many of the CMDs that are known to be highly prevalent in participants with psoriasis may be caused by visceral adiposity rather than psoriasis itself. The exception is T2D, which is strongly and independently associated with psoriasis. Future mechanistic studies should now focus on these possible aetiological pathways to determine the true molecular processes involved in the development of psoriasis-associated CMDs.

In the previous two chapters, we have investigated the classic components of MetS and the mechanistic links between visceral fat, CMD and psoriasis. Non-alcoholic fatty liver disease (NAFLD) is being increasingly recognised as the hepatic expression of the MetS (Kotronen *et al.*, 2008). Furthermore evidence suggests it may be increased in psoriasis (Mantovani *et al.*, 2016, Gisondi *et al.*, 2009). There are no studies on NAFLD and psoriasis in the South African population. We therefore undertook to investigate NAFLD and liver dysfunction in psoriasis

CHAPTER 5 NON-ALCOHOLIC FATTY LIVER DISEASE IN PATIENTS WITH PSORIASIS

5.1 Introduction

Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of disease beginning with steatosis and progressing to steatohepatitis, cirrhosis and hepatocellular carcinoma (Benedict *et al.*, 2017). Its global prevalence is estimated at approximately 25% of the general population (Younossi *et al.*, 2016) with major risk factors for NAFLD including: age (>50 years), obesity, type 2 diabetes (T2D), insulin resistance and genetic variants, most notably the patatin-like phospholipase domain-containing 3 polymorphism (known as *PNPLA3*) (Byrne *et al.*, 2015). Racial and ethnic differences in the prevalence of NAFLD have also been described, with a lower prevalence documented in African-Americans compared to Caucasians (Nguyen *et al.*, 2008).

Non-alcoholic fatty liver disease encompasses a broad spectrum of clinical presentations. This may range from asymptomatic disease with only biochemical derangements in liver enzymes to fatty infiltration, fibrosis and cirrhosis. The gold standard for the diagnosis of NAFLD is by liver biopsy and histology. However, as this is an invasive procedure with the attendant risk of complications, it is reserved for selected patients. Non-invasive modalities including biochemistry and imaging techniques such

as ultrasonography, CT scan, magnetic resonance imaging and, more recently, transient elastography are used more frequently to diagnose NAFLD in clinical practice (Byrne *et al.*, 2015). Biochemically, an ALT level exceeding the AST usually characterises NAFLD as opposed to alcoholic steatosis which is associated with an elevated AST:ALT ratio (Sattar *et al.*, 2014).

Given the strong association between obesity, T2D and psoriasis as discussed in the previous chapters, it is not surprising that several studies have focussed on the relationship between psoriasis and NAFLD (Mantovani *et al.*, 2016, Ganzetti *et al.*, 2015). Thus, studies have shown an increased prevalence of NAFLD in participants with psoriasis compared to the general population with the prevalence of NAFLD in psoriasis varying from 17.4% (Madanagobalane *et al.*, 2012a) to 65.6% (Abedini *et al.*, 2015). Studies have further demonstrated that the risk for NAFLD is higher in patients with PsA (Madanagobalane *et al.*, 2012a, Miele *et al.*, 2009) and in those with severe psoriasis (Gisondi *et al.*, 2009). A meta-analysis has confirmed that NAFLD is more common in participants with moderate-to-severe compared to mild psoriasis, and in patients with psoriatic arthritis (PsA) (Candia *et al.*, 2015). Furthermore, methotrexate, a commonly-used systemic anti-psoriatic drug is associated with both hepatotoxicity and shares risk factors with steatosis (e.g. obesity, T2D)

suggesting it may predispose or aggravate NAFLD (Farrell, 2002, Rosenberg *et al.*, 2007).

There is a paucity of data on the prevalence of NAFLD and its relationship to obesity in the general population in South Africa. A 2010 study conducted in overweight/obese participants in the Western Cape showed that NAFLD was associated with insulin resistance and dysglycaemia (Kruger *et al.*, 2010). Naran *et al* also showed an association of NAFLD with insulin resistance in South African female patients (Naran *et al.*, 2018). Of note, both studies noted lower hepatic fat in African participants compared to other ethnic groups.

There are no South African studies on NAFLD in participants with psoriasis. Therefore, the aim of the present case-control study was to determine the prevalence and predictors of liver dysfunction, particularly NAFLD, in South Africans with psoriasis compared to matched control participants.

5.2 Participants and methods

The methods used in this chapter have been described in detail in Chapter 2. As part of a larger study on cardiometabolic disease (CMD) and psoriasis, participants were invited to take part in this sub-study of liver

dysfunction and NAFLD. Participants who gave a history of excessive ethanol use (defined as consumption of more than 7 units per week in females and more than 14 units per week in males (Niemela *et al.*, 2017)) were excluded from CT scan as described in Chapter 2 and from this analysis (Fig 5.1). Only those participants who consented to imaging were scanned. There were no study participants with a history of chronic liver disease. The psoriasis patients were sub-grouped into cutaneous psoriasis only (PsC) and psoriasis with inflammatory arthritis (PsA). They were further classified by whether they were treated with methotrexate (MTX) or not. Ethnicity (black African, Asian Indian, Caucasian, mixed ancestry) was assigned based on self-reporting by the study participant.

The following clinical and anthropometric characteristics were recorded: blood pressure (BP), weight, height, body mass index (BMI), waist circumference and hip circumference. Subcutaneous, visceral and hepatic fat were measured using a multidetector CT scan. Hepatic fat was quantified using the liver-to-spleen attenuation ratio (LAR). The following biochemical parameters were analysed: plasma glucose, glycated haemoglobin (HbA1c) serum lipids (total cholesterol, triglycerides and HDL (HDL) cholesterol and LDL (LDL) cholesterol) and liver enzymes (gamma glutamyl transferase (GGT), alkaline phosphatase (ALP), aspartate amino transferase (AST) and alanine amino transferase (ALT), high-sensitivity C-reactive protein (hsCRP), insulin, leptin, tumour necrosis factor (TNF), adiponectin and interleukin 6 (IL-6).

Participants were defined as having the metabolic syndrome (MetS) using the 2009 Harmonised guidelines (Alberti *et al.*, 2009). Patients with pre-existing T2D and hypertension were identified based on self-reporting by the patient and a review of clinical records. Non-alcoholic fatty liver disease was defined based on LAR of less than one (Davidson *et al.*, 2006) i.e. the lower the LAR, the greater the hepatic fat content.

5.2.1 Statistical methods

Data were presented using means $\pm$ standard deviations (SD) or medians and interquartile ranges (IQR) for continuous variables with normal or skewed distribution, respectively, and as proportions (%) for categorical variables. Non-parametric data was log transformed to normality before being analysed using parametric statistical tests. Categorical variables were compared across groups using the χ^2 test. Continuous variables were compared between groups using Students unpaired t test.

Liver measurements were compared across controls, psoriasis and PsA groups and across treatment groups by ANOVA followed by a Tukey *post hoc* test if ANOVA was significant. Further sub-group analyses were performed after combining groups where appropriate. A multivariable logistic regression model was performed for NAFLD. Univariate regression analyses were performed for NAFLD against all the appropriate study

variables and those with $p < 0.2$ in the univariate analysis were included in the multivariable model. Backward, stepwise removal of non-significant variables was performed until only those with $p < 0.05$ remained in the model. Multicollinearity was assessed using the variance inflation factor (VIF) and variables with a $VIF > 5.0$ were excluded from the model.

Particular note was taken of variables that were strongly associated with NAFLD in the univariate analysis but did not remain so in the final multivariable logistic regression analysis e.g. visceral fat. Forward regression was performed to determine which variable was responsible for the attenuated effect on NAFLD. The variables chosen for addition to the forward regression model were any of those included in the initial multivariable model and particularly those that continued through to the final model. Variables were also chosen based on scientific plausibility, i.e. there was biological plausibility in terms of them acting as mediators or confounders.

Due to a lack of data on the prevalence of NAFLD in South African populations, we based our sample size on data taken from a review article (Mantovani *et al.*, 2016). This publication included NAFLD prevalence data for psoriasis and control groups from 7 studies. The mean prevalence of NAFLD was calculated for both groups (44.5% for psoriasis and 26.6% for controls) and used to calculate the sample size required to detect such

differences in the current study. It was determined that at $p < 0.05$, a minimum of 55 participants per group would be required.

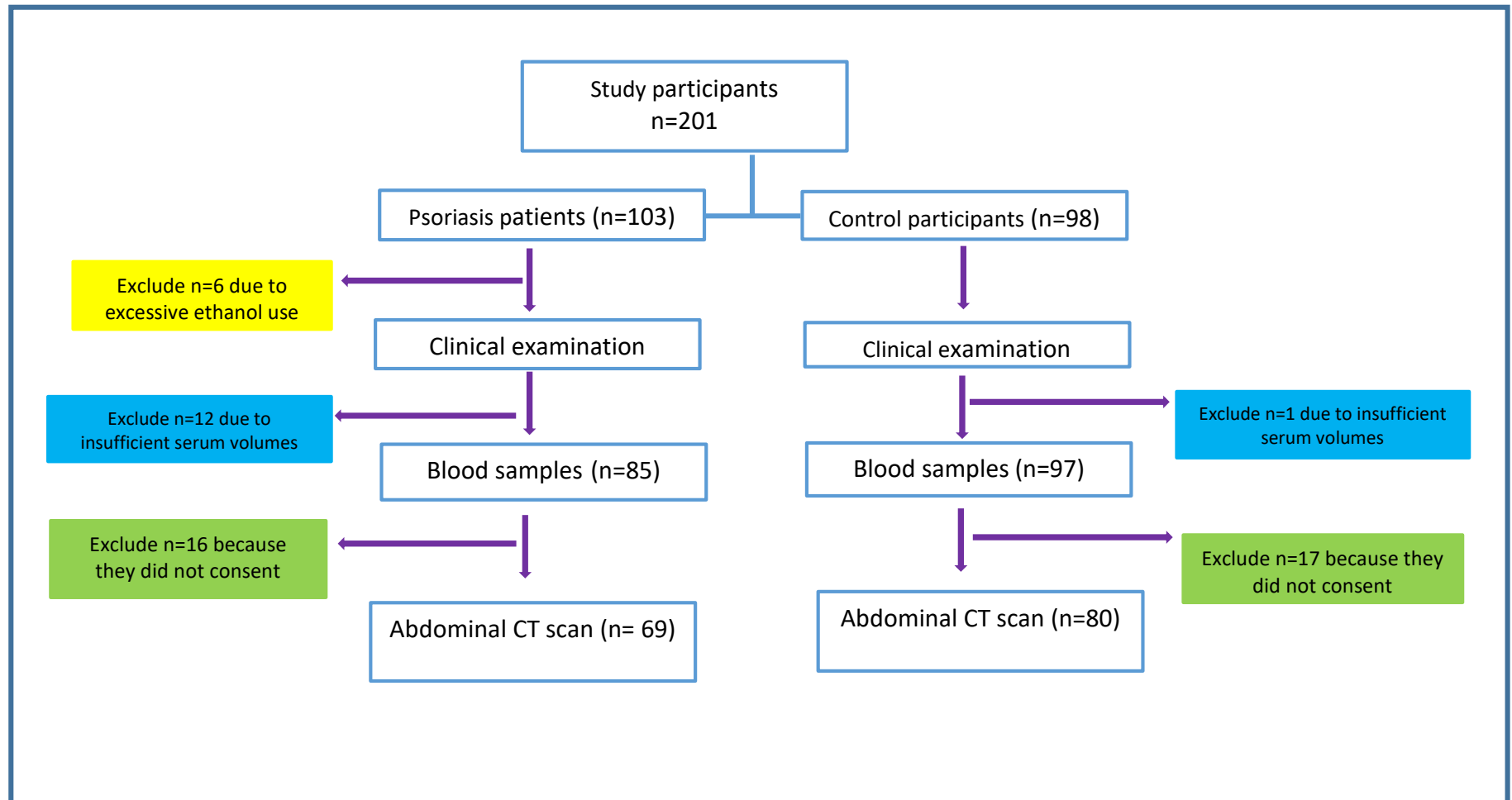


Figure 5.1 Study participants and exclusion criteria

5.3 Results

5.3.1 Clinical, biochemical and metabolic characteristics of patients with cutaneous psoriasis, psoriatic arthritis and controls

Of the 201 participants originally recruited into the study cohort, 6 participants were excluded based on excessive ethanol consumption. All of these were male patients with psoriasis (see Fig. 5.1). Complete biochemical data was available for 182 participants and CT imaging for a total of 149 participants. Initial analyses showed that the prevalence of NAFLD was low in cases and controls, and therefore we sub-divided the psoriasis group into those with psoriatic arthritis (PsA) and cutaneous psoriasis (PsC) (see Tables 5.1 and 5.2), to determine if there was any association between NAFLD and PsA, as observed in previous studies (Madanagobalane *et al.*, 2012a, Miele *et al.*, 2009).

The median (IQR) waist circumference (cm) in the PsC group was significantly higher than in the control group (102 (90,110) vs. (95 (80, 103), $p < 0.05$) (Table 5.1). There were no differences in visceral or subcutaneous fat, however, adiponectin levels ($\mu\text{g/mL}$) were significantly lower and IL-6 levels (pg/mL) significantly higher in the PsC patients compared to control participants (4.56 (2.73, 7.37) vs. 6.25 (4.35, 9.75), $p < 0.005$; 3.00 (1.80, 4.80) vs. 1.70 (1.10, 3.20), $p < 0.005$; respectively). Patients with PsA also had a significantly higher IL-6 compared to PsC

patients (5.90 (2.60, 16.8), $p<0.005$). The prevalence of T2D was higher in both PsA and PsC groups compared to controls (29.6%, 27.6% respectively vs. 4.12%; $p<0.005$ for both) as was the prevalence of MetS in PsA patients compared to controls (70.4% vs. 34.0%; $p<0.0005$).

There was no difference in the liver transaminases between the patients with PsA, PsC and control participants, nor was there a difference in the ALT:AST ratio between the groups. Patients with PsC had a higher ALP (IU/L) than controls (91.0 (66.0, 118) vs. 77.0 (69.0, 98.0), $p<0.02$).

Patients with PsA had a significantly lower albumin level (g/L) than control participants (45.0 (41.0, 48.0) vs. (47.0 (44.0, 50.0) $p<0.0045$). There were no differences in other biochemical parameters of liver function, nor was there any difference in hepatic fat content as measured radiologically by the LAR, or in the prevalence of NAFLD (see Table 5.2).

Table 5.1 Cardiometabolic characteristics of patients with psoriatic arthritis, cutaneous psoriasis and controls

Variable	Psoriatic arthritis (n=27)	Cutaneous psoriasis (n=58)	Controls (n=97)
Waist circumference (cm)	100 (93, 113)	102 (90, 110) *	95.0 (82.0, 103)
BMI (kg/m²)	27.5 (26.4, 32.2)	30.5 (25.7, 35.8)	28.0 (25.0, 32.7)
Visceral fat (cm³)	226 (146, 305)	221 (128, 268)	152.6 (89.5, 218.3)
Subcutaneous fat (cm³)	520 (323, 599)	442 (306, 704)	410.3 (268, 596)
Leptin (ng/mL)	17.9 (10.9, 36.5)	17.0 (7.90, 39.8)	19.0 (8.6, 32.3)
Adiponectin (µg/mL)	5.40 (3.23, 8.95)	4.56 (2.73, 7.37) **	6.25 (4.35, 9.75)
hsCRP (ng/mL)	6.80 (3.00, 12.9) *	4.10 (1.50, 10.4) *	2.00 (1.10, 4.80)
Interleukin 6 (pg/mL)	5.90 (2.60, 16.8) *** §§§	3.00 (1.80, 4.80) **	1.70 (1.10, 3.20)
TNF (pg/mL)	8.30 (6.80, 11.1)	5.50 (4.30, 9.50)	6.68 (4.50, 8.30)
HOMA index	2.89 (1.98 3.50)	2.31 (1.57, 4.43)	2.16 (1.47, 3.06)
Type 2 diabetes	8 (29.6) **	16 (27.6) ***	4 (4.12)
Metabolic syndrome	19 (70.4) *** §	31 (53.4)	33 (34.0)

Data expressed as n (%) or median (IQR) ; *p<0.05, **p<0.005, ***p<0.0005 vs. controls; §p<0.05, §§§p<0.0005 vs. cutaneous psoriasis

Table 5.2 Biochemical and radiological measures of liver function in psoriasis patients and controls

Variable	PsA (n=27)	PsC (n=58)	Controls (n=97)
AST (IU/L)	23.0 (19.0, 26.0)	23.0 (19.0, 26.0)	23.0 (20.0, 28.0)
ALT (IU/L)	23.0 (19.0, 33.0)	22.5 (17.0, 30.0)	23.0 (18.0, 29.5)
ALT:AST	1.06 (0.94, 1.27)	1.00 (0.86, 1.32)	0.94 (0.77, 1.22)
GGT (IU/L)	25.0 (14.0, 36.0)	24.5 (14.0, 37.0)	23.5 (11.5, 36.5)
ALP (IU/L)	85.0 (73.0, 115)	91.0 (66.0, 118) *	76.0 (68.0, 92.0)
Albumin (g/L)	44 ± 5.69 **	46.4 ± 3.92	47.1 ± 4.46
LAR[§]	1.18 ± 0.35	1.19 ± 0.25	1.19 ± 0.22
NAFLD[§]	7 (25.9)	8 (13.8)	13 (13.4)

Data expressed as n (%), mean ± SD, or median (IQR)

*p<0.05, **p<0.005 vs. controls, [§]PsA (n = 23), PsC (n=46), controls (n=80)

5.3.2 Clinical and biochemical characteristics of patients with non-alcoholic fatty liver disease

There were 28 patients (18.9%) in the overall cohort who had radiological evidence of NAFLD (Tables 5.3 and 5.4). There was no significant difference in the prevalence of PsC or PsA in patients with and without NAFLD (Table 5.3). There was, however, a significantly higher prevalence of MetS (82.1% vs. 37.5%, $p<0.0005$) and its components, namely increased waist circumference (96.4% vs. 77.5%, $p<0.05$), T2D (25.0% vs. 10.0%, $p<0.05$), hypertension (85.7% vs. 57.5%, $p<0.005$) and hypertriglyceridaemia (53.6% vs. 20.0%, $p<0.0005$), in patients with NAFLD compared to those without NAFLD. Patients with NAFLD also had a significantly higher abdominal subcutaneous and visceral fat volume (cm^3) (604 (431, 839) vs. 396 (268, 552), $p<0.005$; 280 (195, 356) vs. 154 (87.0, 212), $p<0.0005$, respectively) (Table 5.3) and greater insulin resistance (HOMA index) than controls (3.89 (3.05, 7.00) vs. 1.97 (1.57, 2.89), $p<0.0005$) (Table 5.4). Leptin was significantly higher and adiponectin significantly lower in the NAFLD patients (29.3 (12.1, 49.2) vs. 16.3 (7.90, 33.2) and 4.59 (2.94, 6.33) vs. 5.98 (3.68, 9.50), respectively, $p<0.05$ for both). Furthermore, IL-6 levels were higher in NAFLD ($p<0.05$) but there were no significant differences in TNF or hsCRP between the groups (Table 5.4).

Table 5.3 Clinical and anthropometric differences between patients with and without non-alcoholic fatty liver disease defined by liver-to-spleen attenuation ratio

<i>Variable</i>	<i>LAR >1 (n=121)</i>	<i>LAR <1 (n=28)</i>
<i>Psoriasis</i>	54 (45.0)	15 (53.6)
<i>Psoriatic arthritis</i>	16 (13.3)	7 (25.0)
<i>Body mass index (kg/m²)</i>	29.8 ± 7.71	36.2 ± 8.47 ***
<i>Obesity</i>	47 (39.2)	21 (75.0) *
<i>Waist circumference (cm)</i>	95.7 ± 16.0	110 ± 13.8 ***
<i>Increased waist circumference</i>	93 (77.5)	27 (96.4) *
<i>Systolic blood pressure (mmHg)</i>	133 ± 20.3	141 ± 16.0 *
<i>Diastolic blood pressure (mmHg)</i>	82.6 ± 11.2	90.2 ± 11.5 **
<i>Hypertension</i>	69 (57.5)	24 (85.7) *
<i>Subcutaneous fat (cm³)</i>	396 (268, 552)	604 (431, 839) **
<i>Visceral fat (cm³)</i>	154 (87.0, 212)	280 (195, 356) ***

Data expressed as mean ± SD, median (IQR) or n (%)

*p<0.05, **p<0.005, ***p<0.0005 vs. LAR>1

Table 5.4 Biochemical and metabolic differences between patients with and without non-alcoholic fatty liver disease defined by liver-to-spleen attenuation ratio

Variable	LAR >1 (n=121)	LAR <1 (n=28)
Glucose (mmol/L)	5.10 (4.0, 5.60)	5.70 (5.10, 7.30) ***
Type 2 diabetes	12 (10.0)	7 (25.0) *
Triglycerides (mmol/L)	1.18 (0.91, 1.69)	1.84 (1.30, 2.69) ***
Hypertriglyceridaemia	24 (20.0)	15 (53.6) **
HDL-C (mmol/L)	1.34 (1.10, 1.62)	1.21 (1.01, 1.46) *
Low HDL-C levels	27 (22.5)	13 (46.4)
Metabolic syndrome	45 (37.5)	23 (82.1) ***
HOMA	1.97 (1.57, 2.89)	3.89 (3.05, 7.00) ***
Leptin (ng/mL)	16.3 (7.90, 33.2)	29.3 (12.1, 49.2) *
Adiponectin (µg/mL)	5.98 (3.68, 9.50)	4.59 (2.94, 6.33) *
hsCRP (ng/mL)	3.00 (1.30, 7.20)	4.05 (1.60, 11.5)
TNF (pg/mL)	6.30 (4.60, 9.30)	7.65 (5.65, 8.70)
IL-6 (pg/mL)	2.25 (1.50, 4.40)*	3.30 (1.85, 7.90)

Data expressed as mean ± SD, median (IQR) or n (%), *p<0.05, **p<0.005, ***p<0.0005 vs. LAR>1

5.3.3 Anti-psoriatic therapy and non-alcoholic fatty liver disease

Table 5.5 describes hepatic fat and enzyme levels across the 2 common therapy groups i.e. topical therapy (n=49) and methotrexate (n=23) in comparison to control participants (n=97). Patients receiving oral acitretin (n=13) or other systemic therapies (n=5) such as leflunomide or cyclosporine were excluded from this analysis owing to small patient numbers. The prevalence of NAFLD was highest in patients with PsA (Table 5.2) and this was mirrored in patients receiving methotrexate (Table 5.5). Likewise, albumin levels were lowest in those with PsA (Table 5.1) and in those using methotrexate (Table 5.5). Patients receiving topical therapy or methotrexate had higher serum ALP levels compared to non-psoriatic participants, but this difference was only significant for the patients on topical therapy, probably due to their higher sample size (Table 5.5)

We therefore performed a sub-group analysis comparing the prevalence of NAFLD, LAR and serum albumin levels between the following 5 groups: control participants, PsC patients who were not on methotrexate, PsC patients receiving methotrexate, PsA patients not receiving methotrexate and PsA patients that received methotrexate. The results are shown in Table 5.6, and demonstrate no significant differences for LAR across the groups, although it was lowest in those with PsA and using methotrexate.

However, the prevalence of NAFLD was highest in PsA patients receiving methotrexate and was significantly higher ($p<0.05$) than in the control group. Albumin levels were significantly lower ($p<0.05$) in PsA participants using methotrexate when compared to the control group.

Table 5.5 Prevalence of non-alcoholic fatty liver disease, liver fat content and liver enzyme levels according to therapy for psoriasis

Liver measurements	Treatment groups (n)		
	Controls (n= 97)	Topical (n=49)	Methotrexate (n=23)
<i>Prevalence of NAFLD[§]</i>	13 (15.2)	9 (20.9)	6 (31.6)
<i>Attenuation ratio[§]</i>	1.20 ± 0.22	1.21 ± 0.30	1.12 ± 0.29
<i>Total protein (g/L)</i>	77.9 ± 8.07	79.7 ± 7.65	77.8 ± 10.1
<i>Albumin (g/L)</i>	47.5 ± 4.50	45.7 ± 4.08	45.1 ± 5.63
<i>ALP (IU/L)</i>	76.5 (68.0, 92.0)	89.0 (68.0, 122)*	92.0 (68.0, 104)
<i>GGT (IU/L)</i>	23.5 (11.5, 36.5)	24.0 (18.0, 33.0)	26.0 (15.0, 36.0)
<i>AST (IU/L)</i>	23.0 (20.0, 28.0)	21.0 (18.0, 25.0)	23.0 (19.0, 28.0)
<i>ALT (IU/L)</i>	23.0 (18.0, 29.5)	21.0 (17.0, 30.0)	26.0 (20.0, 31.5)

Data given as n [%], mean ± SD or median (interquartile range);

*p<0.05 vs. controls

[§]Sample numbers for both NAFLD and attenuation ratio are controls (n= 79), topicals, (n=43) and methotrexate (n=23)

Table 5.6 Prevalence of non-alcoholic fatty liver disease, liver attenuation ratio and serum albumin levels according to methotrexate therapy and presence of psoriatic arthritis

Variables	Subject groups (n)				
	Controls not using MTX (80)	PsC not using MTX (36)	PsA not using MTX (13)	PsC using MTX (9)	PsA using MTX (10)
<i>Prevalence of NAFLD</i>	13 (15.2)	7 (19.4)	2 (15.2)	1 (11.1)	5 (50)*
<i>Attenuation ratio</i>	1.20 ± 0.22	1.20 ± 0.27	1.25 ± 0.32	1.16 ± 0.16	1.08 ± 0.37
<i>Albumin (g/L)[§]</i>	47.5 ± 4.50	46.4 ± 4.22	44.8 ± 4.44	47.3 ± 2.28	43.1 ± 7.04*

Data given as n (%) or mean ± SD;

*p<0.05 vs. controls;

[§]sample numbers for albumin: controls (n= 97), PsC not using MTX (n=8), PsA not using MTX (n=15), PsC using methotrexate (n=11), PsA using MTX (n=12);

MTX, methotrexate; PsC, cutaneous psoriasis; PsA, psoriatic arthritis

5.3.4 Predictors of non-alcoholic fatty liver disease in psoriasis

The following variables were included in a backward, stepwise multivariable logistic regression analysis for NAFLD following selection using univariate analyses: gender, ethnicity, age, triglycerides, PsA (with and without methotrexate therapy) HDL-C, hip circumference, subcutaneous and visceral fat, type 2 diabetes, HOMA index, hsCRP, IL-6 and adiponectin. The final model showed that triglycerides, HOMA and PsA with methotrexate were independently associated with NAFLD (Table 5.7).

Table 5.7 Logistic regression model showing risk factors for non-alcoholic fatty liver disease

<i>Categorical variable</i>	<i>Independent variable</i>	<i>Odds ratio (95% CI)</i>	<i>P value</i>
<i>Non-alcoholic fatty liver disease</i>	Triglycerides	1.63(1.05, 2.52)	0.03
	HOMA	1.98 (1.44, 2.72)	<0.0001
	PsA with methotrexate	2.77 (1.31, 5.87)	0.007

Visceral fat was strongly associated with psoriasis in the univariate analysis (OR (95% CI): 2.38 (1.61, 3.51); $p < 0.0001$). As it did not remain significant in the multivariable model, it was further analysed using forward regression analysis to determine which variable was responsible for attenuating its effect. This analysis demonstrated that HOMA index considerably decreased the relationship between visceral fat and NAFLD

i.e. the OR (95% CI) was reduced to 1.72 (1.09, 2.69) with a highly attenuated p-value (p=0.018).

5.4 Discussion

In this case-control study of South Africans with psoriasis we have found a prevalence of NAFLD in the overall cohort of 18.8%. In addition, there was no significant difference in the prevalence of NAFLD between the psoriasis and control groups. However, participants with NAFLD had a higher prevalence of CMDs, including MetS, T2D, and hypertension, as well as higher visceral fat and IL-6 levels compared to those without NAFLD. The sub-group of patients with PsA treated with methotrexate had a significantly higher prevalence of NAFLD than participants who not did not have PsA and were not on methotrexate. Furthermore, we observed that hypertriglyceridaemia, insulin resistance and PsA treated with methotrexate were all risk factors for NAFLD.

Previous studies have shown a significantly higher prevalence of NAFLD in psoriasis patients compared to controls (Mantovani *et al.*, 2016). Studies conducted in Italy, the Netherlands and Iran reported significantly higher prevalences of NAFLD compared to controls: 47% vs. 28%, 46% vs. 33% and 66% vs. 35% respectively, with all studies using ultrasonography as the principle diagnostic modality (Gisondi *et al.*, 2009, van der Voort *et al.*, 2014, Abedini *et al.*, 2015). We postulate that the lower prevalence of NAFLD

noted in this study (18.8%) may be related to the different diagnostic technique used to detect NAFLD i.e. CT scan as opposed to ultrasonography and possibly due to ethnic differences in the prevalence of NAFLD across these studies. The lack of difference in NAFLD prevalence between cases and controls observed in the current study may be partially explained by the high prevalence of obesity in the control group.

The pathophysiology of liver dysfunction in psoriasis is not known. Although we have shown no difference in the prevalence of NAFLD between psoriasis and control groups, the prevalence of NAFLD was highest in patients with PsA who were receiving methotrexate therapy. In addition to a higher prevalence of ethanol use in psoriasis, the “systemic effects of psoriasis” have been suggested as a possible reason for the greater likelihood for patients with psoriasis to develop liver dysfunction (Lindsay *et al.*, 2008).

Within the present study, those individuals who were excluded from the analysis owing to excessive ethanol consumption were limited to the psoriasis group. Misuse of ethanol is common in patients with psoriasis with up to 32% of patients reporting subjective problems with ethanol consumption (McAleer *et al.*, 2011). It has been proposed that consumption of ethanol is a coping strategy, particularly in male patients, once they have developed psoriasis (Fortune *et al.*, 2002). Interestingly, all

the patients excluded from this analysis for excessive alcohol consumption were male.

Not only were anthropometric variables such as BMI, waist circumference and visceral fat significantly higher in participants with NAFLD compared to those without NAFLD, so too were cardiometabolic parameters including insulin resistance, triglyceride levels, hypertension, T2D and MetS. Furthermore, the NAFLD group had significantly higher levels of IL 6 and leptin and lower levels of adiponectin. However, multivariable logistic regression analysis demonstrated that insulin resistance, hypertriglyceridaemia and PsA treated with methotrexate are predictors of NAFLD in this cohort. Forward regression analysis demonstrated that the effect of visceral fat on NAFLD risk is mediated largely by insulin resistance. The association of NAFLD with visceral fat, insulin resistance and hypertriglyceridaemia is well described (Benedict *et al.*, 2017) in the general population.

In addition, in the current study, NAFLD was significantly more prevalent in those patients with PsA who were being treated with methotrexate. These participants also had low serum levels of albumin. A previous study has shown that PsA patients treated with methotrexate are more likely to develop hepatotoxicity than those with rheumatoid arthritis (RA) (Tilling *et al.*, 2006). Although the theoretical risk of hepatotoxicity with methotrexate

has been well-described it has, in general, been considered a cost-effective and useful disease-modifying anti-rheumatic drug, particularly in RA (Lindsay *et al.*, 2008). However, psoriasis patients are at least three times more likely to develop methotrexate-associated liver damage than patients with RA (Whiting-O'Keefe *et al.*, 1991).

The risk of methotrexate-associated hepatotoxicity in psoriasis has been shown to be dose-related, as well as greater in patients with T2D and obesity, which are also known to be risk factors for NAFLD. (Montaudie *et al.*, 2011, Rosenberg *et al.*, 2007) Methotrexate may accelerate NAFLD-associated liver damage or result in hepatotoxicity that may resemble NAFLD histologically (Langman *et al.*, 2001). A recent report has shown that the incidence of methotrexate-associated adverse events including hepatotoxicity was greater in patients with PsA than those with PsC. (Yan *et al.*, 2019).

Serum levels of ALP were noted to be higher in participants with psoriasis, irrespective of the anti-psoriasis treatment regimen. The serum ALP was measured using an assay that does not differentiate between the main isoenzymes or isoforms. The main forms found in human serum are bone, liver and intestinal (Van Hoof *et al.*, 1994) and further studies are required to determine if levels of any of these individual enzymes differ between control and psoriasis groups. Assays specific for bone ALP are available

(Withold *et al.*, 1996) and all 3 types can be discriminated using gel electrophoretic techniques.

The limitations of the study include its cross-sectional design and the fact that liver dysfunction was measured non-invasively. In addition, the sample size was small, particularly for participants with PsA. Using data from previous studies, we did have a sample size that was sufficient to detect significant differences in the prevalence of NAFLD between the controls group and psoriasis patients. However, the unexpectedly low prevalence of NAFLD in our study precluded this possibility. In addition data on the cumulative dose of methotrexate used in patients was not available.

A strength of this study was that a large number of known risk factors for NAFLD were measured including visceral fat volume, assessed using CT scans, adiponectin levels, insulin resistance, serum triglyceride concentrations, metabolic syndrome and T2D.

In this case-control study of South Africans with psoriasis, participants with NAFLD have increased prevalence of T2D, hypertriglyceridaemia and higher visceral fat. Although there was no increase in NAFLD in psoriatic patients compared to controls, the highest risk for NAFLD was seen in patients with PsA treated with methotrexate even after adjusting for

possible confounding variables. This data suggests that this particular patient group may warrant screening for NAFLD.

CHAPTER 6 DISCUSSION AND CONCLUSIONS

To our knowledge, this is the first study to assess cardiometabolic diseases (CMD) in psoriasis patients in a South African setting. This was a cross-sectional, case-control study in which the overall aim was to determine if psoriasis is associated with a higher risk of CMDs (including non-alcoholic fatty liver disease (NAFLD)) and whether visceral fat and its associated adipokines mediate these associations.

We showed a high prevalence of CMDs, specifically metabolic syndrome (MetS), type 2 diabetes (T2D) and hypertension in psoriasis patients compared to matched controls. This association was greater in patients with severe psoriasis in comparison to mild disease. In addition, we demonstrated that psoriasis patients had a higher visceral fat volume than control participants matched for body mass index (BMI); that visceral fat was an independent predictor of psoriasis and that its effect was mediated by the pro-inflammatory cytokine interleukin 6 (IL-6). Furthermore, psoriasis was an independent risk factor for T2D, but the association of psoriasis with hypertension and lipid levels appeared to be mediated by visceral fat and associated adipokines.

The present study highlights the high prevalence of CMDs in psoriasis in the South African setting. Obesity and its attendant complications are an escalating problem in sub-Saharan Africa, and in South Africa in particular

(Shisana *et al.*, 2014). As such, we have noted a high background prevalence of CMDs in this cohort. However, despite being matched for body mass index (BMI), patients with psoriasis had significantly higher prevalence of CMDs than controls, particularly in patients with severe psoriasis. This was particularly noteworthy in the case of T2D which was 6-fold more prevalent in the psoriasis group than control participants. In addition, patients with psoriasis also had a higher prevalence of smoking than controls. Lifestyle modification strategies aimed at weight reduction and smoking cessation may have potential beneficial effects in reducing the burden of psoriasis-related CMD.

By simultaneously measuring clinical, metabolic and anthropometric parameters as well as biomarkers of inflammation in this cohort of patients with psoriasis, we found that visceral fat was an independent predictor of psoriasis and that the effect of visceral fat was mediated by the pro-inflammatory cytokine IL-6. Although the cross-sectional study design, does not allow us to draw any conclusions related to causality, these findings imply the potential role for visceral fat and adipokine dysregulation in the pathogenesis of psoriasis and related CMDs. While many of the CMDs that are prevalent in psoriasis may be associated with visceral adiposity, the exception is T2D which the present study has shown is independently associated with psoriasis. These findings highlight the need

for further research, with a more directed approach for determining the precise aetiology of psoriasis-associated CMDs, particularly T2D.

In this cohort, the prevalence of NAFLD was 18.8%, which is lower than prevalence rates reported in first world studies. We reported no difference in the prevalence of NAFLD between psoriasis patients and controls, which is also in contrast to the literature (Mantovani *et al.*, 2016, Gisondi *et al.*, 2009). This may, in part, be related to the use of CT scanning to detect NAFLD, as it is less sensitive than other modalities such as MRI and transient elastography (Bohte *et al.*, 2011, Hashemi *et al.*, 2016). There was, however, a high prevalence of metabolic comorbidities in NAFLD. In addition patients with PsA on methotrexate therapy had a significantly higher prevalence of NAFLD compared to those without PsA who did not take methotrexate. We further demonstrated that PsA in combination with methotrexate therapy, as well as insulin resistance and hypertriglyceridaemia were independently associated with risk for NAFLD. Most previous studies used ultrasonography as the imaging modality to diagnose NAFLD whilst the present study used non-contrast CT scanning. The differences in diagnostic test may partly explain the lower prevalence of NAFLD in this study. The ideal method to diagnose NAFLD in the clinical setting is not clearly defined. However, transient elastography is a practical and clinically useful method to detect NAFLD in patients. Patients with PsA had the highest prevalence of NAFLD suggesting that this is an especially vulnerable subset of patients who may perhaps

require more clinical vigilance particularly when treated with methotrexate. It also raises the question as to how liver disease should be managed in this group of patients and whether methotrexate therapy should be discontinued.

The limitations of this study were its cross-sectional design and relatively small sample size. As previously mentioned, it should be noted that it is not possible to make causal arguments in the setting of a cross-sectional study. Further prospective and/or Mendelian randomisation studies must be conducted to verify the associations noted in this cohort. Secondly, although the overall cohort number was based on a sample size calculation, sub-group analyses that involved 3 or more groups may have been underpowered. Study participants were recruited from public hospitals, therefore results may not be generalisable to all South Africans. In addition, patients were not treatment-naïve at the time of inclusion into the study and no data on methotrexate dose was available.

A further limitation was the slightly higher BMI of the patient group (although not statistically different from the controls), and also the significantly older age of the patient group. Although these differences were taken into account in the multivariable logistic regression models, further studies should endeavour to match important group characteristics more carefully. However, the study also had a number of important

strengths. We were able to measure a large number of highly relevant variables that allowed us to concurrently interrogate the relationships between psoriasis, visceral fat, adipokines and CMDs. This allowed us to develop possible mechanistic pathways for how psoriasis may lead to higher risk for CMDs, and to propose aetiological pathways for psoriasis.

The present work has identified several areas for future research that may improve the understanding of psoriasis and CMD. In particular, there is a need for further research into the precise pathophysiological pathways linking visceral obesity with psoriasis, notably the role of IL-6. In addition, the association of PsO with T2D was very strong but no mediators of this relationship were identified. Further studies are required to identify the possible factors linking PsO with increased T2D risk. There is also a need for longitudinal studies looking at large groups of newly diagnosed patients with psoriasis to monitor their progression to CMD and determine which baseline characteristics are predictors of CMD with specific reference to anti-psoriatic therapies, visceral fat and adipokines. Prospective studies looking at the effect of weight reduction on the course of cutaneous and cardiometabolic disease in these patients also warrants further investigation.

In conclusion, there is a high burden of CMD in this cohort of South Africans with psoriasis and this risk was most marked in those with severe

psoriasis. Visceral fat increases the risk of psoriasis and cardiometabolic disease, but T2D, in particular, is independently associated with psoriasis. Although the prevalence of NAFLD is not increased in this cohort, patients with PsA using methotrexate are potentially at greater risk. Public health interventions such as lifestyle modification aimed at weight loss and smoking cessation are needed to modify the risk of CMD in psoriasis. This study also reinforces the need for greater clinical vigilance for CMD by screening routinely for hypertension, T2D and dyslipidaemia especially in severe psoriasis. This may be achieved by the inclusion of blood pressure, glycated haemoglobin and non-fasting lipid measurements as part of routine clinical assessment. Furthermore, given the increased risk of NAFLD in patients with PsA on methotrexate, ideally all such patients should be screened for NAFLD.

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APPENDICES

Appendix 1- Plagiarism declaration

Appendix 2- Turnitin report

Appendix 3- Supplementary data

Appendix 4 - Psoriasis Area and Severity Index score

Appendix 5 - Socio-economic status questionnaire

Appendix 6 - Framingham Score

Appendix 7 - Ethics clearance certificates

Appendix 8- Publication

Goolam Mahyooddeen, N., Crowther, N.J., Tikly, M. 2018. Double trouble: psoriasis and cardiometabolic disorders. *Cardiovasc J Afr*, 29, 189-194.

Appendix 9- Publication

Goolam Mahyooddeen, N., Crowther N.J., Snyman, T., Pillay, L., Tikly, M. 2018. High burden of the metabolic syndrome and its component disorders in South Africans with psoriasis. *Int J Dermatol*, 58, 557-562.



PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Nasrin Goolam Mayoodeen (Student number: 9500537K) am a student registered for the degree of PhD in the academic year 2019.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

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APPENDIX 3

SUPPLEMENTARY DATA

Table A1. Comparison of clinical and demographic characteristics of participants who did and did not undergo abdominal CT scan

Variable	Participants who did not undergo CT scan	Participants who underwent CT scan
<i>n</i>	52	149
<i>Males</i>	21 (40.3)	64 (43.0)
<i>Age (years)</i>	52.2 ± 15.6	50.1 ± 14.4
<i>Body mass index (kg/m²)</i>	29.1 ± 5.63	30.9 ± 8.24
<i>Waist circumference (cm)</i>	96.3 ± 15.0	98.3 ± 16.4
<i>Low socio-economic status</i>	19 (36.5)	58 (38.9)
<i>Hypertension</i>	27 (52.0)	94 (63.1)
<i>Type 2 diabetes</i>	10 (19.2)	20 (13.4)
<i>Low HDL cholesterol</i>	10 (19.2)	40 (26.8)
<i>Hypertriglyceridaemia</i>	7 (13.4)	39 (26.2)
<i>Metabolic syndrome</i>	18 (34.6)	69 (46.3)
<i>Smoking</i>	28 (53.4)	59 (40.0)
<i>Completed high school</i>	34 (65.4)	99 (66.4)

Data expressed as mean ± SD or n (%); p >0.05 for all comparisons

Table A2. Prevalence of cardiometabolic diseases in psoriasis patients by therapy group

<i>Variable</i>	Topical Therapy	Methotrexate	Controls
<i>n</i>	60	25	98
<i>Metabolic syndrome</i>	28 (46.7)	16 (64.0)**	33 (33.7)
<i>Type 2 diabetes</i>	13 (21.7)***	7 (28.0)***	4 (4.10)
<i>Hypertension</i>	41 (61.3)*	16 (64.0)	48 (49.0)
<i>Low HDL-C levels</i>	13 (21.7)	10 (40.0)	21 (21.4)
<i>Hypertriglyceridaemia</i>	16 (26.6)	8 (32.0)	19 (19.4)

Data expressed as n (%)

*p<0.05, **p<0.005, ***p<0.0005 vs controls

Patients on acitretin and other anti-psoriatic therapies (e.g. leflunamide, cyclosporine A) were not included in this analysis due to small n numbers (n=13 and n=5, respectively).



PSORIASIS AREA AND SEVERITY INDEX (PASI) WORKSHEET

HOSPITAL NO.: é é é é é é é é é é é é é é é é .

PATIENT NAME: é é é é é é é é é é é é é é é é .

DATE OF VISIT: é é é é é é é é é é é é é é é é .

The Psoriasis Area and Severity Index (PASI) is a quantitative rating score for measuring the severity of psoriatic lesions based on area coverage and plaque appearance.

Plaque characteristic	Lesion score	Head	Upper Limbs	Trunk	Lower Limbs
Erythema	0 = None				
	1 = Slight				
Induration/Thickness	2 = Moderate				
	3 = Severe				
Scaling	4 = Very severe				
Add together each of the 3 scores for each body region to give 4 separate sums (A).					
Lesion Score Sum (A)					

Percentage area affected	Area score	Head	Upper Limbs	Trunk	Lower Limbs
Area Score (B) <i>Degree of involvement as a percentage for each body region affected (score each region with score between 0-6)</i>	0 = 0% 1 = 1% - 9% 2 = 10% - 29% 3 = 30% - 49% 4 = 50% - 69% 5 = 70% - 89% 6 = 90% - 100%				
Multiply Lesion Score Sum (A) by Area Score (B), for each body region, to give 4 individual subtotals (C).					
Subtotals (C)					
Multiply each of the Subtotals (C) by amount of body surface area represented by that region, i.e. x 0.1 for head, x 0.2 for upper body, x 0.3 for trunk, and x 0.4 for lower limbs.					
Body Surface Area		x 0.1	x 0.2	x 0.3	x 0.4
Totals (D)					
Add together each of the scores for each body region to give the final PASI Score.					

PASI Score =

APPENDIX 5

SOCIO-ECONOMIC STATUS QUESTIONNAIRE

Table A3: Socioeconomic status questionnaire

Television	☐
Radio	☐
Satellite television	☐
DVD player	☐
Electricity	☐
Microwave	☐
Motor vehicle	☐
Computer	☐
Refrigerator	☐
Washing machine	☐
Telephone	☐
Cellular telephone	☐
Award a score of 1 for each appliance/amenity:	
Total	____/12

Interpretation:

- ≥ 10 High socio-economic status
- < 10 Low socio-economic status

Adapted from Griffiths *et al*, Socio-economic status and body composition outcomes in urban South African children, 93., 863-867.

FRAMINGHAM RISK SCORE (FRS)

Estimation of 10-year Cardiovascular Disease (CVD) Risk

Date: _____

Patient's Name: _____

Step 1¹
In the "points" column enter the appropriate value according to the patient's age, HDL-C, total cholesterol, systolic blood pressure, and if they smoke or have diabetes. Calculate the total points.

Risk Factor		Risk Points		Points		
		Men	Women			
Age						
30-34		0	0			
35-39		2	2			
40-44		5	4			
45-49		7	5			
50-54		8	7			
55-59		10	8			
60-64		11	9			
65-69		13	10			
70-74		14	11			
75+		15	12			
HDL-C (mmol/L)						
>1.6		-2	-2			
1.3-1.6		-1	-1			
1.2-1.3		0	0			
0.9-1.2		1	1			
<0.9		2	2			
Total Cholesterol						
<4.1		0	0			
4.1-5.2		1	1			
5.2-6.2		2	3			
6.2-7.2		3	4			
>7.2		4	5			
Systolic Blood Pressure (mmHg)		Not Treated	Treated	Not Treated	Treated	
<120		-2	0	-3	-1	
120-129		0	2	0	2	
130-139		1	3	1	3	
140-149		2	4	2	5	
150-159		2	4	4	6	
160+		3	5	5	7	
Diabetes	Yes	3		4		
	No	0		0		
Smoker	Yes	4		3		
	No	0		0		
Total Points						

Step 2¹
Using the total points from Step 1, determine the 10-year CVD risk* (%).

Total Points	10-Year CVD Risk (%)*	
	Men	Women
-3 or less	<1	<1
-2	1.1	<1
-1	1.4	1.0
0	1.6	1.2
1	1.9	1.5
2	2.3	1.7
3	2.8	2.0
4	3.3	2.4
5	3.9	2.8
6	4.7	3.3
7	5.6	3.9
8	6.7	4.5
9	7.9	5.3
10	9.4	6.3
11	11.2	7.3
12	13.3	8.6
13	15.6	10.0
14	18.4	11.7
15	21.6	13.7
16	25.3	15.9
17	29.4	18.5
18	>30	21.5
19	>30	24.8
20	>30	27.5
21+	>30	>30

* Double cardiovascular disease risk percentage for individuals between the ages of 30 and 59 without diabetes if the presence of a positive history of premature cardiovascular disease is present in a first-degree relative before 55 years of age for men and before 65 years of age for women. This is known as the modified Framingham Risk Score.³

Step 4^{2,3}
Using 10-year CVD risk from Step 2, determine if patient is Low, Moderate or High risk.¹
Indicate Lipid and/or Apo B targets

Risk Level ¹	Initiate Treatment If:	Primary Target (LDL-C)	Alternate Target
High FRS ≥20%	• Consider treatment in all (Strong, High)	• ≤2 mmol/L or ≥50% decrease in LDL-C (Strong, Moderate)	• Apo B ≤0.8 g/L or • Non-HDL-C ≤2.6 mmol/L (Strong, High)
Intermediate FRS 10-19%	• LDL-C ≥3.5 mmol/L (Strong, Moderate) • For LDL-C <3.5 mmol/L consider if: • Apo B ≥1.2 g/L • OR Non-HDL-C ≥4.3 mmol/L (Strong, Moderate)	• ≤2 mmol/L or ≥50% decrease in LDL-C (Strong, Moderate)	• Apo B ≤0.8 g/L or • Non-HDL-C ≤2.6 mmol/L (Strong, Moderate)
Low FRS <10%	• LDL-C ≥5.0 mmol/L • Familial hypercholesterolemia (Strong, Moderate)	• ≥50% decrease in LDL-C (Strong, Moderate)	N/A
Lipid targets LDL-C: _____ or Apo B: _____			

¹ Consider moving some patients with metabolic syndrome up a risk level based on their 'load' of metabolic risk factors or the 'severity' of their metabolic syndrome.
² Atherosclerosis in any vascular bed, including carotid arteries.
apoB: apolipoprotein B stat; CAD: coronary artery disease; FRS: Framingham Risk Score; HDL-C: high-density lipoprotein cholesterol; hs-CRP: high-sensitivity C-reactive protein; PVD: peripheral vascular disease; RRS: Reynolds Risk Score; TC: total cholesterol.

¹ Adapted from: D'Agostino RB et al. (i). General cardiovascular risk profile for use in primary care. The Framingham Heart Study. Circ 2008;117:743-53.
² Adapted from: Genest J et al. (i). 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult. Can J Cardiol. 2009;25(10):567-579.
³ Adapted from: Anderson T et al. (i). 2012 Update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. Can J Cardiol. 2013;29(2):151-167.

M1403100



HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M1403100

NAME: Dr NG Mahyooden
(Principal Investigator)

DEPARTMENT: Medicine
Chris Hani Baragwanath Academic Hospital

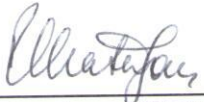
PROJECT TITLE: The Cardio Metabolic Aspects of Psoriasis

DATE CONSIDERED: 28/03/2014

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Prof M Tickly, Prof N Crowther and Dr L Pillay

APPROVED BY: 
Professor PE Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 09/05/2014

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.**


Principal Investigator Signature

31/5/2014
M1403100Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Human Research Ethics Committee (Medical)

Research Office Secretariat: Senate House Room SH 10005, 10th floor. Tel +27 (0)11-717-1252
Medical School Secretariat: Phillip Tobias Building. 2nd Floor Tel +27 (0)11-717-2700
Private Bag 3, Wits 2050, www.wits.ac.za. Fax +27 (0)11-717-1265



17 June 2015

Dr NG Mahyooden

Chris Hani Baragwanath Academic Hospital

Department of Medicine

Division of Endocrinology

Sent by email to: mahyooden@yahoo.com

Dear Dr Mahyooden

Re: Protocol Ref no: M1403100

Protocol Title: The cardio-metabolic aspects of psoriasis

Principal Investigator: Dr NG Mahyooden

Protocol Amendments

This letter serves to confirm that the Chairperson of the Human Research Ethics Committee (Medical) has approved your request to include a CT scan for all the patients on the above mentioned protocol, as detailed in your letter.

Thank you for keeping us informed and updated,

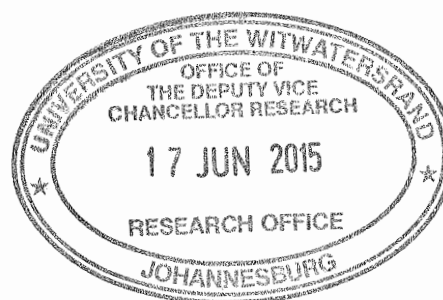
Yours Sincerely,

A handwritten signature in black ink, appearing to be "Langutani Masingi", written over a dotted line.

Mr Langutani Masingi

Administrative Officer

Human Research Ethics Committee (Medical)



Review Article

Double trouble: psoriasis and cardiometabolic disorders

Nasrin Goolam Mahyooden, Nigel J Crowther, Mohammed Tikly

Abstract

Psoriasis (PsO) is a chronic immune-mediated inflammatory skin disorder associated with numerous co-morbidities. This descriptive review focuses on the cardiometabolic co-morbidities of PsO with reference to the epidemiology and pathogenetic mechanisms linking PsO and cardiometabolic disease (CMD). Registry-based studies have shown PsO to be associated with an increased risk of cardiovascular morbidity and mortality. Factors linking PsO and CMD include: chronic inflammation, obesity, classic cardiovascular risk factors, and the effects of systemic therapy used to treat PsO. Chronic inflammation is associated with PsO itself, and with obesity. Adipose tissue is responsible for the secretion of various adipokines, which together with pro-inflammatory cytokines arising from the psoriatic plaque, contribute to the pro-inflammatory and pro-atherogenic environment. Systemic therapy aimed at decreasing inflammation has been shown to improve CMD in PsO. Screening for and treating CMD and initiating lifestyle modifications will remain the most important interventions until further data emerge regarding the effect of systemic therapy on CMD progression.

Keywords: psoriasis, cardiovascular disease, cardiometabolic disease, co-morbidities, metabolic syndrome, obesity

Submitted 26/6/17, accepted 6/12/17

Cardiovasc J Afr 2017; 28: online publication

www.cvja.co.za

DOI: 10.5830/CVJA-2017-055

Psoriasis (PsO) is a complex, chronic, immune-mediated inflammatory skin disorder, which has a global prevalence ranging between 0.91 and 8.5%.¹ It is recognised by the World Health Organisation as a major global health challenge,² and is associated with impaired psychological quality of life, which

exceeds that observed in several chronic conditions including malignancy and heart failure.³ A wide range of co-morbidities are associated with PsO, ranging from chronic inflammatory disorders such as inflammatory arthritis, [often referred to as psoriatic arthritis (PsA)],⁴ Crohn's disease,⁴ neuropsychiatric disorders such as Parkinsonism,⁵ psychiatric disease,^{6,7} malignancies,^{4,8} as well as cardiometabolic diseases⁹⁻¹³ (Table 1).

In this descriptive review, we examine the epidemiological and pathological evidence linking PsO and cardiometabolic disorders, with a particular focus on cardiovascular disease (CVD). We conducted a PubMed search using the term 'psoriasis' in combination with the terms 'cardiovascular disease', 'co-morbidities', 'diabetes', 'metabolic syndrome', 'obesity', 'hypertension', 'dyslipidaemia', 'non-alcoholic fatty liver disease' and 'inflammation'. Our search was limited to articles published in English.

Immunopathogenesis of psoriasis

The interplay between genetic factors and environmental triggers results in the classic psoriatic plaque, characterised histologically by epidermal hyperplasia, vascular hyperproliferation and chronic inflammation.⁴ Common triggers for the disease are local skin trauma (Koebner phenomenon), stress, *Streptococcus pyogenes*, infection and smoking.⁴ About a third of patients have a family history of PsO and genome-wide analysis studies have shown the *PSORS1* gene, located on chromosome 6p, accounts for between 35 and 50% of the heritability of PsO.²⁴

Table 1. Co-morbidities associated with psoriasis

- Psoriatic arthritis⁴
- Crohn's disease⁴
- Parkinson's disease⁵
- Psychiatric disease
 - Major depression⁶
 - Alcohol abuse⁷
- Malignancy^{4,8}
- Chronic kidney disease¹⁴
- Cardiometabolic diseases
 - Obesity¹⁵
 - Metabolic syndrome^{13,16}
 - » Type 2 diabetes¹⁷
 - » Hypertension¹⁷
 - » Dyslipidaemia¹⁸
 - Myocardial Infarction¹⁰
 - Stroke^{19,20}
 - Abdominal aortic aneurysms²¹
 - Non-alcoholic fatty liver disease²²
- Hyperuricaemia and gout²³

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Department of Chemical Pathology, National Health Laboratory Services and University of the Witwatersrand, Johannesburg, South Africa

Nigel J Crowther, PhD

A complex cross-talk between keratinocytes and dendritic cells (DCs) in the skin, and T lymphocytes, mediated by a variety of cytokines, results in keratinocyte hyperplasia, the characteristic histological feature of PsO.²⁵ Initially, keratinocytes recruit DCs to produce IL-23 and IL-12, which in turn activate mostly T helper (Th) 1 and Th17 cells, resulting in further up-regulation of cytokine secretion, especially IL-17, interferon- γ (IFN γ), tumour necrosis factor (TNF) and IL-22.¹² These cytokines amplify psoriatic inflammation and keratinocyte hyperplasia.⁴ Moreover, pro-angiogenic factors produced by keratinocytes such as vascular endothelial growth factor drive abnormal vascular proliferation within the psoriatic plaque.^{4,25}

Psoriasis and cardiometabolic disorders

Recent interest has focused on the wide spectrum of cardiometabolic co-morbidities observed in subjects with PsO. These include obesity,¹⁵ the metabolic syndrome (MetS) and its components,^{13,16} non-alcoholic fatty liver disease (NAFLD)²² and CVD^{10,19,20,26–28} (Table 1). The dual burden of PsO and associated co-morbidities impacts negatively on health-related quality of life and is associated with an increased risk of premature death.^{8,29}

There is now a large body of evidence linking chronic inflammation to accelerated atherosclerosis.^{30,31} Rheumatoid arthritis (RA) was the first chronic inflammatory condition to be associated with an increased risk of premature cardiovascular death, by as much as 50%.³² The traditional Framingham risk factors such as type 2 diabetes mellitus (T2DM), hypertension and smoking have been shown to only partly account for the increased cardiometabolic risk in RA.³³

Mechanistically, the pro-inflammatory state of RA leads to cytokine-mediated accelerated atherosclerosis.^{34,35} The epidemiological evidence supporting the notion that PsO is associated with a similar increased CMD risk is less well-established and the precise pathobiology driving atherosclerosis in PsO is complex and not fully elucidated. One hypothesis is that the chronic inflammatory state of PsO triggers a 'psoriatic march' where the pro-inflammatory milieu leads to insulin

resistance and endothelial cell dysfunction, predisposing to accelerated atherosclerosis, finally manifesting as clinical CMD.³⁶

Epidemiology of cardiometabolic disease in psoriasis

The association of PsO with cardiovascular disease (CVD) was first proposed by McDonald and Calabresi in 1973 in a letter published in the *New England Journal of Medicine*.³⁷ In a subsequent retrospective record review comparing 323 PsO and 325 non-psoriatic dermatology patients, they reported an increased prevalence of 'occlusive vascular disease', which included myocardial infarction (MI), stroke, thrombophlebitis and pulmonary embolism in PsO patients.³⁸

Several recent registry-based studies, mainly from the United Kingdom (UK) and Denmark have supported these initial observations (Tables 2, 3). In a prospective study of 130 000 PsO patients and more than 500 000 control subjects in the UK General Practice Research Database (UKGPRD), PsO was found to be a risk factor for MI, with hazard ratios (HR) of 1.54 (95% CI: 1.24–1.91) and 7.08 (95% CI: 3.06–16.36) in mild and severe cutaneous PsO, respectively.¹⁰ The increased risk remained even after controlling for major cardiovascular risk factors such as age, gender, smoking, T2DM, hypertension, prior MI, dyslipidaemia and body mass index (BMI).

In the Danish studies of more than 36 000 PsO patients, PsO was associated with an increased risk of adverse CV events and all-cause mortality.²⁶ Younger patients and those with severe cutaneous disease appeared to have the greatest risk, a finding that was similar to that for the UKGPRD cohort.²⁴ Two meta-analyses, comprising 14 cohorts of patients from Europe and the United States have shown that the risk for CVD is greatest in patients with severe PsO.^{27,28} A major limitation of many studies included in the meta-analyses was the lack of adjustment for traditional cardiovascular (CV) risk factors.

Some smaller studies have failed to show the association between PsO and CVD. A prospective study of 1 380 PsO patients, followed up for 10 years, showed no increase in

Table 2. Longitudinal studies arising from the UK General Practice Research database

Reference	Sample size	Control group size	Variables in multivariate models	Main outcomes	HR mild PsO	HR severe PsO
Gelfand <i>et al.</i> ¹⁰	Mild: 127 139 Severe: 3 837	556 995	Age, gender, HT, DM, BMI, previous MI, cholesterol, smoking	PsO may confer an independent risk of MI	1.54 (1.24–1.91)	7.08 (3.06–16.36)
Gelfand <i>et al.</i> ²⁰	Mild: 129 143 Severe: 3 603	Mild: 496 666 Severe: 14 330	Age, gender, HT, DM, cholesterol, smoking, cerebrovascular disease	Both mild and severe PsO were independent risk factors for stroke	1.06 (1.0–1.1)	1.43 (1.1–1.9)
Mehta <i>et al.</i> ⁵¹	Severe: 3 603	14 330	Age, gender, smoking, DM, HT, hyperlipidaemia	Severe PsO was an independent risk factor for cardiovascular mortality	–	1.57 (1.26–1.96)
Abubara <i>et al.</i> ⁵²	Severe: 3 603	14 330	Age, gender	Patients with severe PsO were at increased risk for death from CVD	–	1.57 (1.26–1.96)

HT, hypertension; DM, diabetes mellitus; BMI, body mass index; MI, myocardial infarction.

Table 3. Longitudinal studies arising from the Danish Nationwide cohort

Reference	Sample size	Control group size	Variables in multivariate models	Main outcomes	RR mild PsO	RR severe PsO
Ahlehoff <i>et al.</i> ²⁶	Mild: 34 371 Severe: 2 621	4 003 625	Age, gender, co-morbidities, medication	Cardiovascular mortality was increased in patients with PsO	1.14 (1.06–1.22)	1.57 (1.27–1.94)
Ahlehoff <i>et al.</i> ²⁶	Mild: 34 371 Severe: 2 621	4 003 625	Age, gender, co-morbidities, medication	MI was increased in patients with PsO	1.22 (1.12–1.33)	1.45 (1.10–1.90)
Ahlehoff <i>et al.</i> ¹⁹	Mild: 36 765 Severe: 2 793	4 478 926	Age, gender, co-morbidities, medication	PsO was associated with an increased risk of ischaemic stroke	1.25 (1.17–1.64)	1.65 (1.33–2.05)

MI, myocardial infarction.

cardiovascular mortality (standard mortality ratio: 0.83, 90% CI: 0.7–1.0).³⁹ In another study comparing over 15 000 patients and over 27 000 controls, PsO was found to be an equivocal risk factor for admission for ischaemic heart disease (IHD), after controlling for age and gender (HR = 1.10, 95% CI: 0.99–1.23).⁴⁰ Moreover, age- and gender-matched survival analysis revealed no difference in the risk of acute MI.

A recent Dutch study of 262 ambulatory PsO patients over 55 years of age showed no increase in CV morbidity and mortality.⁴¹ The strength of this study was that CV events were identified using clinical data and specialised investigations, including CT scans, and electro- and echocardiography to minimise classification bias (all previous studies had used diagnostic codes). However, the limitations of this study were the small sample size, older age of the cohort (mean = 64 years), and that most patients had mild cutaneous PsO. Overall, the balance of evidence suggests that PsO, especially severe cutaneous disease, is associated with an increased risk of CVD.

Other metabolic disorders shown to occur more frequently in PsO are the MetS (and its components), hyperuricaemia, and non-alcoholic fatty liver disease (NAFLD). In a UK study, the MetS was more prevalent in PsO patients compared to the general population, more so in patients with severe than with mild cutaneous disease (OR for mild PsO = 1.22, 95% CI: 1.11–1.35; severe PsO = 1.98, 95% CI: 1.62–2.43).¹³ Furthermore, systematic reviews suggest that individual components of the MetS (dysglycaemia, obesity and hypertension) occur more frequently in PsO patients^{15,42,43} (Table 4).

A meta-analysis of 16 observational studies found that PsO patients were more likely to be obese (pooled OR = 1.66, 95% CI: 1.17–1.82).¹⁵ A combined mean BMI of 30.6 kg/m² has been observed in a review of clinical trials where biologics have been tested for the treatment of moderate to severe cutaneous PsO.⁴⁴ Studies have also shown that PsO is associated with abdominal obesity, which is a proxy measure of visceral adipose tissue, and is a well-recognised risk factor for T2DM, hypertension, coronary artery disease and decreased life expectancy.⁴⁵ The prospective Nurses' Health Study II identified 809 incident cases of PsO and observed that it was more common in subjects with an increased waist circumference, a surrogate marker for abdominal visceral fat.⁴⁶ In a cross-sectional case-control study, subjects with PsO were shown to have higher levels of visceral fat measured by computed tomography (CT) compared to controls.⁴⁷ The role of visceral fat in chronic inflammation is discussed below.

Several studies have shown an increased prevalence of hypertriglyceridaemia in PsO patients.^{13,16,18} Comparisons of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) between patients and controls have yielded conflicting results. Some studies show an increase in TC and LDL-C levels in PsO patients compared to controls,¹⁸ whereas others show no significant differences or decreased levels.⁴⁸ Asymptomatic hyperuricaemia is more common in PsO, even after correcting

for confounders (age, gender and features of the MetS).²³ Likewise, the risk of gout is also increased in PsO and PsA (HR = 1.71, 95% CI: 1.36–2.15).⁴⁹

Several studies have demonstrated an increased prevalence of NAFLD in subjects with PsO.²² The diagnostic methods used in these studies included ultrasonography, biochemistry, transient elastography, liver biopsy, or combinations thereof. The prevalence of NAFLD was 65.6 versus 35% in matched controls ($p < 0.001$) when measured by ultrasonography.⁵⁰

Pathophysiological basis linking psoriasis with cardiometabolic disease

Inflammation: the common denominator

There is now overwhelming evidence that chronic sub-clinical systemic inflammation accelerates atherosclerosis,²⁹ including histological studies demonstrating the presence of inflammation in atherosclerotic lesions.⁵³ Both innate and adaptive immunity are known to play a role in this process.³⁰ This has been well-documented in type 2 diabetes,⁵⁴ and also in RA⁵⁴ and systemic lupus erythematosus.⁵⁵ Further evidence linking inflammation to atherosclerosis is that C-reactive protein (CRP), a well-recognised biomarker of inflammation, is also associated with atherothrombotic disease, as well as the MetS and its components.⁵⁶

As PsO is a systemic disease, the prevailing pro-inflammatory milieu is considered to contribute to the increased CMD risk.⁵⁷ A meta-analysis of 78 studies found significantly elevated levels of pro-inflammatory cytokines, namely IL-6, TNF, CRP, E-selectin and ICAM 1, in PsO patients compared to controls.⁵⁸

Obesity, which, as discussed previously, is prevalent in subjects with PsO, is a further source of inflammation. White adipose tissue (WAT), which is the primary component of visceral fat, is composed of both adipocytes and other immunologically active cells such as macrophages.⁵⁹ Hence it is both metabolically and immunologically active. Adipocytes secrete adipokines, which are mainly pro-inflammatory, such as leptin, visfatin and resistin; as well adiponectin, which has anti-inflammatory properties.⁵⁹ Other pro-inflammatory factors that are produced by WAT include TNF, IL-1, IL-6 and plasminogen activator inhibitor type 1 (PAI-1), all of which have been shown to directly or indirectly affect endothelial cell function and insulin sensitivity.⁶⁰

Possible genetic links

Epidemiological studies suggest a common genetic link between PsO, T2DM and obesity. In a 2016 cross-sectional, population-based twin study in 33 588 Danish subjects, a significant association between PsO, T2DM and obesity was observed.⁶¹ Analysing data from twins discordant for PsO and including both monozygotic and dizygotic twin pairs, the study observed evidence for a shared genetic aetiology of obesity and PsO.

Moreover, there is evidence indicating that the strongest predictor of major adverse cardiovascular events (MACE) in patients with PsO is a family history of CVD.⁶² In a study of more than 25 000 mainly young Danes with mild PsO, and over 4 000 patients with severe disease, approximately two-thirds of patients in each group had a family history of CVD. The adjusted incidence rate ratios of MACE (with 95% CI) in patients with a family history of cardiovascular events were 1.28 (1.12–1.46) in those with mild PsO, and 1.62 (1.14–2.30) in

Table 4. Systematic reviews showing association of type 2 diabetes, hypertension and obesity with psoriasis

Risk factor	No of studies	Odds ratio		
		Overall	Mild PsO	Severe PsO
Type 2 diabetes ⁴²	27	1.59 (1.38–1.83)	1.53 (1.16–2.04)	1.97 (1.48–2.62)
Hypertension ⁴³	24	1.58 (1.42–1.76)	1.30 (1.15–1.47)	1.49 (1.20–1.86)
Obesity ¹⁵	16	1.66 (1.49–1.89)	1.46 (1.17–1.82)	2.23 (1.63–2.05)

subjects with severe PsO. There was no increased risk for MACE in PsO patients without a family history of CVD.

Conventional cardiovascular risk factors

Patients with PsO have a higher burden of classic CV risk factors compared to the general population.^{11,63} In particular, and as discussed previously, there are higher prevalences of T2DM, dyslipidaemia, hypertension and obesity in subjects with PsO. Furthermore, it is known that patients with PsO have a higher prevalence of smoking than those who do not have PsO.⁶⁴

Drug therapy

Several drugs used to treat cutaneous PsO and PsA potentially increase the risk of cardiometabolic disorders. These include oral corticosteroids, cyclosporine and acitretin, which may precipitate weight gain and unmask hypertension, T2DM and dyslipidaemia.^{8,65} Non-steroidal anti-inflammatory drugs, used in the treatment of PsA, increase the risk of hypertension and CVD.⁶⁶

Strategies to reduce cardiovascular risk in psoriasis

Psoriasis management guidelines highlight the importance of addressing cardiometabolic risk factors in PsO.⁶⁷ There is a need for further research to address whether systemic therapy for PsO may potentially ameliorate CV risk.^{67,68}

General measures

Several expert groups recommend clinical and biochemical screening of PsO patients for early detection and management of co-morbidities such as hypertension, dysglycaemia and lipid abnormalities.^{69,70} The cessation of smoking, which is common in PsO,^{71,72} is critical in the management of this group of patients.⁶⁸

Weight reduction not only reduces CV risk but has also been shown to attenuate the severity of PsO. A randomised, control study investigating the impact of hypocaloric dietary intervention and physical activity over 20 weeks in 303 overweight/obese patients with moderate to severe plaque PsO demonstrated a 48% reduction in PsO area and severity index score in the interventional arm, compared to only 25.5% in the information-only arm ($p = 0.02$).⁷³ The weight loss target of $\geq 5\%$ was achieved in 29.8% of the interventional arm compared with 14.5% in the information-only arm ($p = 0.001$). There are also anecdotal case reports of improvement in PsO following bariatric surgery.^{74,75}

Drug therapy

Anti-inflammatory agents used in the treatment of psoriasis

Given the earlier discussion on chronic systemic inflammation as a risk factor for CMD, there is emerging evidence that controlling inflammation reduces the risk of CMD. There are several lines of clinical and biochemical evidence suggesting that methotrexate (MTX), a drug widely used for the treatment of moderate–severe cutaneous PsO and PsA, has anti-inflammatory and cardioprotective properties. MTX was found to provide a

substantial survival benefit, mainly by reducing cardiovascular mortality rate in RA.⁷⁶ The cardioprotective effect of MTX is mediated by increased adenosine levels that bind to adenosine A2 receptors on macrophages and block foam cell formation.^{77,78}

In PsO, MTX and biologics such as the TNF inhibitors have been shown to lower the risk for CVD.⁷⁹ Use of these agents in a Danish study have shown lower incidence rates of death, MI and stroke than patients on other therapies, with incidence (95% CI) rates of 6.0 (2.7–13.4) and 17.3 (12.3–24.3) for biologics and MTX, respectively, compared to 44.5 (34.6–57.0) for other therapies. Data from a small, prospective study and retrospective analyses suggest that systemic anti-inflammatory therapies (such as MTX or TNF blockers) in subjects with PsO or PsA may have the potential to ameliorate cardiovascular disease.^{79,80} While these have generated considerable interest, no conclusive data from randomised clinical trials are available to date.

Impact of therapies for co-morbidities

The anti-diabetic drugs pioglitazone⁸¹ and glucagon-like peptide 1 (GLP 1) agonists⁸² have been shown to improve PsO. Pioglitazone is a well-known insulin-sensitising agent, hence its efficacy may support the role of insulin resistance in the pathogenesis of PsO. The GLP 1 agonists are thought to be effective as a result of their extra-pancreatic effects, particularly their anti-inflammatory action.⁸³ However, they may also exert indirect effects as their use is also associated with weight loss.

Conclusions

A growing body of evidence supports the association between cardiometabolic diseases and PsO. The risk for CMD appears to be greatest with moderate–severe PsO and PsA. A complex interaction seems to exist between body adiposity, chronic inflammation and the psoriatic plaque, which leads to increased CVD risk.⁵⁷ Screening and appropriate intervention, including lifestyle modification, to reduce the burden of cardiometabolic disease are important in the overall management and health-related quality of life of patients with PsO.

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Report

High burden of the metabolic syndrome and its component disorders in South Africans with psoriasis

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Introduction

Psoriasis is a complex, chronic immune-mediated inflammatory skin disorder that has a global prevalence ranging between 0.91% and 8.5%.¹ A wide range of comorbidities associated with psoriasis have been identified, including inflammatory arthritis (referred to as psoriatic arthritis [PsA]),² Crohn's disease,² malignancies,² and chronic kidney disease.³ Furthermore, several studies in mainly Caucasian populations have shown an increased

Abstract

Background Psoriasis is associated with cardiometabolic diseases (CMDs) in Caucasians, but no data is available from sub-Saharan populations on either CMD prevalence or psoriasis risk factors. Our aim was to investigate the prevalence of CMDs in a predominantly non-Caucasian cohort of South Africans with psoriasis and to determine the principal risk factors associated with psoriasis.

Methods This was a cross-sectional case-control study of adult psoriasis patients ($n = 103$) and controls ($n = 98$), comparing sociodemographic, anthropometric, clinical, and biochemical characteristics. The groups were matched for gender, ethnicity, and body mass index (BMI).

Results The prevalence of metabolic syndrome (MetS) (52.4% vs. 33.7%; $P = 0.007$), type 2 diabetes (T2D) (25.2% vs. 4.1%; $P < 0.0001$), and hypertension (70.9% vs. 46.6%; $P = 0.001$) were all higher in the psoriasis group. High-sensitivity CRP was higher in psoriasis patients than controls (4.70 (2.00, 10.9) vs. 2.00 (1.10, 4.80) ng/ml; $P < 0.0005$). Multivariable logistic regression analysis showed that severe psoriasis was independently associated with MetS (odds ratio [95% CIs]: 4.42 [1.72, 11.4]; $P = 0.002$), T2D (11.3 [3.07, 41.3]; $P = 0.0002$), and hypertension (2.48 [0.97, 6.32]; $P = 0.05$), whilst for psoriasis the principal risk factors were smoking (3.87 [1.97, 7.63]; $P < 0.0001$) and hsCRP (1.05 [1.00, 1.10]; $P = 0.029$), with completion of high school (0.23 [0.11, 0.48]; $P < 0.0001$) being protective.

Conclusions In this population, psoriasis is characterized by a high burden of CMDs, particularly in those subjects with severe psoriasis. Inflammation plays a role in the etiology of psoriasis, whilst smoking and poor education further increase disease risk.

prevalence of metabolic syndrome (MetS)⁴ and its component disorders, i.e., obesity,⁵ hypertension,⁶ type 2 diabetes mellitus (T2D),⁷ and dyslipidemia,⁸ in psoriasis. These cardiometabolic diseases (CMDs) are particularly more prevalent in patients with severe psoriasis.^{4–8} Previous studies have also shown lower vitamin D levels in psoriasis patients compared to controls.⁹

There is increasing evidence that there is a link between chronic inflammation and CMDs, including atherosclerosis.¹⁰ Chronic subclinical systemic inflammation accelerates

atherosclerosis, and histological studies demonstrate the presence of inflammation in atherosclerotic lesions.¹¹ Further evidence linking inflammation to atherosclerosis is C-reactive protein (CRP), a well-recognized biomarker of inflammation is also associated with atherothrombotic disease.¹² Inflammation has also been linked to the development of rheumatoid arthritis,¹³ T2D,¹⁰ and MetS and its component disorders.¹⁰ It has therefore been hypothesised that the high prevalence of CMDs in psoriasis may arise from the high inflammatory milieu.^{14,15}

In the absence of any published data on CMD comorbidities in sub-Saharan Africa, the primary aim of this study was to determine the burden of MetS, and its component diseases, in a predominantly non-Caucasian cohort of South African psoriasis patients. The secondary aims were to determine the relation of MetS with disease severity and the association of hsCRP, as a marker of inflammation, serum vitamin D levels, estimated glomerular filtration rate (eGFR), and sociodemographic factors with psoriasis.

Patients and methods

This is a cross-sectional case-control study of patients with psoriasis attending the dermatology and rheumatology clinics at three academic hospitals in Johannesburg, South Africa. Consenting adult psoriasis and PsA patients, 18 years and older, were recruited. The diagnosis of psoriasis and/or PsA was made by a consultant dermatologist or rheumatologist. Exclusion criteria were human immunodeficiency virus infection, inflammatory arthritis due to another cause, and pregnancy. Control subjects were individuals without any known chronic immune-mediated inflammatory disorder and were matched for geographical area of residence, gender, ethnicity, and body mass index (BMI). They were recruited by requesting patients to bring in an unrelated individual from their area of residence. The study was approved by the University of the Witwatersrand Human Research Ethics Committee (M1403100).

A combination of clinical records review, clinical examination, and blood investigations, done at the time of the clinical examination, were documented. Socioeconomic status was assessed using a validated questionnaire based on access to 12 common personal assets such as a motor vehicle, refrigerator, and television set.¹⁶ A score of >10 was categorized as high SES. Level of education status was categorized as either completion of high school or not. Smoking status was categorized as either current/ex-smoker or never smoked. Severity of cutaneous involvement was assessed by the Psoriasis Area and Severity Index (PASI) score.¹⁷ Severe psoriasis was defined as the presence of one or more of the following: (1) PASI score >10,¹⁸ (2) systemic therapy for psoriasis,^{19,20} and (3) PsA.²⁰

Anthropometric data included weight in kilograms (kg), measured with light clothing and no shoes, and height measured to the nearest centimeters (cm) to calculate the BMI. Waist circumference (WC) was measured using a soft tape measure at the mid-point of the upper border of the iliac crest

and the lower border of the last rib. Hip circumference (HC) was taken around the widest portion of the buttocks. Blood pressure (BP) was measured with the subject seated, and the mean of two readings, 10 minutes apart, was documented.

Metabolic syndrome was defined according to 2009 Harmonized Guidelines.²¹ In patients without a history of T2D and hypertension, newly diagnosed T2D was based on fasting plasma glucose >7 mmol/l,²² and impaired fasting glucose and hypertension were defined as per the Harmonized Guidelines.²¹ Estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modified Diet in Renal Disease equation.²³ The Framingham 10-year risk of general cardiovascular disease (CVD) score²⁴ was used to calculate CVD risk in all patients.

Overnight fasting venous blood samples were tested for plasma glucose, serum lipids (total cholesterol, triglycerides and high density lipoprotein cholesterol [HDL-C]), urea, and creatinine, using enzymatic methods on the ADVIA 1800 Chemistry Systems Analyzer (Siemens Healthcare Diagnostics, Tarrytown, NY, USA). The LDL-C was calculated using the Friedewald formula.²⁵ High-sensitivity C-reactive protein (hsCRP) and lipoprotein (a) (Lp[a]) were measured using an immunoturbidimetric method and 25-hydroxyvitamin D levels (25[OH]D) using a chemiluminescence assay on the ARCHITECT c8000 System (Abbott, Lake Forest, Illinois, USA).

Statistical methods

Descriptive statistics for continuous variables are presented as mean $\pm$ standard deviation (SD) or median and interquartile ranges (IQR) for normal or skewed data, respectively. Skewed non-normal continuous variables were log transformed before applying parametric statistical tests. Categorical variables were compared across groups using the χ^2 test. Continuous variables were compared between groups using Student's unpaired *t*-test and where appropriate ANCOVA was used with adjustment for age and WC. Logistic regression analysis was used to assess whether the relationships of mild and severe psoriasis with MetS, T2D, hypertension, high triglycerides, and low HDL-C were affected after adjusting for possible confounders. Risk factors for psoriasis were isolated by performing univariate regression analyses of study variables. All variables with $P < 0.20$ in the univariate models were included into a single multivariable logistic regression model. Backward, stepwise removal of non-significant variables was performed until all variables in the model were significantly ($P < 0.05$) related to psoriasis. All analyses were performed using Statistica version 13.2 (StatSoft, Tulsa, OK, USA).

Results

Demographic and clinical and cardiometabolic characteristics

The demographic, clinical, and cardiometabolic characteristics of the 103 patients and 98 control subjects are shown in Table 1. Most of the patients were of either Indian (42.1%) or mixed

ancestry (31.8%), and only 11.7% were Caucasian and 14.6% black African patients. The mean $\pm$ SD disease duration for psoriasis was 18.9 ± 13.3 years and median (IQR) PASI score was 4.80 (2.40, 11.7). Sixty-one (59.2%) patients were deemed to have severe psoriasis, and 28 (27.2%) had PsA. There were no differences in age and gender between patients with severe and mild psoriasis ($P = 0.85$ and $P = 0.81$, respectively). The prevalence of smoking was significantly higher in psoriasis patients compared to the control group ($P < 0.0005$). The psoriasis group was of lower SES than the control group, with respect to both ownership of household items and education (both comparisons, $P < 0.0005$).

There was a high prevalence of obesity in both patients and controls (50.5% and 38.8% respectively). The psoriasis group had a significantly greater WC ($P = 0.004$), higher systolic and diastolic BP ($P = 0.0002$ and $P = 0.005$, respectively), triglyceride ($P = 0.047$), and HbA1c levels ($P < 0.0005$); and a trend towards lower HDL-C levels ($P = 0.054$). The difference in WC remained significant after adjustment for age ($P = 0.023$) and differences in systolic BP and

HbA1c levels remained statistically significant ($P = 0.015$ and $P = 0.013$, respectively) after adjusting for age and WC.

The median hsCRP in the psoriasis group was more than twice that in the control group ($P < 0.0005$), the difference persisting after adjusting for age and WC ($P = 0.002$). The Framingham CVD risk score was significantly higher in psoriasis patients than in controls ($P < 0.0001$). No significant differences in cholesterol-related lipid levels, glucose and vitamin D levels, urea, creatinine, and eGFR were observed.

Prevalence of metabolic syndrome and its components

The prevalence of MetS was significantly higher in the psoriasis group than the control group (52.4% vs. 33.7%; $P = 0.007$), as were T2D (25.2% vs. 4.1%; $P < 0.0005$) and hypertension (70.9% vs. 46.6%; $P = 0.001$). There were no significant differences in the prevalence of low HDL-C levels (28.2 vs. 21.4%; $P = 0.27$) or hypertriglyceridemia (26.2 vs. 19.4%; $P = 0.25$) between the two groups.

Table 1 Demographic, clinical, and cardiometabolic characteristics of South Africans with psoriasis and control subjects

Variable	Psoriasis <i>n</i> = 103	Controls <i>n</i> = 98	<i>P</i> value
Female gender (<i>n</i> [%])	55 (53.4)	61 (62.2)	0.204
Age (years)	53.3 ± 14.5	47.9 ± 14.5	0.009
Disease duration (years)	18.9 ± 13.3	–	–
PASI score	4.80 (2.40, 11.7)	–	–
Psoriatic arthritis (<i>n</i> [%])	28 (27.1)	–	–
Smokers (<i>n</i> [%])	61 (59.2)	26 (26.5)	<0.0001
Systemic therapy (<i>n</i> [%])	43 (41.7)	–	–
High SES (<i>n</i> [%])	50 (48.5)	74 (75.5)	<0.0001
Completed high school (<i>n</i> [%])	52 (50.5)	81 (82.7)	<0.0001
BMI (kg/m ²)	31.6 ± 8.42	29.3 ± 6.67	0.058
Obesity (<i>n</i> [%])	52 (50.5)	38 (38.8)	0.095
Waist circumference (cm)	101 ± 16.4	94.5 ± 15.2	0.004
Hip circumference (cm)	107 ± 14.7	103 ± 12.1	0.073
Waist : hip ratio	0.946 ± 0.09	0.916 ± 0.11	0.035
Systolic BP (mmHg)	141 ± 24.6	129 ± 17.2	0.0004
Diastolic BP (mmHg)	86.4 ± 12.8	81.5 ± 11.6	0.005
HbA1c (%) ^a	6.20 (5.90, 6.90)	5.95 (5.55, 6.30)	<0.0001
Glucose (mmol/l) ^a	5.71 (4.70, 6.00)	5.20 (4.20, 5.60)	0.744
Total cholesterol (mmol/l) ^a	5.31 (4.45, 6.20)	5.31 (4.62, 6.29)	0.176
HDL cholesterol (mmol/l) ^a	1.21 (1.05, 1.56)	1.37 (1.10, 1.73)	0.054
LDL cholesterol (mmol/l) ^a	3.24 (2.55, 4.04)	3.38 (2.64, 4.13)	0.180
Triglycerides (mmol/l) ^a	1.60 (1.05, 2.01)	1.11 (0.83, 1.76)	0.047
Lipoprotein (a) (mg/dL) ^a	25.3 (9.40, 38.8)	21.4 (10.0, 38.8)	0.971
hsCRP (ng/ml) ^a	4.70 (2.00, 10.9)	2.00 (1.10, 4.80)	<0.0001
Framingham risk score ^b	19.1 (8.47, 32.5)	7.25 (3.65, 13.8)	<0.0001
Vitamin D (ng/ml) ^a	19.0 (12.6, 24.1)	18.1 (13.1, 24.3)	0.582
Urea (mmol/l) ^a	5.40 (4.20, 6.85)	5.40 (4.40, 6.00)	0.421
Creatinine (μmol/l) ^a	87.0 (71.0, 102)	79.0 (71.0, 94.0)	0.130
Estimated GFR (ml/min/m ²) ^a	70.8 (63.8, 83.4)	74.9 (66.0, 91.8)	0.140

PASI, Psoriasis Area and Severity Index; SES, socioeconomic status; BMI, body mass index; BP, blood pressure; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; hsCRP, highly sensitive quantification of C-reactive protein; GFR, glomerular filtration rate.

Data given as mean $\pm$ SD, median (interquartile range) or *n* (%).

^a*N* = 91 and *N* = 97, for cases and controls, respectively.

^b*N* = 80 and *N* = 79, for cases and controls, respectively.

Subgroup analysis showed the prevalence of MetS was significantly higher in the severe psoriasis subgroup (65.6%) compared to both the mild psoriasis subgroup and control group (33.3% and 33.7%, respectively, $P < 0.0005$ for both) (Fig. 1). In the case of T2D, compared to a prevalence of 4.1% in the control group, the prevalence was increased in both the severe and mild psoriasis subgroups (31.1%, $P < 0.0005$ and 16.7%, $P = 0.01$, respectively). Hypertension was more prevalent only in the severe psoriasis subgroup (73.8% vs. 49.0% in control group, $P = 0.002$). The prevalence of a low HDL-C was higher in the severe psoriasis subgroup (36.1%) when compared to both the control group (21.4%, $P = 0.043$) and the mild psoriasis subgroup (16.7%, $P = 0.025$). There was no difference in the Framingham CVD risk score between patients with severe and mild disease (21.4 [8.05, 34.2] vs. 18.0 [8.66, 30.9], respectively, $P = 0.61$). However, both groups had a significantly higher score compared to controls (7.25 [3.65, 13.8], $P < 0.0001$ for both groups).

When we compared patients with PsA ($n = 28$) to those with cutaneous psoriasis only ($n = 75$), the former group had a higher prevalence of MetS (71.4% vs. 45.3%, $P = 0.018$) and low HDL-C levels (53.6% vs. 18.7%, $P = 0.0004$). However, no significant differences were noted in the prevalence of T2D (32.1% vs. 22.7%, $P = 0.33$), hypertension (78.6% vs. 68.0%, $P = 0.28$), or high TG levels (32.1% vs. 24%, $P = 0.52$) or in the Framingham CVD risk score (22.1 [8.05, 42.7] vs. 18.0 [8.66, 30.7], $P = 0.52$) between those with PsA and those with cutaneous psoriasis, respectively.

Logistic regression analysis showed that, after adjusting for potential confounders (age, BMI, hsCRP, smoking, education, and SES), severe but not mild psoriasis, compared with no psoriasis, was associated with a higher risk of MetS ($P = 0.002$), T2D ($P < 0.0005$), and a trend towards an association with hypertension ($P = 0.05$) (Table 2). Neither mild ($P = 0.48$) nor severe psoriasis ($P = 0.32$) were associated with an increased risk of low HDL-C or an increased risk for high TG levels (data not shown).

Risk factors associated with psoriasis

Logistic regression analysis demonstrated that the principal risk factors associated with psoriasis were smoking (3.87 [1.97, 7.63]; $P < 0.0001$) and hsCRP (1.05 [1.00, 1.10]; $P = 0.029$), with completion of high school (0.23 [0.11, 0.48]; $P < 0.0001$) being protective (Table 3).

Discussion

In this case-control study of mainly indigent urban South Africans, we found a higher prevalence of MetS, hypertension, and T2D in patients with psoriasis, even after adjusting for possible confounders. Moreover, we observed a risk-gradient for CMD, sometimes referred to as the 'psoriatic march',¹⁴ where the risk is greatest in severe psoriasis and less so in mild disease. The Framingham CVD risk score was also found to be higher in the psoriasis group compared with the control group.

A third of the control group fulfilled the criteria for MetS, compared to more than 50% in the psoriasis group of whom 70% had hypertension and 25% had T2D. The prevalence rates of MetS in both the general population and in patients with psoriasis are substantially higher than reported in Western industrialized countries but similar to those in developing countries. The prevalence of MetS varies from 13.5–25.9% for the general population to 20.8–34.2% in psoriasis patients in the United States,²⁶ United Kingdom,²⁷ and Italy.²⁸ In developing countries like India²⁹ and Tunisia,³⁰ the prevalences are in the order of 30% for the general population and 40–44% in psoriasis patients.

That more than 50% of the patients and 38% of controls in the present study were obese is a reflection of the growing problem of obesity in South Africa. In the South African National Health and Nutrition Examination Survey (of 7,267 subjects), the overall prevalence of obesity was 28.9%.³¹

The risk gradient where the highest risk for CMD is associated with severe psoriasis is a phenomenon that has been elegantly demonstrated in several previous studies. The seminal

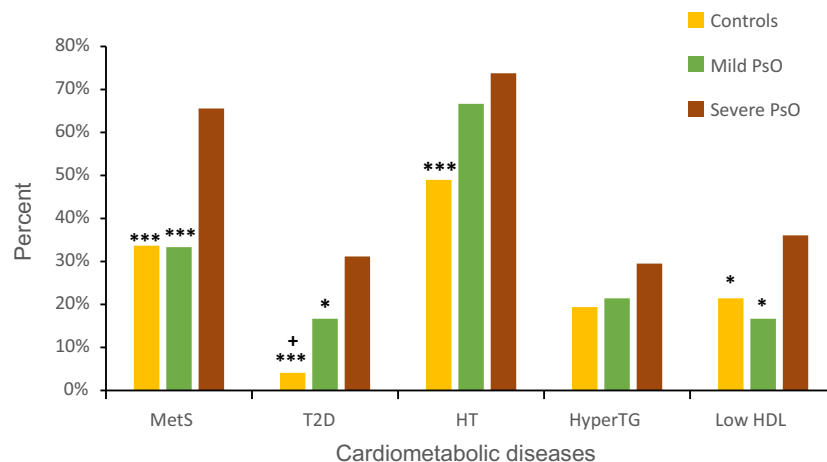


Figure 1 Prevalence of cardiometabolic diseases in South Africans with psoriasis. PsO, psoriasis; MetS, metabolic syndrome; T2D, type 2 diabetes; HT, hypertension; HyperTG, hypertriglyceridemia; HDL, high density lipoprotein cholesterol. * $P < 0.05$, ** $P < 0.005$, *** $P < 0.0005$ vs. severe PsO; + $P < 0.05$ vs. mild PsO.

Table 2 Logistic regression models showing relationship of mild and severe psoriasis with cardiometabolic diseases

	Metabolic syndrome OR (95% CI), <i>P</i> value	Type 2 diabetes OR (95% CI), <i>P</i> value	Hypertension OR (95% CI), <i>P</i> value	Low HDL OR (95% CI), <i>P</i> value
Psoriasis severity (unadjusted)				
Mild disease	0.98 (0.46, 2.11), 0.97	4.70 (1.29, 17.2), 0.02	2.08 (0.97, 4.45), 0.06	0.73 (0.28, 1.90), 0.52
Severe disease	3.75 (1.90, 7.39), 0.0001	10.6 (3.38, 33.4), <0.0001	2.93 (1.46, 5.89), 0.002	2.07 (1.01, 4.23) 0.04
Psoriasis severity (adjusted) ^a				
Mild disease	0.49 (0.16, 1.49), 0.20	3.27 (0.72, 14.9), 0.12	1.39 (0.50, 3.85), 0.53	0.67 (0.22, 2.05), 0.48
Severe disease	4.42 (1.72, 11.4), 0.002	11.3 (3.07, 41.3), 0.0002	2.48 (0.97, 6.32), 0.05	1.57 (0.63, 3.90), 0.32

OR, odds ratio; HDL, high-density lipoprotein.

^aAdjusted for age, body mass index, hsCRP, smoking, education, and socioeconomic status; *P* values relative to the reference group (non-psoriatic).

Table 3 Logistic regression model showing risk factors for psoriasis

Dependent variable	Independent variables	Odds ratio (95% CI)	<i>P</i> value
Psoriasis	Smoking	3.87 (1.97, 7.63)	<0.0001
	Level of education	0.23 (0.11, 0.48)	<0.0001
	hsCRP	1.05 (1.00, 1.10)	0.029

hsCRP, highly sensitive quantification of C-reactive protein.

Data shown is from a multivariable logistic regression model in which backward, stepwise removal of nonsignificant variables (age, waist circumference, hip circumference) was performed to yield the final model shown above.

study on psoriasis and CMD concluded that psoriasis conferred an independent risk for myocardial infarction with the risk being greatest in severe psoriasis.¹⁹ Subsequent studies have demonstrated similar relationships in terms of CVD,³² T2D,⁷ and hypertension.⁶ Subgroup analysis in the present study showed the increased risk of MetS and hypertension was exclusively in the severe psoriasis subgroup. Of note, we observed a very strong association between T2D and severe psoriasis (OR [95% CIs]: 11.3 [3.07, 41.3]) which far exceeds the pooled risk documented in a previous meta-analysis (1.97 [1.48–2.62]).⁷

The serum lipid levels for the psoriasis and control groups were similar for total cholesterol, LDL-C and Lp(a), HDL-C, and triglycerides after adjusting for confounders. A previous study has shown higher total cholesterol levels in psoriasis but, similar to our findings, did not demonstrate any difference in LDL-C or Lp(a) between the psoriasis patients and controls.³³

The pathophysiological mechanism linking psoriasis and CMD is not entirely understood, but there is some evidence in psoriasis, and in other chronic inflammatory disorders such as rheumatoid arthritis, that the cytokine-driven pro-inflammatory systemic state contributes to increased risk of atherosclerosis and CMD.¹⁵ The significantly higher hsCRP levels in psoriasis in the present study are noteworthy in this respect.

Previous studies have observed a higher prevalence of chronic kidney disease³ and lower vitamin D levels⁹ in psoriasis, but this was not evident in the present study. However, as in other studies, we found associations between lower education³⁴ and smoking with psoriasis.³⁵

Although not the primary focus of the study, a disproportionately high number of patients were of South Asian Indian or mixed ancestry and relatively few black African patients. This is against a background of the majority of patients attending state-run services being Black Africans. These findings mirror those of an earlier study performed at the same dermatology clinics³⁶ and may reflect ethnic differences in genetic risk for psoriasis.

Some of the limitations of the study are the cross-sectional design, the relatively small sample size, and that patients had already been initiated on systemic therapy at the time of recruitment into the study. In addition, patients were recruited from public hospitals, and these findings may therefore not be generalizable to all South African patients.

In this study of mainly indigent non-Caucasian South Africans, the burden of MetS and its components was increased in psoriasis as was the Framingham CVD risk score. Moreover, the risk of these CMDs is greater in severe psoriasis, supporting the notion of a 'psoriatic march' and an etiological link between the severity of chronic inflammation of psoriasis and the burden of MetS. These findings therefore highlight the need for all psoriatic patients, especially those with severe psoriasis, to be screened for CMDs. Our study also suggests that public health initiatives for reducing obesity and smoking could have a positive effect on the severity of psoriasis.

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