ABDOMINAL AORTIC CALCIFICATION IN PSORIASIS

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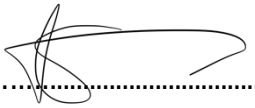
A research report submitted to the Faculty of Science, University of the Witwatersrand, in fulfilment of the requirements for the degree of Master of Medicine in Diagnostic Radiology.

Johannesburg, 2020

DECLARATION

I, Sofia Ramos, student number 300589, declare that this research report is my own work and that I contributed adequately towards research findings published in the article stated below. It is being submitted for the degree of Master of Medicine (Diagnostic Radiology), University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

Signature…… 

12th day of July 2021

DEDICATION

To my dear husband, Roman

and

beloved daughter, Catarina:

the girl with the messy hair and curious heart.

For always understanding.

You are loved.

PRESENTATIONS AND PUBLICATIONS ARISING FROM THIS PROJECT

PRESENTATIONS

1. Abdominal aortic calcification in psoriasis - a case control study. South African Rheumatism and Arthritis Association (SARAA) Congress 2019, Durban, South Africa. March 2019 (poster presentation).

2. Abdominal aortic calcification in psoriasis. University of the Witwatersrand School of Clinical Medicine – Biennial Research Day 2019, Johannesburg, South Africa. October 2019 (oral presentation)

3. Abdominal aortic calcification in psoriasis. Radiological Society of South Africa (RSSA)/South African Society of Paediatric Imaging (SASPI) Congress 2020, Johannesburg, South Africa. February 2020 (poster presentation)

4. Abdominal aortic calcification in psoriasis. Endocrine Society Annual Congress (ENDO) 2020. San Francisco, USA. March 2020 (virtual poster presentation)

AWARDS

Best MMed/Registrar Oral Presentation - University of the Witwatersrand School of Clinical Medicine – Biennial Research Day 2019

ABSTRACT

Background

Psoriasis is associated with a high prevalence of cardiovascular disease. Abdominal aortic calcification (AAC) is a strong predictor of future cardiovascular events and all-cause mortality in the general population. We investigated the prevalence and risk factors for AAC in South African patients with psoriasis.

Methods

Adult psoriasis patients (n=69) and controls (n=80), matched for gender, ethnicity and body mass index (BMI), who attended tertiary Dermatology and Rheumatology clinics in South Africa, underwent non-contrast abdominal CT scans. Images were assessed for AAC at the supra-coeliac aorta, supra-mesenteric aorta and aortic bifurcation using Horos DICOM viewer.

Results

AAC at any site was significantly higher in the psoriasis group than control group (47.8% vs 22.5%, $p<0.005$). The aortic bifurcation was the commonest site for AAC in both groups, but significantly higher in the psoriasis group (42.0% vs 21.3%, $p<0.005$). The psoriasis group was also more likely to smoke and have hypertension and type 2 diabetes (T2DM) (56.5% vs 25.0%, $p<0.005$; 72.0% vs 55.0%, $p<0.005$; 24.6% vs 3.80%, $p<0.0005$, respectively). Multivariable logistic regression analysis demonstrated that age, smoking and T2DM were independently associated with AAC (odds ratio (95% CIs): 1.16 (1.07, 1.20), 4.30 (2.15, 8.61) and 3.45 (1.09, 15.7) respectively), but psoriasis was not. Forward regression analysis demonstrated that smoking attenuated the association of psoriasis with AAC.

Conclusion

Smoking cessation is essential in psoriatic patients to reduce the risk of cardiovascular events. The clinical utility of AAC detection by CT imaging to risk stratify for hard cardiovascular outcomes needs to be explored.

ACKNOWLEDGEMENTS

"Without labour, nothing prospers."

- Sophocles

This project would not have been possible without the help of some truly amazing people.

I would like to thank:

- Dr Nasrin Goolam Mahyoodeen, an incredible mentor, for her direction and vital assistance in undertaking this research report and her unwavering support throughout this endeavour.
- Dr Sheetal Daya, for her thoughtful guidance and invaluable radiological mentorship.
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- My family, for their constant support and reassuring perspective.

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ABBREVIATIONS

AAC	Abdominal aortic calcification
BMI	Body mass index
CAC	Coronary artery calcification
CHBAH	Chris Hani Baragwanath Academic Hospital
CI	Confidence interval
CMD	Cardiometabolic disease
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CT	Computed tomography
CVD	Cardiovascular disease
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HJH	Helen Joseph Hospital
IMID	Immune-mediated inflammatory disease
LASSA	Lipid and atherosclerosis society of Southern Africa
LDL	Low-density lipoprotein
MetS	Metabolic syndrome
OR	Odds ratio
PASI	Psoriasis area and severity index
PsA	Psoriatic arthritis
PsO	Psoriasis
SD	Standard deviation
T2DM	Type 2 diabetes mellitus

PREFACE

Psoriasis is an immune-mediated inflammatory disorder that is increasingly recognised as risk factor for cardiovascular disease. Abdominal aortic calcification has been shown to be a predictor of cardiovascular events and all-cause mortality. However, there is little known about the prevalence of abdominal aortic calcification in patients with psoriasis.

In light of this paucity of data, the broad aim of this study was to determine the prevalence of abdominal aortic calcification in psoriasis patients using computed tomography. The study then sought to determine the relationship between abdominal aortic calcification and cardiometabolic risk factors. This study was conducted as a cross-sectional case control sub-study of a larger project examining the cardiometabolic aspects of psoriasis.

This research report is presented in a format recommended by the Faculty of Health Sciences, University of the Witwatersrand. As such, it is divided as follows:

- Chapter 1 covers the introduction, literature review, and study methodology. These are written in the traditional monograph format.
- Chapter 2 consists of the research report and is presented in research publication format.
- Chapter 3 comprises the conclusion.

STUDENT CONTRIBUTIONS

Despite taking on a substudy of a larger project with existing data, I was involved in all stages of research for this study, including conceptualisation of the radiological investigations and methodology needed to conduct the project. The original hypothesis for this study was refined in collaboration with all of my supervisors. I was responsible for ethics approval as well as radiological assessment of all CT scans and subsequent calcification volume quantification. The CT data was then re-read and verified by one of my supervisors, Dr Sheetal Daya, a consultant radiologist.

I recorded and collated all data, and performed statistical analyses with the assistance of Dr Nasrin Goolam Mahyoodeen, under the supervision of Professors Nigel Crowther and Mohammed Tikly.

CHAPTER 1. PROTOCOL WITH EXTENDED LITERATURE REVIEW

INTRODUCTION

Psoriasis is a common chronic immune-mediated inflammatory skin disorder [1], with a global prevalence of approximately 0.91 to 8.5% [2]. Literature regarding the prevalence of psoriasis in Africa is limited but is thought to be approximately 1 – 3% [3]. A South African study has reported an incidence of up to 9.6% in the Indian ethnic community[4]. Psoriasis manifests as raised, well-demarcated, erythematous plaques with adherent silvery scales (Fig 1 A-C). Histologically it is characterised by epidermal hyperproliferation, parakeratosis and abnormal vascular proliferation (Fig 1 D, E). This process is driven by an interplay between innate and adaptive immunity [1].

There are 5 variants of psoriasis: psoriasis vulgaris, guttate, palmoplantar, generalized pustular and erythrodermic. In addition, up to 25% of patients may have an associated psoriatic arthritis [5]. Psoriasis is associated with multiple co-morbidities e.g. inflammatory bowel disease [5], chronic kidney disease [6] and cardio-metabolic diseases such as the metabolic syndrome (MetS) and its components [7, 8]. It has been suggested that chronic inflammatory conditions, such as psoriasis, be considered as independent risk factors for cardiovascular disease (CVD) and that these conditions potentially contribute to the increasing burden of CVD in this patient population [9].

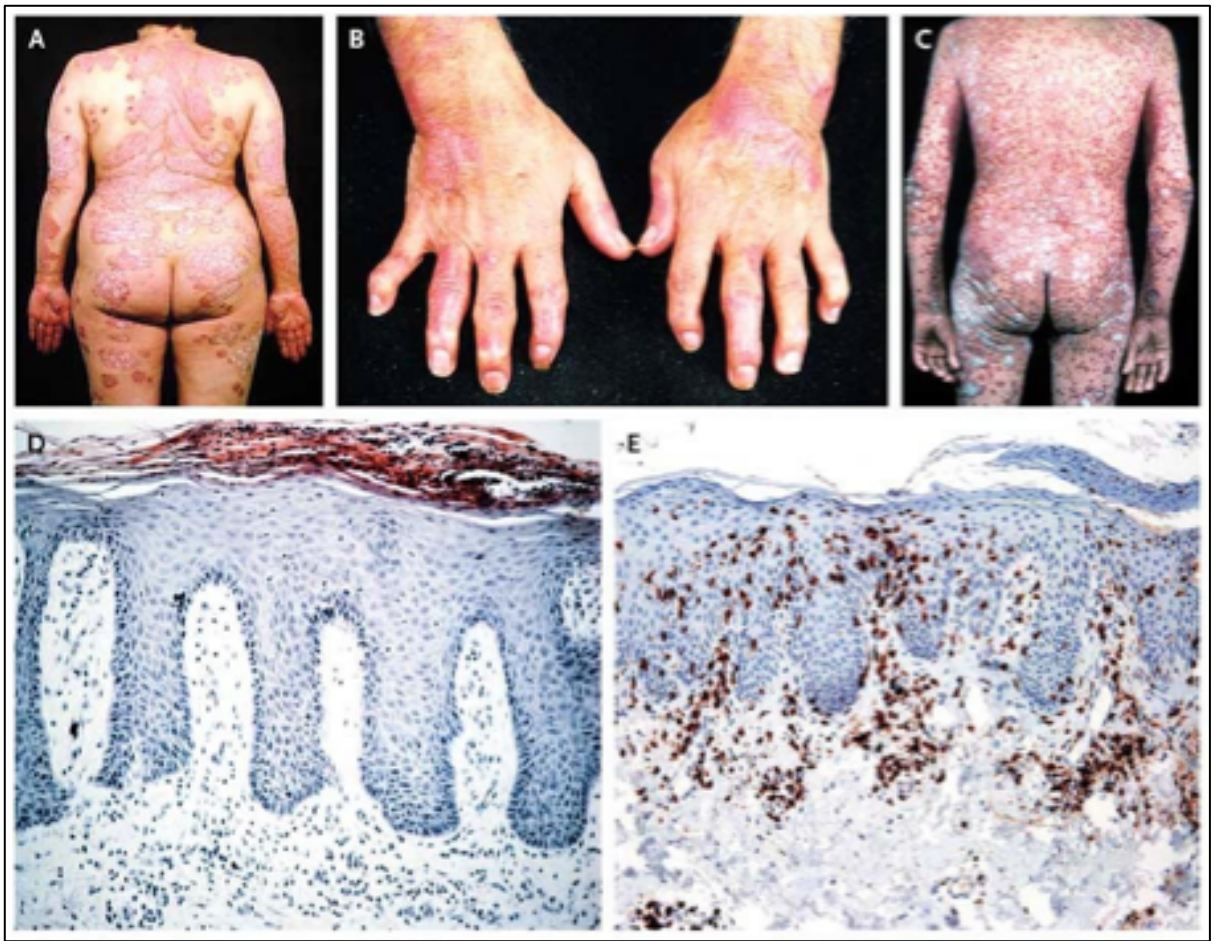

FIGURE 1 Clinical and histologic features of psoriasis

A-C demonstrate erythematous, scaly, sharply demarcated psoriatic plaques covering the skin surface of the body. **B** demonstrates concurrent psoriatic arthritis changes, affecting the interphalangeal joints of the hands. **D, E** represent histopathological images demonstrating characteristic thickening of the epidermis, parakeratosis, elongated rete ridges as well as cell infiltrates, specifically, CD3+ T cells (E). Clinical photographs courtesy of St. John's Institute of Dermatology.

Reproduced with permission, Nestle et al. Psoriasis. N Engl J Med. 2009; 361: 496-509.

SPECTRUM OF CARDIOVASCULAR DISEASE ASSOCIATED WITH PSORIASIS

An association between psoriasis and cardiovascular disease (CVD) was first described in 1978, where it was shown that psoriasis patients had twice the incidence of arterial vascular events compared to matched controls [10]. A recent South African study has shown a higher prevalence of MetS and its components in patients with psoriasis compared to controls [11]. Further afield, studies in mainly Caucasian populations have shown the prevalence of CVD in psoriasis patients to be comparable to that seen in patients with rheumatoid arthritis and type 2 diabetes mellitus (T2DM) [12]. A cross-sectional study of a large UK psoriasis cohort reported a higher death rate from CVD in patients with severe psoriasis compared with the general population [13]. Traditional cardiovascular risk factors, such as hypertension, dyslipidaemia and T2DM were more common in this patient population [9]. These patients also suffered from a higher incidence of myocardial infarction [13], stroke [14] and abdominal aortic aneurysms [15], which are complications related to atherosclerosis.

THE ROLE OF IMAGING IN THE ASSESSMENT OF ATHEROSCLEROSIS

Various modalities may be used to identify atherosclerosis such as: plain radiography (Fig 2 A, B), ultrasonography, magnetic resonance imaging, computed tomography (CT) (Fig 2 C, Fig 3) [16] and positron emission computed tomography (PET CT) [17]. Multi-detector CT is considered the gold standard for detection and quantification of vascular calcification. Non-contrast CT scanning has shown improved sensitivity, specificity and overall accuracy compared to both coronary angiography and intracoronary ultrasound for calcification [18]. CT is highly sensitive for the detection of calcified atherosclerosis, based on its high spatial resolution, contrast and beam attenuation principles. Although CT angiography has also been used for the detection of vascular calcification, this modality lacks a systematic method for the quantification of disease [19]. Consequently, non-enhanced CT remains the leading method for the detection of calcification [19].

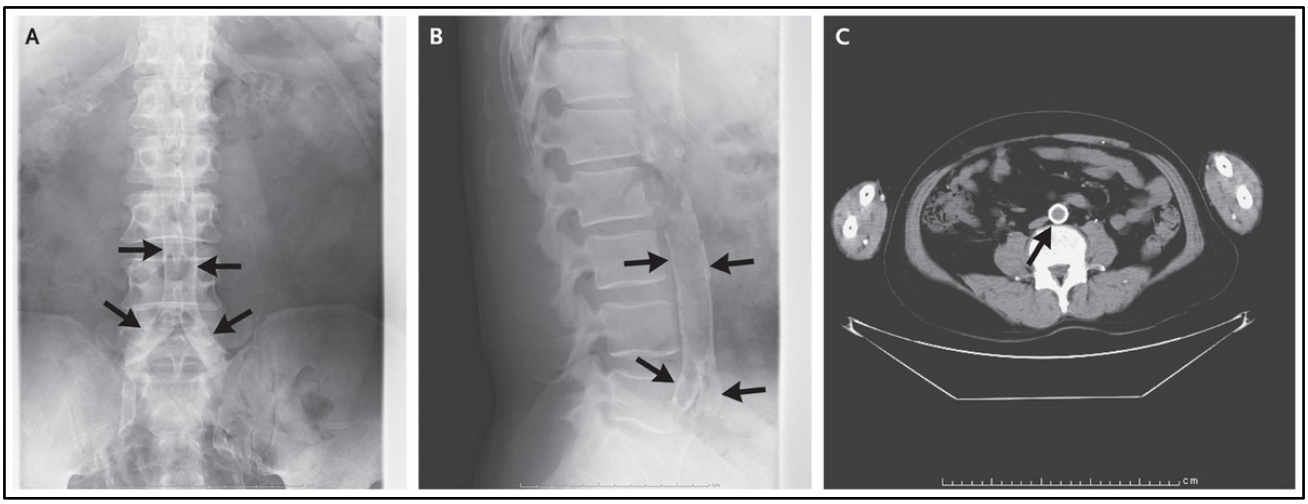

FIGURE 2 Calcification of the aorta and common iliac arteries

A and **B** represent anteroposterior and lateral plain films of the lumbar spine respectively, demonstrating significant diffuse calcification of the distal abdominal aorta and common iliac arteries (arrows). **C** is a selective slice of an axial non-contrast CT which confirms the circumferential calcification of the distal abdominal aorta (arrow).

Reproduced with permission, Sudo, K. and Harada, H. Calcification of the aorta and common iliac arteries. N Engl J Med. 2011; 364:1449.

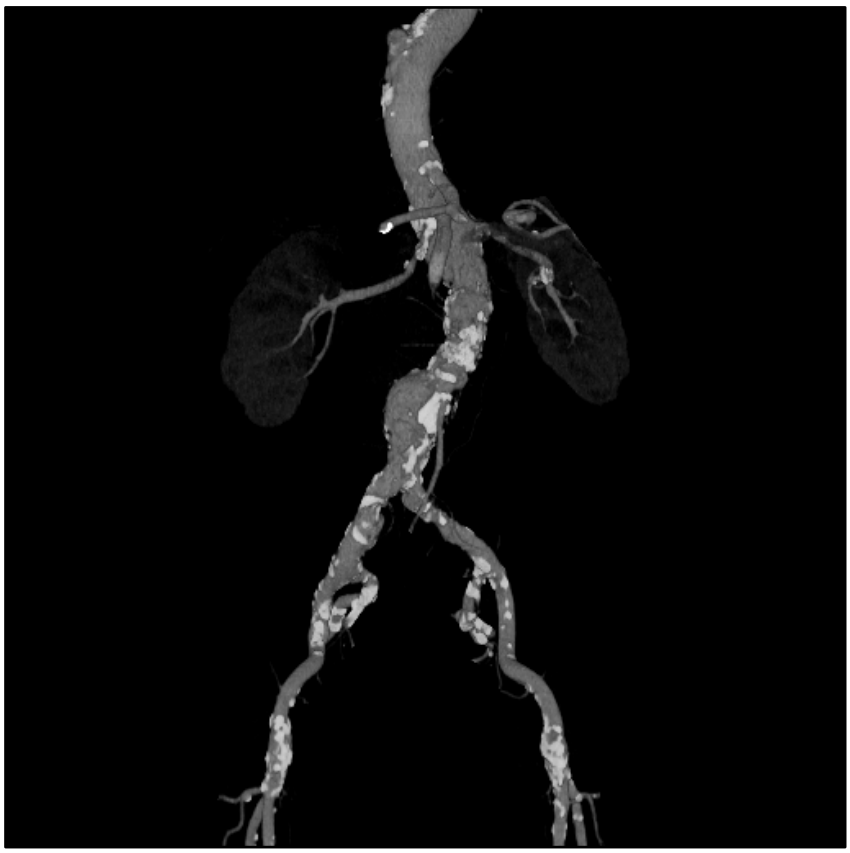

FIGURE 3 Diffuse atherosclerotic calcification of the abdominal aorta

3D volume rendered CT illustrating diffuse calcification along the abdominal aorta and the common iliac arteries.

Reproduced with permission. Case courtesy of Dr Di Muzio, Radiopaedia.org rID: 19221.

Retrieved from https://radiopaedia.org/cases/diffuse-aortic-atherosclerosis.

The presence of calcified plaque in specific vascular territories has been independently associated with both cardiovascular and all-cause mortality [20]. Arterial plaque distribution is categorized as follows: coronary arteries, the major branches of the aortic arch, the abdominal aorta, visceral and major lower extremity branches of the abdominal aorta. Calcification, when present within the abdominal aorta, is a marker of subclinical atherosclerotic disease as well as an independent predictor of subsequent vascular morbidity [19] and demonstrates significant association with CVD mortality [16, 20]. Most patients have atherosclerosis of the distal abdominal aorta. Plaque within this

region was associated with the highest probability of symptomatic atherosclerosis at other sites and showed the highest tendency for recurrence [21].

Although coronary artery calcification (CAC) (assessed radiologically) is the most widely-used marker of subclinical CVD, recent studies have demonstrated that CT-based abdominal aortic calcification (AAC) is a strong predictor of future cardiovascular events and all-cause mortality [20, 22]. The Multi-Ethnic Study of Atherosclerosis (MESA) concluded that both AAC and CAC were independently predictive for coronary heart disease and CVD, however, only AAC was found to be independently predictive for CVD mortality. The predictive value of CAC for mortality was also attenuated when AAC was added to the model [23].

Furthermore, the presence of AAC predicts greater CAC levels and atherosclerosis in other vascular beds, such as the carotid arteries and lower extremities. AAC, therefore, provides an opportunity to measure the extent of atherosclerosis in other vascular beds, including the coronary arteries [24]. AAC, when compared to CAC, forms denser plaque, accumulates at a younger age and is more easily measured [22]. Atherosclerosis and calcification, when present in the abdominal aorta, are observed more frequently at the distal aorta and aortic bifurcation, where turbulent flow occurs, making this the preferred location for quantifying AAC [25].

METHODS OF QUANTIFYING AORTIC CALCIFICATION USING COMPUTED TOMOGRAPHY

Three principal methods are described for the CT-quantification of aortic calcification i.e., the Agatston method, calcium volume score and relative calcium mass score.

AGATSTON METHOD

This method has been widely used and cited since its description in 1990. Traditionally used for the quantification of coronary artery calcification, this method can be translated for use in aortic calcification quantification [16]. Calcium scores are calculated using the number, areas and peak Hounsfield CT numbers of the calcific plaques detected on each CT slice [26]. The Agatston method utilises the weighted sum of lesions only with a density above 130 HU, and then multiplies the area of calcium by a factor related to the maximum density of the calcification i.e., for lesions with a density of 130–199 HU, multiply by a factor of 1; 200–299 HU, factor 2; 300–399 HU, factor 3; and ≥ 400 HU, factor 4 (Fig 4) [27]. Despite its wide-spread use, the Agatston method suffers from lower reproducibility and lower accuracy in terms of arterial calcification amount measurements when compared to other available scoring techniques. It remains a complex method, dependent on CT number levels and small variations in noise and motion [28].

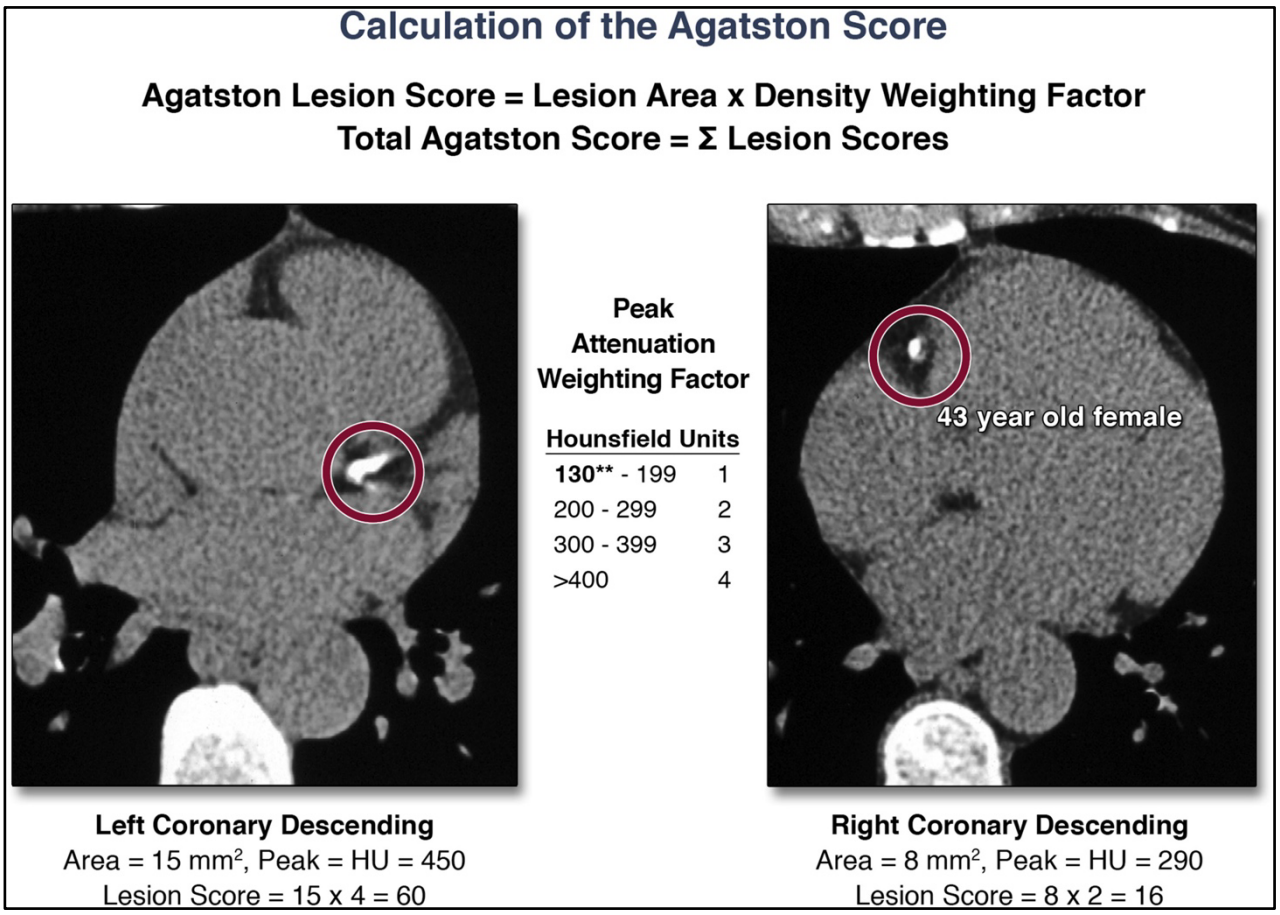

FIGURE 4 Methodology for calculation of Agatston score

The Agatston score for each calcified lesion is a function of the CAC area and the maximal CAC density. The total Agatston score is a simple sum of all CAC lesions. Contiguous voxels >130 HU are defined as a calcified lesion.

Reproduced with permission, Blaha, M.J. et al. Coronary artery calcium scoring: is it time for a change in methodology? JACC Cardiovasc Imaging. 2017;10(8):923–37.

CALCIUM VOLUME SCORE

The calcium volume score was suggested as a remedy to address the potential problematic density factors presented by the Agatston score and provides a relatively simpler method [28]. Developed by Callister and colleagues in 1998, and described by Mori et al. in the April 2015 issue of Atherosclerosis, this method has been validated as a volume rendering approach for the quantification of aortic calcification [16, 29]. The strength of this method lies in the fact that it does not rely solely on lesion density, but provides a volume metric of the calcified plaque [30]. The calcium volume score has been shown to be the most robust and reproducible method [31]. It is assessed by multiplying the number of voxels included within a calcification, with a density of >130 HU, by the volume of each voxel. The total volume score is the summation of all individual lesions, irrespective of differences in their regional distribution [30]. Despite its strength in reproducibility, this method can be sensitive to partial volume artefact (mostly in high-density plaques) [27]. The interscan variability of volume score is known to be better than that of Agatston scoring, with more stable estimates of calcification. Results of clinical verification and technical stability have led to the inclusion of volume scoring in the CAC scoring protocol, together with the Agatston method, in recent clinical practice and research [28].

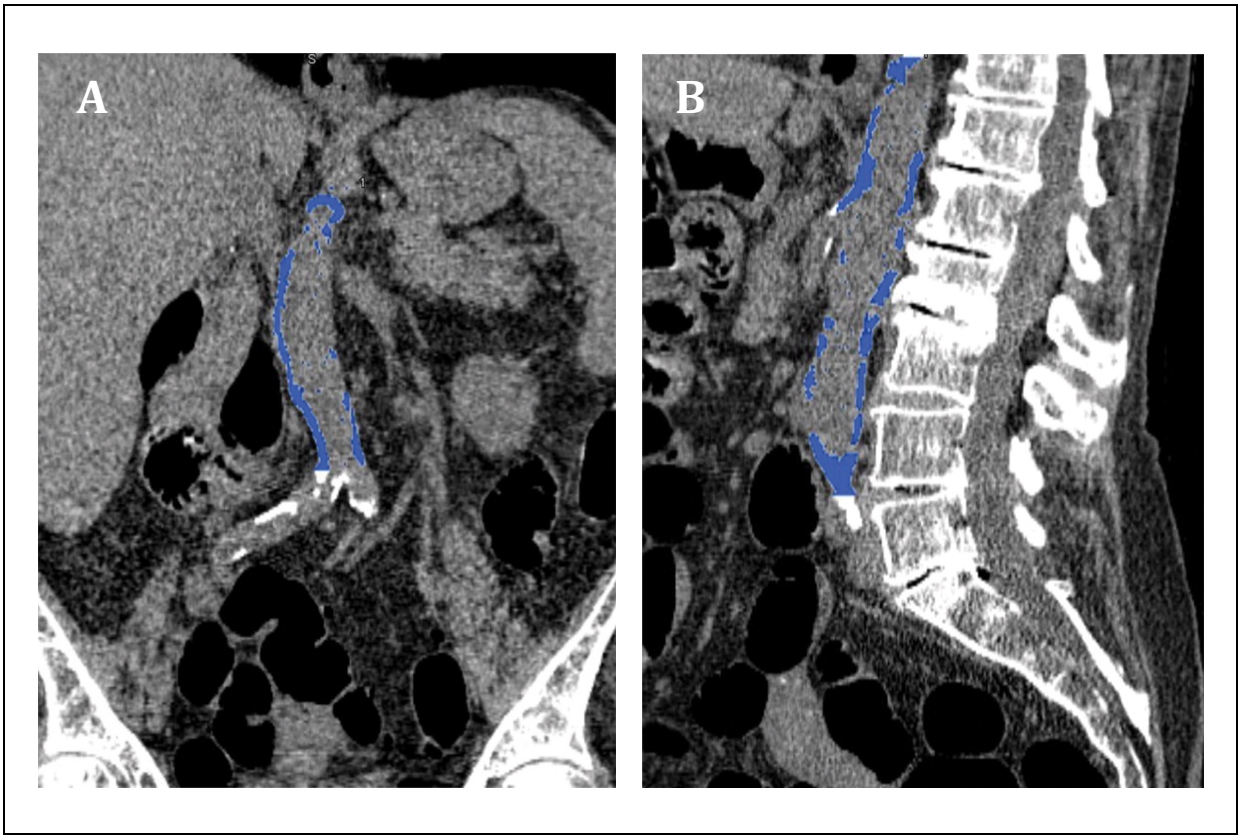

FIGURE 5 Quantification of abdominal aortic calcification

Images from non-contrast CT showing methodology for segmenting abdominal aortic calcification measured with semiautomated CT tool on A (coronal) and B (sagittal) images for use in the volume scoring method. Within region of interest over aorta selected by user, the tool automatically segments and quantifies aortic calcification (shown in blue).

Reproduced with permission, O'Connor, S.D. et al. Does nonenhanced CT-based quantification of abdominal aortic calcification outperform the framingham risk score in predicting cardiovascular events in asymptomatic adults? Radiology 2019; 290:108–115.

CALCIUM MASS SCORE

The relative calcium mass score is analysed by multiplying the mean density of the calcified plaque by the plaque volume in each slice. This decreases the variation caused by partial volume artifact. The absolute calcium mass score is then measured by using a correction factor based on the attenuation of water [27]. Mass score requires prior calibration with calcium hydroxyapatite phantoms but provides an absolute value of mineral mass. This may improve measurement accuracy and reproducibility by lowering threshold-dependent variability of arterial calcification. Due to its complexity of performance, mass score has not been widely applied in clinical practice and lacks an accepted reference standard for absolute quantification of plaque burden [28].

Based on the above findings and the availability of software, volume scoring will be used to quantify calcification of the distal abdominal aorta in the present study.

SUMMARY

Cardiovascular disease in psoriasis patients appears to be under-diagnosed and undertreated [32]. Non-contrast abdominal CT provides a reliable, accurate, non-invasive method for the assessment of atherosclerotic disease burden [18, 23]. There is a paucity of data related to the prevalence distal AAC in psoriasis patients. In view of this we sought to investigate AAC in a South African cohort of patients with psoriasis.

HYPOTHESIS AND OBJECTIVES

HYPOTHESIS

Patients with psoriasis may have increased AAC compared to controls

PRIMARY OBJECTIVE

To compare the prevalence and volume of calcified aortic atherosclerosis in the distal abdominal aorta in patients with psoriasis and matched controls.

SECONDARY OBJECTIVE

To determine if there is an association between calcified atherosclerosis in psoriasis patients and disease severity and/or co-existing cardiovascular risk factors such as smoking, T2DM, dyslipidaemia and MetS.

SUBJECTS AND METHODS

1. STUDY DESIGN

Cross-sectional case control study.

2. PARTICIPANTS

As part of an ongoing study, an existing dataset containing 148 CT scans was analysed.

Initial participant selection:

The primary study entitled, '*The cardiometabolic aspects of psoriasis'*, recruited a cohort of 103 unrelated, consenting patients with psoriasis or psoriatic arthritis, and 98 geographically, ethnically and gender-matched control subjects [11]. The sample size, inclusion criteria and exclusion criteria for this study were based on the number of patients recruited in to the original study. Controls were enlisted by asking psoriasis patients to bring in an unrelated individual e.g. a friend or neighbour. The controls and patients were matched for ethnicity, BMI and gender.

3. INCLUSION CRITERIA

Patients 18 years or older who were diagnosed clinically with psoriasis or psoriatic arthritis.

4. EXCLUSION CRITERIA

The following patients were excluded from the cohort:

- Those with inflammatory arthritis due to another cause e.g. rheumatoid arthritis, ankylosing spondylitis.
- Human immunodeficiency virus sero-positivity as HIV itself may be associated with both a pro-inflammatory state and CVD.
- Participants with either inadequate or no CT scans of the abdomen

5. SITE SELECTION

Patients were recruited from the state hospitals in the Wits Academic Complex i.e. Charlotte Maxeke Academic Hospital (CMJAH), Chris Hani Baragwanath Academic Hospital (CHBAH) and Helen Joseph Hospital (HJH). Patients were from the rheumatology and dermatology clinics at these hospitals. Patients were then scanned at HJH and CMJAH.

6. CLINICAL DATA

Clinical data were obtained by a combination of a review of case records, fasting blood samples and once-off clinical examination. The patient variables included: age, gender, socio-economic status, level of education, smoking, weight, height, waist circumference, hip circumference, blood pressure, psoriasis area and severity index (PASI) score, fasting glucose, lipid profile, hs CRP, serum interleukin-6, tumour necrosis factor, leptin and adiponectin, and CT estimates of subcutaneous and visceral fat volume [11].

7. REPORTING OF CT SCANS

The following technical parameters were used at the time of scanning:

- Patients were scanned from the level of L4 vertebral body superior end-plate, down to the level of the anterior superior iliac crest, a distance covered by 16 slices.
- Phillips Brilliance 16-slice multi-detector CT (scanner at either CMJAH or HJH)
- Slice thickness 3 mm
- Tube current: 250 mAs
- Tube voltage: 120 kV
- Standard Resolution
- Pitch 0.958
- Rotation time 0.5 sec
- FOV 350 mm
- Filter used: Sharp (C)
- Window 50 – 350
- Matrix 512

The calcium volume score was used to quantify distal AAC as it has better reproducibility. Horos DICOM Viewer, an Apple Mac-based image processing application, was used to analyse CT image stacks for presence of calcium in the lower abdominal aorta and calculate the calcium volume score. In cases where the proximal abdominal aorta was visible, secondary data was collected for the presence of calcification at the supra-coeliac and supramesenteric aorta.

For assessment of calcification at the aortic bifurcation, slices were limited to the segment of abdominal aorta 3 cm above the bifurcation, to the level of the bifurcation, in an effort to standardise the CT data. The level of the bifurcation was determined as the most distal point at which the aorta is still approximately circular with no clear evidence of bifurcation [33].

A region of interest (ROI) was drawn around the distal abdominal aorta, on axial views, 3 cm (approximately 10 slices) above the bifurcation. This ROI was propagated to extend inferiorly to the level of the aortic bifurcation. Each consecutive image slice was viewed to ensure that the aorta is completely included within the ROI. When necessary, the repulse tool was used to adjust the ROI boundary, in order to include the aorta or exclude adjacent unnecessary tissue such as the vertebral bodies.

The tissue outside of the ROI was excluded, with pixel values set to -1024 HU. This resulted in only the tissue within the encircled segment of aorta being visible on the viewer. These images were saved as separate key images under each participant number. The calcified plaques were then selected, using a threshold of above 130 HU [16, 26], in order to ensure that any non-calcified tissue was not selected. The grow-segmentation tool was used to calculate the volume of each calcific lesion, in mm^3.

8. Quality Control

Images were assessed by two readers, Sofia Ramos (SR) and Sheetal Daya (SD). A pilot of the volume score method was conducted on 10 random scans with both readers present, as a means to establish consensus. The entire dataset was reviewed independently by both readers, using the same method. SD was blinded to the initial results in an effort to assess inter-observer variability. The mean of the measurements was used. In the event of discrepancy exceeding 10%, both readers met to jointly assess flagged studies so that consensus could be reached.

DATA COLLECTION AND ANALYSIS

Data were entered and collated on an Excel spreadsheet and descriptive statistics was applied. Chi-squared test was used for categorical variables e.g., presence or absence of calcification and an unpaired T-test was used to compare continuous variables e.g., calcification scores. The kappa statistic was used to assess inter-observer agreement. Data was also tested for normality. If the continuous variables presented a normal distribution, Pearson's correlation was used to provide a complete correlation of the association i.e., the association between calcified atherosclerosis in psoriasis patients and disease severity and/or co-existing cardiovascular risk factors such as smoking, diabetes, dyslipidaemia and metabolic syndrome. If the data was skewed, Spearman's correlation was applied and the data log transformed. The Mann-Whitney *U* test was used ascertain measures of central tendency and significance on the volume data, which did not follow a normal distribution (Appendix A). Logistic and linear regression modelling was used to assess predictors of AAC and calcium volume scores respectively.

ETHICS

The study was approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, certificate no. M1810105 (Appendix C). The research was conducted in accordance with the principles contained in the Declaration of Helsinki.

FUNDING

For the original study, NGM received grants from the Carnegie Corporation of New York, NY, USA (Grant Number: B 8749.RO1), the National Research Foundation (Thuthuka) and from the Astra Zeneca Research Trust. MT received a grant from the Medical Research Council (self-initiated research grant). The funding bodies had no role in the design of the study and collection, analysis, and interpretation of data, or in writing the manuscript.

No further running costs were incurred in this substudy.

LIMITATIONS

Small sample size.

Use of non-contrast CT does not evaluate non-calcified plaque burden.

CHAPTER 2: PREVALENCE AND CARDIOMETABOLIC PREDICTORS OF ABDOMINAL AORTIC CALCIFICATION IN PATIENTS WITH PSORIASIS

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Keywords

Psoriasis; abdominal aorta calcification; atherosclerosis; cardiometabolic disease; smoking; metabolic syndrome.

Conflict of Interest

The authors have no conflicts of interest to declare.

ABSTRACT

Background

Psoriasis is associated with a high prevalence of cardiovascular disease. Abdominal aortic calcification (AAC) is a strong predictor of future cardiovascular events and all-cause mortality in the general population. We investigated the prevalence and risk factors for AAC in South African patients with psoriasis.

Methods

Adult psoriasis patients (n=69) and controls (n=80), matched for gender, ethnicity and body mass index (BMI), who attend tertiary Dermatology and Rheumatology clinics in South Africa, underwent non-contrast abdominal CT scans. Images were assessed for AAC at the supra-coeliac aorta, supra-mesenteric aorta and aortic bifurcation using Horos DICOM viewer.

Results

AAC at any site was significantly higher in the psoriasis group than control group (47.8% vs 22.5%, $p<0.005$). The aortic bifurcation was the commonest site for AAC in both groups, but significantly higher in the psoriasis group (42.0% vs 21.3%, $p<0.005$). The psoriasis group was also more likely to smoke and have hypertension and type 2 diabetes (T2DM) (56.5% vs 25.0%, $p<0.005$; 72.0% vs 55.0%, $p<0.005$; 24.6% vs 3.80%, $p<0.0005$, respectively). Multivariable logistic regression analysis demonstrated that age, smoking and T2DM were independently associated with AAC (odds ratio (95% CIs): 1.16 (1.07, 1.20), 4.30 (2.15, 8.61) and 3.45 (1.09, 15.7) respectively), but psoriasis was not. Forward regression analysis demonstrated that smoking attenuated the association of psoriasis with AAC.

Conclusion

Smoking cessation is essential in psoriatic patients to reduce the risk of cardiovascular events. The clinical utility of AAC detection by CT imaging to risk stratify for hard cardiovascular outcomes needs to be explored.

INTRODUCTION

Psoriasis is a chronic immune-mediated inflammatory skin disorder characterised by raised, erythematous plaques with adherent, silvery scales [1]. Numerous studies in recent years have shown that psoriasis is associated with metabolic syndrome (MetS) and its components, i.e. hypertension, dyslipidaemia, and type 2 diabetes mellitus (T2DM). Consequently patients with psoriasis have a higher risk of cardiovascular disease compared to the general population [9], similar to that observed in patients with rheumatoid arthritis and T2DM [12]. The increased risk of CVD is mediated not only by a higher prevalence of traditional risk factors such as smoking [34], obesity and insulin resistance in psoriasis [9], but also the systemic pro-inflammatory milieu of the disease [8].

Atherosclerotic plaques are a strong predictor of cardiovascular events [35] in the general population. Cytokine up-regulation, a hallmark of psoriasis, and production of pro-angiogenic factors, accelerates atherosclerosis and plaque formation [36]. The extent and severity of atherosclerotic plaques in psoriasis correlates with disease activity and traditional risk factors [37]. The American College of Cardiology and American Heart Association guidelines recommend computed tomography (CT) based imaging to assess atherosclerotic cardiovascular disease [38]. The use of non-contrast enhanced multidetector CT (MDCT) provides highly sensitive and reliable detection of calcified atherosclerosis [18].

Atherosclerosis in the abdominal aorta occurs most frequently at the distal aorta and bifurcation, resulting from turbulent flow in this region [25]. Plaque within this region is also associated with the highest probability of symptomatic atherosclerosis at other sites and shows the highest tendency for recurrence [21]. To date, there is a paucity of data on the prevalence of AAC in psoriasis. The aim of the present cross-sectional study was to determine the prevalence and predictors of AAC in adult patients with established plaque psoriasis.

PARTICIPANTS AND METHODS

As part of a larger study on psoriasis and cardiometabolic disease (CMD), adult psoriasis patients (n=69) and controls (n=80) were recruited at tertiary public service Dermatology and Rheumatology clinics. Appropriate ethical clearance was received. Patients were 18 years or older, who had a diagnosis of psoriasis or psoriatic arthritis (PsA), were HIV seronegative and had no other immune mediated inflammatory diseases (IMIDs). Control participants had no history of any IMIDs, were of a similar socio-geographic background, were matched for gender, ethnicity and body mass index (BMI).

Clinical and laboratory data were obtained by review of case records and a once-off clinical examination and a fasting blood sample. The patient variables included age, ethnicity (black African, Asian, Caucasian, mixed ancestry), gender, level of education (completing high school or less), smoking status, BMI (weight, in kg, was measured in subjects with light clothing and without shoes), and blood pressure (mean blood pressure of at least two readings taken 10 minutes apart with the participant seated). Waist circumference was measured at the mid-point of the upper border of the iliac crest and the lower border of the last rib using a soft tape measure. Hip circumference was measured at the widest level of the buttocks. The psoriasis area and severity index (PASI) was used to assess severity and extent of cutaneous psoriasis [39].

Laboratory investigations included a fasting glucose and serum lipid profile. Venous blood samples were obtained at the time of clinical examination after overnight fasting. Plasma glucose and serum lipids (total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides), were measured using enzymatic methods on the ADVIA 1800 Chemistry Systems Analyser (Siemens Healthcare Diagnostics, Tarrytown, NY, USA). The Friedewald formula was used to calculated low-density lipoprotein (LDL) [40].

MetS was diagnosed according to the 2009 Harmonized guidelines [41]. In patients with no previous history of T2DM and hypertension, newly diagnosed T2DM was based on a

fasting plasma glucose of >7mmol/l [42]; newly diagnosed hypertension was based on the blood pressure criteria within the Harmonized guidelines [41]. High LDL was defined according to the South African Heart Association and LASSA guidelines [43]. More detailed descriptions of the methods used in this study are available in previous publications [11, 44].

Non-contrast abdominal CT imaging was performed at the level of L4/L5, using a Philips 16 slice multidetector CT (Brilliance 16, Philips, Netherlands), with slice thickness of 3 mm (250 mAs and 120kV, FOV 350 mm), within a month of the clinical assessment. Standard resolution (matrix 512 x 512); sharp (C) filter was applied with window range set at 50-350. Subcutaneous and visceral fat volumes, expressed as g/cm^3, were calculated from CT image data and by using fat selection technology on Osirix Dicom viewer (Osirix foundation, Geneva Switzerland). For the vascular studies, Horos DICOM Viewer version 3.3.0 (GNU L-GPL, Nimble Co LLC d/b/a Purview in Annapolis, MD USA), an Apple Mac-based image processing application, was used to analyse 149 available CT image stacks for presence and location of calcium in the abdominal aorta. The aortic bifurcation was the primary site for evaluation. The principal investigator (SR) read the images twice to assess intra-observer variability and a second radiologist (SD) performed an independent reading to determine inter-observer variability. Other abdominal aortic segments were also visible in several patient image stacks and were therefore also assessed. The secondary sites were the supra-coeliac aorta and supra-mesenteric aorta.

This study received ethics clearance received from the Human Research Ethics Committee (Medical), University of the Witwatersrand. Clearance certificate no. M1810105.

STATISTICAL ANALYSIS

Student's unpaired t test was used to compare continuous variables between groups, with log transformation of data that was not normally distributed. Categorical variables were compared across groups using the χ^2 test. Logistic regression analysis was used to determine the independent predictors of aortic calcification. Thus, study variables that correlated with aortic calcification at $p<0.20$ in univariate logistic regression models were included in a multivariable model. Backward, stepwise removal of non-significant variables from the multivariable model was performed until only those with $p<0.05$ remained. In the models where psoriasis did not continue through to the final model, forward regression analysis was performed to determine which variable was responsible for attenuating its effect on the outcome variable of calcification. 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. Statistical analyses were achieved using Statistica version 13.5 (StatSoft, Tulsa, OK, USA).

RESULTS

From the original cohort, 148 patients had a non-contrast CT scan of the abdomen. These patients were included in the current study. As shown in Table 1, most patients were middle-aged with a mean (SD) age of 53.3 (14.5) years and long-standing disease. Mean (SD) disease duration was 18.9 (13.3) years, with an almost equal gender representation. Over 60% of patients were either of Asian or mixed ethnicity. The prevalence of smoking, MetS, hypertension and T2DM was significantly higher in the psoriasis group compared to the control group (56.5% vs. 25.0%, $p<0.005$; 56.5% vs. 37.5%, $p<0.05$; 72.5% vs. 55.0%, $p<0.005$; 24.6% vs. 3.80%, $p<0.0005$, respectively). There were no significant differences in serum lipids or abdominal fat.

TABLE 1. Clinical characteristics of patients with psoriasis and controls

Variable	Psoriasis group (n=69)	Controls group (n=80)	p value
Age in years - mean ± SD	53.3 ± 14.5	47.9 ± 14.5	0.02
Ethnicity (%): Black White Asian Mixed ethnicity	9 (13.0) 8 (11.6) 29 (42.0) 23 (33.3)	15 (18.8) 12 (15.0) 32 (40.0) 21 (26.3)	NS
Male n (%)	32 (46.4)	32 (40.0)	NS
Disease duration in years - mean ± SD	18.9 ± 13.3	-	
Smokers n (%)	39 (56.5)	20 (25.0)	<0.0001
Metabolic syndrome n (%)	39 (56.5)	30 (37.5)	0.02
Hypertension n (%)	50 (72.5)	44 (55.0)	0.03
Type 2 diabetes n (%)	17 (24.6)	3 (3.80)	0.0002
High LDL-C n (%)	52 (75.4)	52 (65.0)	NS
Low HDL-C levels n (%)	21 (30.4)	19 (23.8)	NS
Hypertriglyceridaemia n (%)	21 (30.4)	18 (22.1)	NS
BMI in kg/m^2- mean ± SD	32.4 ± 9.38	29.7 ± 6.94	0.05
Abdominal fat – median (IQR) Visceral (g/cm^3) Subcutaneous (g/cm^3)	 197.8 (132.5, 277.7) 439.4 (323.0, 647.8)	 152.6 (89.5, 218.3) 410.0 (267.7, 595.9)	 NS NS
NS: Not significant			

The aortic bifurcation was the commonest site for AAC in both groups (Table 2) (Fig 6). AAC was more prevalent at all sites in the psoriasis group than the control group (aortic bifurcation 48.5% vs. 23.2%, p<0.005; supra-coeliac aorta 21.2% vs. 3.8%, p<0.005; supramesenteric aorta 24.3% vs. 2.3%, p<0.05). Subgroup analysis revealed no difference in AAC between psoriasis patients with or without psoriatic arthritis.

TABLE 2. Abdominal aortic calcification in psoriasis patients vs controls

Variable	***Psoriasis*** **n (%)**	***Controls*** **n (%)**	***Odds Ratio (95% CI)***	***p value***
Aortic bifurcation	33/68 (48.5)	16/69 (23.2)	3.12 (1.50, 6.51)	0.002
Supra-coeliac area	14/66 (21.2)	3/79 (3.8)	6.82 (1.87, 24.92)	0.003
Supra-mesenteric area	9/37 (24.3)	1/43 (2.3)	13.50 (1.62, 112.54)	0.005

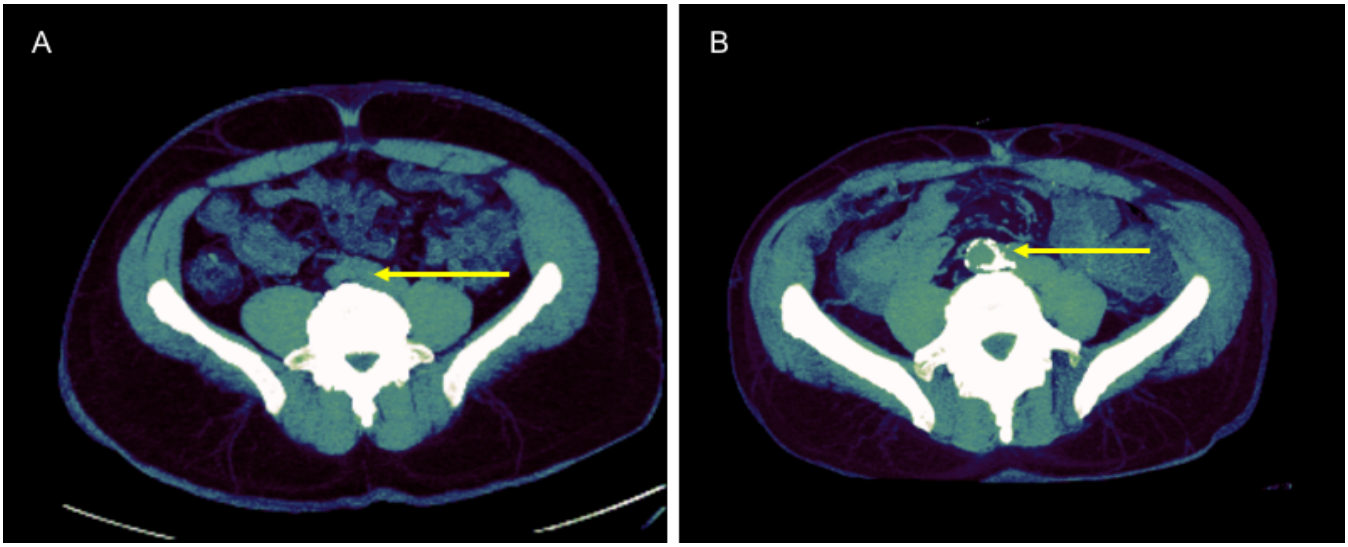

FIGURE 6 Distal abdominal aortic calcification in control vs psoriasis patient

A 3D reconstructed axial maximum intensity projection (MIP) of non-contrast CT of the lower abdomen, in a control participant, demonstrating normal distal aorta with no evidence of calcific atherosclerosis (arrow: non-calcified distal abdominal aorta). **B** 3D reconstructed axial MIP of non-contrast CT of the lower abdomen, in a psoriasis patient, demonstrating circumferential calcification of the distal abdominal aorta (arrow: calcified atherosclerosis of the distal abdominal aorta).

Table 3 is a summary of predictors for AAC at the aortic bifurcation for the entire cohort of patients and controls. Univariate analysis showed a significantly higher burden of traditional CV risk factors i.e. smoking history, T2DM, hypertension and metabolic syndrome in males and psoriasis patients. A lower level of education was also found to correlate with AAC in psoriasis patients in the univariate analysis. Multivariable logistic regression analysis showed age, smoking and T2DM to be independent predictors of AAC at the aortic bifurcation.

TABLE 3. Predictors of abdominal aortic bifurcation calcification

	Aortic bifurcation calcification		Univariate analysis		Multivariate analysis	
	Present n (%)	**Absent n (%)**	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**
Age in years – mean (SD)	61.1 (8.6)	45.5 (13.6)	1.13 (1.08, 1.17)	<0.0001	1.14 (1.07, 1.20)	<0.0001
Ethnicity						
Black	3 (6.1)	16 (18.2)	0.29 (0.08, 1.06)	0.07	-	-
White	10 (20.4)	9 (10.2)	2.25 (0.85, 5.99)	0.10	-	-
Asian	24 (49.0)	35 (39.8)	1.45 (0.72, 2.94)	0.29	-	-
Mixed ancestry	12 (24.5)	28 (31.8)	0.70 (0.31,1.53)	0.38	-	-
Males	28 (57.1)	31 (35.2)	0.36 (0.17, 0.73)	0.005	-	-
Psoriasis	33 (67.3)	35 (39.8)	3.12 (1.50, 6.51)	0.002	-	-
Psoriatic arthritis	10 (45.5)	12 (54.5)	1.62 (0.64, 4.09)	NS	-	-
Smoking	31 (63.3)	25 (28.4)	4.34 (2.06, 9.12)	<0.0001	4.30 (2.15, 8.61)	<0.0001
Metabolic syndrome	32 (65.3)	33 (37.5)	3.18 (1.51, 6.51)	0.002	-	-
Hypertension	37 (75.5)	49 (55.7)	2.45 (1.13, 5.33)	0.02	-	-
Type 2 diabetes	14 (28.6)	6 (6.8)	6.03 (2.16, 16.85)	0.0006	4.14 (1.09, 15.6)	0.035
High LDL-C*	44 (91.7)	56 (63.6)	5.89 (1.91, 18.2)	0.002	-	-
Low HDL-C	15 (30.6)	22 (25.0)	1.32 (0.61, 2.88)	NS	-	-
Hypertriglyceri-daemia	16 (39.0)	18 (20.5)	1.32 (0.86, 4.16)	0.11	-	-
BMI in kg/m2 – mean (SD)	32.2 (8.28)	30.1 (7.94)	1.03 (0.99, 1.07)	0.15	-	-
Abdominal fat) – median (IQR)						
Visceral (g/cm^3)	256.3 (163.8, 345.5)	157.6 (89.5, 207.2)	1.08 (1.04, 1.11)	<0.0001	-	-
Subcutaneous (g/cm^3)	493.6 (279.0, 621.3)	465.7 (287.3, 600.1)	1.99 (0.99, 1.02)	0.56	-	-
Level of Education	25 (51.0)	63 (71.6)	0.43 (0.21, 0.90)	0.02	-	-

While psoriasis was significantly associated with aortic bifurcation calcification in the univariate analysis (OR (95% CI): 3.12 (1.50,6.51); p=0.002), it did not remain significant in the multivariable model (0.992 (0.31,3.15); p= 0.99). This model was further analysed using forward regression analysis to determine which independent variable was responsible for attenuating the effect of psoriasis on aortic bifurcation calcification. This showed that smoking was the principal covariate that attenuated the relationship between psoriasis and aortic bifurcation calcification (2.12 (0.93, 4.83); p=0.07 (for psoriasis); 3.31 (1.92, 5.69); p<0.0001 (for smoking)).

DISCUSSION

In this case-control, multi-ethnic study of AAC, detected by CT imaging, we found the prevalence of AAC to be especially common at the aortic bifurcation in both the psoriasis and control groups. Psoriasis patients had a significantly higher prevalence of AAC at all three aortic anatomical sites i.e. aortic bifurcation, supracoeliac and supramesenteric. Most of the risk of AAC was associated with traditional cardiometabolic factors, notably smoking, T2DM and age.

Subclinical atherosclerosis in psoriasis has been well-documented in several non-invasive studies. Ultrasound imaging has consistently shown increased carotid intimal thickening and increased risk of carotid plaques in both psoriasis and PsA [45–47]. A more recent cross-sectional study of coronary artery calcification (CAC) determined by CT imaging, showed that patients with moderate to severe psoriasis had similar scores to patients with T2DM after adjusting for confounders [48].

Plaques at the distal aorta and bifurcation are associated with the highest probability of symptomatic atherosclerosis at other sites [21]. Moreover, numerous studies in the general population have shown that AAC is an independent predictor of cardiovascular and all-cause mortality, irrespective of the Framingham risk score [19, 20, 23, 49, 50]. In the prospective US Multi-Ethnic Study of Atherosclerosis, both CAC and AAC

independently predicted coronary heart disease, but AAC was the only independent predictor of cardiovascular mortality and a better predictor of all-cause mortality than CAC [23]. From a health economics perspective, AAC in a community-based observational study in men was found to predict overall health costs, independent of prevalent clinical cardiovascular disease [51].

In the present study, psoriasis was associated with AAC only in the univariate analysis. The multivariate analysis subsequently demonstrated that the effects of psoriasis on AAC are, in fact, mediated by smoking. It should be noted that a higher prevalence of smoking has been observed in psoriatic patients [52], and is associated with an increased risk for psoriasis, with a meta-analysis demonstrating that the odds ratio for psoriasis in smokers is 1.78 (95% CI 1.53-2.06) [53]. Smoking is known to accelerate atherosclerosis through its induction of oxidative stress, which leads to lipid abnormalities, platelet activation, chronic inflammation and endothelial dysfunction [53, 54].

Psoriasis is associated with cardiometabolic diseases such as MetS, and in particular, T2DM [13, 55–59] as well as cardiovascular risk factors, specifically smoking [34, 53, 60, 61]. Furthermore, studies demonstrate an association between psoriasis and atherosclerosis [57, 62, 63] with one study demonstrating increased vascular inflammation in psoriasis using PET/CT imaging [32]. To our knowledge, this is the first study to demonstrate that the heightened risk of AAC in psoriasis patients, is explained by smoking. This serves as an important finding as other studies have similarly shown that the higher risk of particular CMDs in psoriasis is due to the high prevalence of other risk factors, rather than psoriasis being the causative agent [44, 64–66].

LIMITATIONS

Limitations of the present study were the cross-sectional design and relatively small sample size, which did not allow us to examine the relationship of AAC with hard cardiovascular outcomes and mortality in psoriasis. Non-contrast CT imaging does not evaluate non-calcified plaque burden and thus potentially underestimates the prevalence and extent of non-calcified atherosclerosis as compared to CT imaging with intravenous contrast.

Notwithstanding these limitations, the strength of the study is the use of a sensitive, robust and reliable diagnostic method of detecting AAC. From a bedside perspective, our findings underscore the need to address modifiable cardiometabolic risk factors, in particular smoking, to mitigate both the burden of psoriasis and attendant cardiovascular risks.

The clinical utility of this imaging modality as a predictor of cardiovascular and all-cause mortality requires a larger prospective study.

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CHAPTER 3. CONCLUSION

There is a paucity of data regarding the prevalence of abdominal aortic calcification in patients with psoriasis and even less known about psoriasis patients in a Sub-Saharan context. In light of this, this cross-sectional multi-ethnic South African study sought to determine the prevalence and potential predictors of abdominal aortic calcification in this particular subset of patients.

The majority of patients were middle-aged with long-standing psoriasis. Half of the patients with psoriasis had distal abdominal aorta calcification, which was significantly higher than the control group, however, the higher burden of abdominal aortic calcification in this population was attributed to their greater cardiovascular disease burden rather than psoriasis alone. On further analysis, smoking was found to be the principal covariate responsible for attenuating the relationship between psoriasis and aortic bifurcation calcification.

To our knowledge, this study is the first to show that the heightened risk of abdominal aortic calcification in psoriatic patients is principally explained by smoking. This study highlights the increased cardiovascular disease risk within this population and the need for lifestyle modification, particularly smoking cessation, in order to decrease risk factor burden and progression of atherosclerosis.

APPENDICES

APPENDIX A. SUPPLEMENTARY DATA

The data below describes the volume of atherosclerotic calcification found at the aortic bifurcation in several patients and controls. The volumes were calculated according to the volume score method, as defined in the literature review and protocol. The volume score data was calculated using post-processing and 3D rendering tools on Horos Dicom Viewer (version 3.3.0 (GNU L-GPL, Nimble Co LLC d/b/a Purview in Annapolis, MD USA)), a Mac-based image processing application. 4 participant's (2 psoriasis patients, 2 controls) CT studies were excluded as the region of interest was not adequately represented. An additional psoriasis case was excluded on the basis of having a non-measurable punctate calcification (too small to accurately characterise).

The calculated volumes were assessed twice by the primary reader (SR), with no significant intra-observer variability. The volume scores were then calculated independently by a second reader, a consultant radiologist (SD), and compared to the primary reader values to assess interobserver variability. Less than 10% variability was considered acceptable. Values with more than 10% interobserver variability were flagged for joint re-assessment and agreement. Consensus was reached on all flagged values.

The total volume score for each participant with aortic bifurcation calcification is demonstrated in the spreadsheet below. The scores failed to show a normal distribution, despite multiple configurations. Application of the Mann-Whitney U test revealed that the volume scores between psoriasis patients and controls was not significant (Table 4). In light of these findings, the data was excluded from the final paper.

We postulated that there was no significant difference between the two groups for the following reasons:

- Small n number and excluded cases
- The use of non-contrast CT which does not demonstrate non-calcified plaque

Table 4. Median volume score in psoriasis patients vs. controls

	Psoriasis (n = 30)	**Controls (n = 14)**	**p value**
Median volume score (mm^3) (IQR)	254.02 (90.98, 591.50)	84.49 (13.60, 351.90)	0.10

APPENDIX B. DATA COLLECTION SHEET

Participant	Age	Gender	Weight (kg)	Height (cm)	Waist circumference (cm)	Hip circumference (cm)	Blood pressure (mmHg)	PASI Score	Smoking	Fasting glucose (mmol/L)	Lipid profile	hs CRP	Subcutaneous Fat Volume	Visceral Fat Volume
P001														
P002														
P003														
P004														
P005														
P006														
P007														
P008														
P009														
P010														

	Calcification		Calcium Volume - Aortic bifurcation (mm3)				
Participant	Calcification Present	Location of Calcification	First Read	Second Read	Intra-observer variability	Second Reader	Inter observer variability
P001							
P002							
P003							
P004							
P005							
P006							
P007							
P008							
P009							
P010							

APPENDIX C. ETHICS CLEARANCE CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr S Ramos

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M1810105

NAME: (Principal Investigator)	Dr S Ramos
DEPARTMENT:	School of Clinical Medicine Department of Radiation Sciences Division of Diagnostic Radiology Medical School University
PROJECT TITLE:	Abdominal aortic calcification in psoriasis
DATE CONSIDERED:	Ad hoc
DECISION:	Approved unconditionally
CONDITIONS:	Sub-study under M1403100
SUPERVISOR:	Drs NG Mahyoodeen & S Daya; Prof M Tikly
APPROVED BY:	C B Penny Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	21/11/2018

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 Research Office Secretary on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/We fully understand the conditions under which I am/we are authorised 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 to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date of the meeting when the study was initially reviewed. In this case, the study was initially reviewed in **2018/10/01** and will therefore reports and re-certification will be due early in the month of **2018/10/01** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

22/11/2018
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX D. TURNITIN PLAGIARISM REPORT