T-BIRD

TISSUE BIOMECHANICS AND INFLAMMATION IN THE RHEUMATIC DISEASES

[THE RELATIONSHIP BETWEEN ARTICULAR, CUTANEOUS AND VASCULAR BIOMECHANICAL PROPERTIES, THE RISK OF DEVELOPING AND THE SEVERITY OF AND THE INFLAMMATORY ARTHRITIS AND CARDIOVASCULAR DISEASE OCCURRING IN RHEUMATOID AND PSORIATIC ARTHRITIS – A PRELIMINARY STUDY]

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TABLE OF CONTENTS

INTRODUCTION

CARDIOVASCULAR DISEASE IN INFLAMMATORY ARTHRITIS

The risk of cardiovascular (CV) events like myocardial infarction and stroke is elevated in two forms of inflammatory arthritis – Rheumatoid Arthritis (RA) and Psoriatic Arthritis (PsA). This increase occurs independent to the conventional CV risk factors such as smoking, diabetes and hypertension and is directly related to the disease processes.

The articular (joint) damage in RA and PsA is a result of autoimmune and inflammatory processes. It has been broadly accepted that these inflammatory processes are also responsible for the elevated CV risk. This is supported by observational studies showing firstly that CV risk is increased in RA (1) and by studies showing that arterial stiffness (which is a marker of CV risk) is increased in RA (2,3). Additionally, arterial stiffness correlates with the cumulative disease burden of RA (4) and observational studies indicate patients treated more aggressively with stronger immunosuppression have lower CV risk (5) and exhibit improvements in CV risk biomarkers such as arterial stiffness.

However, observational studies are prone to confounding through selection bias. People who develop RA and PsA may already have elevated CV risk for other reasons and the link between arthritis and CV risk might represent a common cause. There is also a tendency to prescribe stronger immunosuppression to healthier patients while patients with comorbidities like diabetes mellitus, a condition with elevated CV risk, are less likely to receive these treatments because they have increased risk of infection. The “inflammation hypothesis” is not supported by pooled randomised controlled trial (RCT) data (5) which is not affected by selection bias and confounding. Additionally, the recently concluded RCT (Hunter HEART-RA) conducted at found no relationship between inflammation and assessments of vascular function (6).

This suggests that in fact inflammation is not the primary mechanism of increased CV risk. If this is the case then an alternate explanation is that other factors responsible for the development and severity of inflammatory arthritis may also separately be responsible for the increased CV risk seen in RA and PsA.

PATHOGENESIS OF INFLAMMATORY ARTHRITIS

There have been substantial advances in our understanding of the pathogenesis of inflammatory arthritis in the last decade. Much is explained by the interaction between risk genes and environmental factors and the microbiome is emerging as being of key importance. However, much regarding the risk of development and predicting the severity of inflammatory arthritis is not known. In particular, only one third of the genetic risk for RA has been explained and PsA is even less well understood. One area that has been largely overlooked is the potential contribution of biomechanical forces.

Biomechanical characteristics of connective tissues influence the nature and magnitude of biomechanical stresses upon the joint. There is clear evidence that biomechanical stressors influence the severity of inflammatory arthritis and it is plausible that inherited and acquired connective tissue biomechanical characteristics may contribute to the development and severity of inflammatory arthritis. There is also evidence to suggest that inherited connective tissue biomechanical properties pervade and characterise all tissue compartments so that people born with stiff joints also have stiff arteries and stiff skin. If this is true then people who develop inflammatory arthritis will be those who also have stiff arteries and stiff skin.

EVIDENCE FOR CORRELATION BETWEEN ARTICULAR, VASCULAR AND CUTANEOUS BIOMECHANICAL PROPERTIES

Joints, skin and arteries are made from the same "bricks and mortar" (collagens, glycoproteins and water) and exhibit similar biomechanical properties. Benign joint hypermobility (BJH) describes the state of increased joint laxity / range of movement that occurs in 20% of the general population. This is the result of greater elasticity in the connective tissues and while this is an inherited (genetic) trait the genetic and molecular basis of BJH is complex and poorly understood (7). Similarly, arterial stiffness appears to be largely genetically determined but the mode of inheritance is poorly understood (9). There is evidence to suggest that there is a correlation between articular, cutaneous and arterial stiffness. The skin of people with BJH has been shown to be more elastic (less stiff)(9, 11). BJH is associated with cardiovascular symptoms (postural hypotension) and mitral valve prolapse (8). It is therefore plausible that people with BJH may also have less stiff arteries and theoretically lower CV risk.

This possible relationship between articular and arterial biomechanical properties has been explored previously in a study at HNE LHD (11) comparing biomechanical assessments of joint mobility with assessments of aortic stiffness (carotid-to-femoral pulse wave velocity). The study found no correlation between the vascular and joint stiffness. However, biomechanics is a complex field and “stiffness” can be measured many ways. While tensile modulus (discussed below) was used to evaluate articular stiffness the aortic stiffness was evaluated using carotid-femoral pulse wave velocity. This method is distinctly different to tensile modulus and while it can be used to infer the stiffness of the aorta is not a direct measurement of tensile modulus.

During subsequent studies of endothelial function (the ability of arteries to dilate) using measurements of peripheral artery one (EndoPAT) in patients with rheumatoid arthritis (RA) (Hunter HEART-RA) (6) it has been noted that patients who are hypermobile have arteries that dilate to a much greater degree. Vasodilation occurs when the endothelial cells lining the inner surface of the large and medium muscular arteries produce nitric oxide that relaxes the smooth muscles in the arterial wall. It is regarded as an assessment of the health of the endothelial cells. However, this vasodilation occurs within the constraints of the connective tissue scaffold of the arterial wall and therefore will also be partly determined by the biomechanical properties of the arterial wall. Viewed this way, these assessments are conceptually analogous to the biomechanical assessments used to evaluate articular stiffness in that they quantify tissues lengthening in response to a tensile or distending force (tensile modulus).

EVIDENCE THAT BIOMECHANICAL FACTORS INFLUENCE SEVERITY OF RHEUMATOID ARTHRITIS

During the Hunter HEART-RA study (6) the observation has been made anecdotally that patients with RA who have joint hypermobility tend to follow a more benign course of disease with less articular damage on X-rays and more easily controlled RA. This suggests that the resting tension within articular structures influences inflammation. This notion is supported by other observations in patients with RA. While rheumatoid arthritis is clearly an immunologically mediated disease it appears that biomechanical factors contribute to joint inflammation and damage. Simple rest and splinting of joints have long formed the foundation of therapy and remain an essential adjunct to effective modern drugs. When people with RA become paralysed, due to stroke, the arthritis becomes inactive in the affected limb whilst remaining active elsewhere. Clinically, it is well known that erosions develop in the feet, which are subject to much greater biomechanical stresses), before they develop in the hands in individuals with RA. Formal research indicates that bone erosions occur in anatomical locations subject to greater tensile forces in patients with rheumatoid arthritis (12).

RA occurs predominantly in women with bimodal peaks of onset with the first in early adulthood and then a larger peak in the peri-menopausal age group. In this latter group rheumatoid arthritis develops at a time

when oestrogen levels fall dramatically. Conversely young women with rheumatoid arthritis typically find that their arthritis spontaneously goes into remission during pregnancy when oestrogen levels are very high. These two observations suggest that oestrogen suppresses inflammatory arthritis but the mechanism of this effect is not known. It is assumed that the very high levels of oestrogen might have corticosteroid-like anti-inflammatory effects. However, the skin of pregnant women has been shown to have greater elasticity (13) (i.e. it is less stiff) and if skin stiffness correlates with articular stiffness it seems plausible that oestrogen and other hormones produced during pregnancy might reduce articular inflammation by reducing the biomechanical stresses on articular supporting structures.

Alcohol consumption is now well established as having protecting effects against the development of both RA (14) and cardiovascular disease (15) but the mechanisms of these effects are not known. A single small study suggested that alcohol consumption might reduce skin stiffness (16). If connective tissue biomechanical properties correlate in the joints, arteries and skin then it is plausible that the protective effects of alcohol might be mediated by direct effects upon connective tissue stiffness.

Penicillamine, one of the oldest RA disease modifying drugs, has also been used to treat scleroderma because of its ability to reduce the stiffness in the skin. Penicillamine, was originally developed as a copper chelating agent. A 1979 review paper (17) on the possible mechanisms of action of penicillamine noted firstly that in RA there are increased amounts of collagen in the joints and that there was increased cross-linking which would make the tissue more stiff. The implication was that this was a result of the RA. However, it is equally plausible that these differences were present prior to the onset of RA and contributed to its development. The article referenced previous work (18) showing that penicillamine might break down collagen cross-links and on this basis it is plausible that the anti-rheumatic effects might be partly mediated by reductions in articular stiffness.

Based upon this it also appears plausible that inherited and acquired articular biomechanical characteristics might influence the risk of developing and the severity of RA and cardiovascular disease.

EVIDENCE THAT BIOMECHANICAL STRESSES INFLUENCE SEVERITY OF BIOMECHANICAL STRESSES AND PSORIATIC ARTHRITIS

The evidence for a biomechanical contribution to pathogenesis is even more compelling for psoriatic arthritis where research using magnetic resonance imaging clearly shows that the primary site of inflammation lies not within the joint but rather at attachment points of tendons and ligaments supporting the joint that are subject to high tensile forces (14). This suggests that these people develop an inflammatory reaction in tissues subject to tensile forces. The same mechanisms may be responsible for the cutaneous manifestations of psoriasis since skin lesions tend to occur at locations subject to tension (extensor surfaces of elbows, knees) and attachments of the integumentary structures of the skin (hair and nails). Positron Emission Tomography (PET) scan evidence indicates that the same process may occur in the large arteries of people with psoriasis (15). This suggests that psoriatic arthritis and psoriasis develop preferentially in people with stiffer connective tissues. It is therefore quite conceivable that the inflammatory response to biomechanical stressors (tensile forces) that occurs in the joints, skin and arteries might be amplified or mitigated by inherited connective tissue biomechanical properties (see Figure 2).

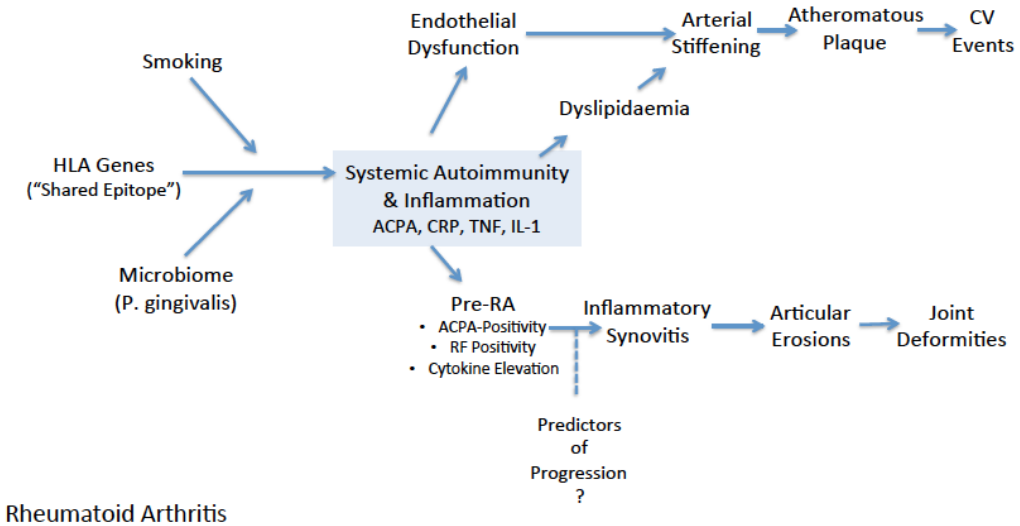
SUMMARY AND SIGNIFICANCE

The prevailing paradigms (figures 1 and 2 below) hold that the inflammatory processes responsible for RA and PsA also cause the associated cardiovascular disease. The T-BIRD study inverts the existing paradigm to explore the hypothesis that while autoimmunity sets the stage for the development of both RA and PsA, inherited and acquired connective tissue biomechanical properties (stiffness) then:

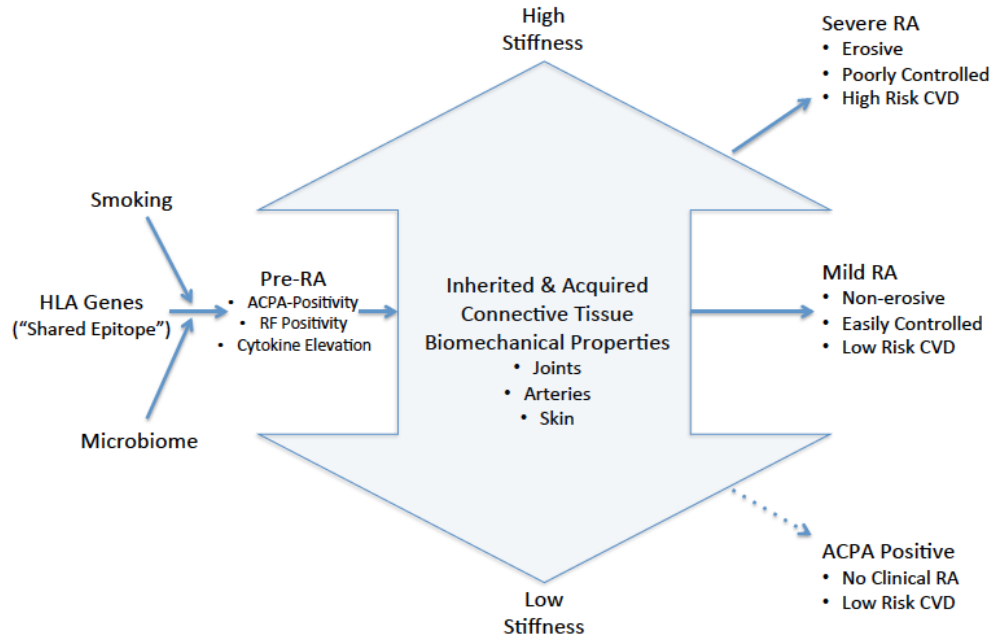
1. Influence the risk of developing RA and PsA
2. Influence the severity of RA and PsA and;
3. Determine the risk of the CV disease seen in association with RA and PsA .

If this hypothesis is confirmed then a considerable part of the as yet unaccounted for heritability of RA and PsA might be explained. There would be important clinical implications as it would change the way clinicians undertake risk assessment and therapeutic decisions in managing inflammatory arthritis and its associated cardiovascular disease. The study may even open new areas for possible therapeutic developments.

This preliminary cross-sectional study will begin exploring this hypothesis by evaluating the relationship between articular biomechanical characteristics in the joints, skin and arteries and exploring the relationships between tissue biomechanical properties upon rheumatoid and psoriatic arthritis and vascular and cutaneous disease.

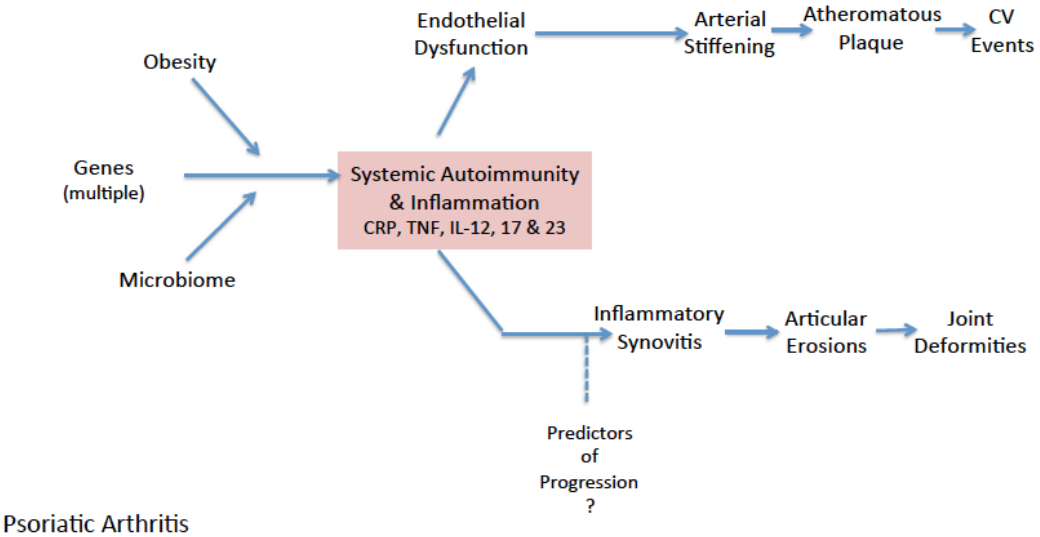


Rheumatoid Arthritis
Current Paradigm Pathogenesis Inflammatory Arthritis and Cardiovascular Disease

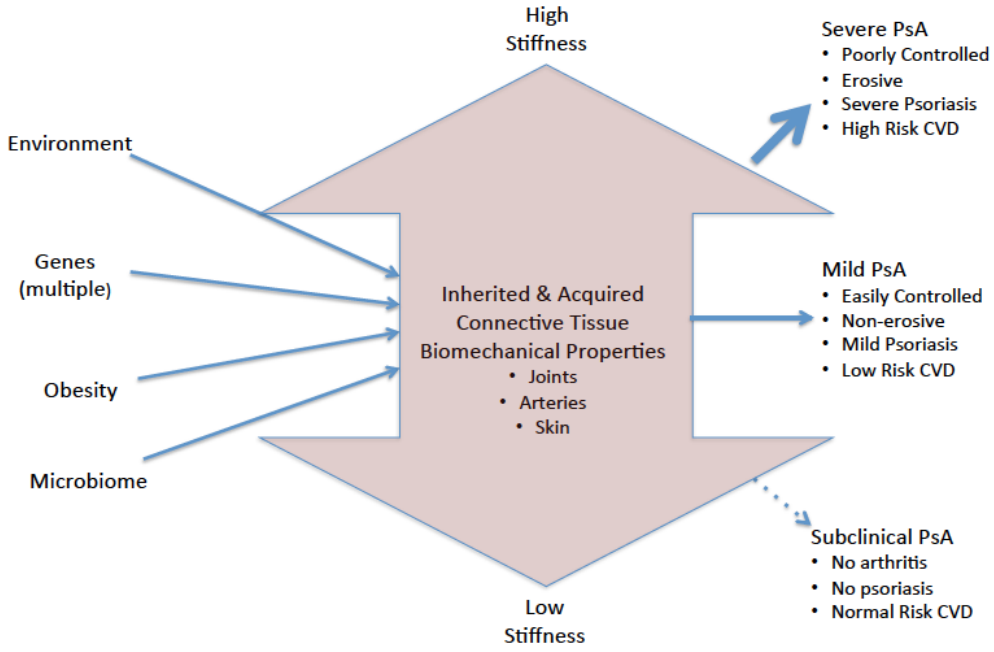


Rheumatoid Arthritis
Proposed Paradigm of Pathogenesis illustrating Role of Inherited Tissue Biomechanics Properties

Figure 1: Pathogenesis of Rheumatoid Arthritis - Current Paradigm (above) and Proposed Paradigm (below). In the current paradigm systemic autoimmunity and inflammation are responsible for both the inflammatory arthritis and cardiovascular disease. This is not borne out by the evidence. In the proposed model genetic and environmental factors (smoking, microbiome) set the stage for the development of RA in the form of a Pre-RA state. Progression to and severity of RA is then determined by the biomechanical properties (stiffness) of the joints. As people with stiff joints also have stiff arteries, those who develop RA have stiffer arteries and those with the most severe RA have the stiffest arteries.



Psoriatic Arthritis
Current Paradigm Pathogenesis Inflammatory Arthritis and Cardiovascular Disease



Psoriatic Arthritis
Proposed Paradigm of Pathogenesis illustrating Role of Inherited Tissue Biomechanics Properties Contributing to Inflammatory Response to Biomechanical Tensile Forces

Figure 2: Pathogenesis of Psoriatic Arthritis - Current Paradigm (above) and Proposed Paradigm (below). In the current paradigm systemic autoimmunity and inflammation are responsible for the inflammatory arthritis, cutaneous disease and cardiovascular disease. Genetic, acquired and environmental factors set the stage for the development of psoriatic arthritis. However, subsequent development and severity of psoriatic arthritis is determined by the inherited biomechanical properties (stiffness) of the joints. As people with stiff joints also have stiff arteries, those who develop psoriatic arthritis have stiffer arteries and skin and those with the most severe psoriatic arthritis will have the stiffest arteries and skin. In addition to this, the connective tissues of people with psoriatic arthritis develop a prominent inflammatory reaction in response to tensile forces amplifying the destructive effects of biomechanical factors upon connective tissues.

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AIMS

The aims of this study are to determine whether:

1. Articular biomechanical characteristics (joint stiffness) correlates with assessments of arterial stiffness and skin stiffness and;

2. Articular, arterial and cutaneous biomechanical characteristics differ (are stiffer) in people with Rheumatoid Arthritis, Psoriatic Arthritis and Cutaneous Psoriasis compared to other groups;

3. Articular, arterial and cutaneous biomechanical characteristics correlate with the severity of Rheumatoid and Psoriatic Arthritis and Cutaneous Psoriasis;

METHODS

This preliminary cross-sectional study will formally evaluate articular, cutaneous and vascular biomechanical properties (joint, skin and arterial stiffness) in several case and control groups:

Case Groups

1. ACPA-positive Rheumatoid Arthritis (RA);
2. People at risk of developing ACPA-positive RA;
    a. First Degree Relatives of people with ACPA-Positive RA;
    b. People with a positive ACPA blood test who do not have RA;
3. Psoriatic Arthritis (PsA)
4. Cutaneous Psoriasis without psoriatic arthritis

Control Groups

1. Healthy Controls Unrelated to people with RA ;
2. Benign Joint Hypermobility (BJH)

Comparison will be made between biomechanical assessments in the skin, joints and arteries within the different groups to determine if there is a correlation between biomechanical characteristics in the joints, skin and arteries.

The biomechanical characteristics of the joints, skin and arteries will be compared between "cases" from three groups (RA, PsA and psoriasis) compared to three "control groups" - Healthy Controls, people at risk of developing RA and a negative control group – people with benign joint hypermobility.

Within the RA, PsA and psoriasis groups biomechanical assessments of the joints, skin and arteries will be compared to the severity of inflammatory arthritis and skin disease.

Footnote on Rheumatoid Arthritis (RA)

RA is a symmetrical destructive autoimmune inflammatory arthritis and diagnosis has long been made on clinical signs. Approximately 70% of people with RA have a positive blood test for anti-CCP antibodies (ACPAs). This new test has largely replaced Rheumatoid Factor, which occurs in the same group of RA patients but is frequently falsely positive occurring in people with other autoimmune diseases, chronic infections and malignancy. Furthermore, it is now known that ACPAs are present for many years prior to the development of arthritis, are pathogenic contributing directly to joint damage, that ACPA-positive patients have more severe arthritis and that the elevated CV risk occurs principally in this sub-group. It is not known what proportion of people with a positive ACPA blood test will progress to develop RA. The ACPA-blood test now forms an important part of the definition of RA (see Appendix IV). The ACPA-positive subgroup is also more homogeneous than ACPA-negative group, which probably represents a group of phenotypically similar arthritides. For these reasons the Hunter HEART-RA studies have focused on this group and the same sub-group will be the focus of the T-BIRD study.

I. CONCURRENT RECRUITMENT FROM EXISTING STUDIES

The Hunter HEART-RA-2 study (HNEHREC Ref 15/09/16/3.03) currently recruiting at HNE LHD offers an opportunity to study people already undergoing comprehensive assessments of vascular biomechanical properties and RA disease characteristics. Informed consent for participating in Hunter HEART-RA-2 included "permission to contact for future studies". The participants in this study include people with:

1. Rheumatoid Arthritis (RA)
2. Increased risk of developing RA including:
    a. First-degree relatives of people with RA and
    b. Incidentally found to be ACPA-positive on blood test but do not have RA and;
3. Healthy Controls who have no first-degree relatives with RA, Psoriatic Arthritis or Psoriasis.

Participants in this study are undergoing comprehensive cardiovascular biomechanical assessments and assessments for RA activity and severity. These participants have provided consent to be contacted for further research. It would be a minor inconvenience to concurrently enrol them in this additional study to undergo assessments of articular and skin biomechanics that can be conducted in 5 minutes.

II. ADDITIONAL RECRUITMENT

In addition to this we will recruit 3 other groups from clinics:

1. RA with a range of disease severity (defined below).
2. Psoriatic Arthritis (PsA);
3. Cutaneous Psoriasis (with no evidence of Psoriatic Arthritis)
4. Benign Joint Hypermobility Syndrome with a Beighton score≥4

III. "SYRINGE TEST" SUB-STUDY (SKIN ELASTIC MODULUS)

The single most important assessment in this study is that of Elastic Modulus of the skin. This is a measurement that potentially may be confounded by the effect of corticosteroids. Furthermore, this novel method described in the Methods (the "Syringe Test") has never previously been described or evaluated.

Reproducibility and discriminant validity will be evaluated in the 10 patients without RA, PsA or psoriasis enrolled for the main study. This will include 5 with Joint Hypermobility and 5 without joint hypermobility. Corticosteroid exposure will be noted during the study. However, in addition to this, the potential confounding effects of corticosteroid use upon skin Elastic Modulus will be evaluated in a small sub-study.

Ten hospital outpatients about to commence extended treatment with corticosteroids for any condition will undergo the Syringe Test for Skin Elasticity described below. They will be followed up after 3 months of corticosteroid therapy and assessed using the Syringe Test a second time.

Inclusion Criteria

- Any medical condition requiring corticosteroid therapy that does not affect the skin (e.g. giant cell arteritis, asthma, interstitial lung disease or systemic vasculitis).
- Age 18-80 years

Exclusion Criteria

- Conditions affecting the skin such as psoriasis, Systemic Lupus Erythematosus, scleroderma or high alcohol intake;
- Case or Control groups for the study – RA, PsA, psoriasis, Joint Hypermobility;
- Prior corticosteroid exposure.

ASSESSMENTS

Study participants will undergo a panel of assessments including:

A. Standard clinical assessments for Articular Hypermobility
B. Articular Biomechanical Assessments
C. Cutaneous Biomechanical Assessment
D. Vascular Biomechanical Assessment
E. Rheumatoid and Psoriatic Arthritis Disease Severity
F. Severity of Cutaneous Psoriasis (PASI score)

BIOMECHANICAL ASSESSMENTS – PRINCIPLES

There are many ways to assess the biomechanical properties (stiffness /elasticity) of biological tissues. Forces may be applied to produce displacement (tissue distortion) in the form of tension (stretch), compression, torsion (twist) and shear. The magnitude of the displacement in response to applied forces provides an indication of stiffness. Forces may be applied in a dynamic (vibrating / oscillatory) or static (uniform) fashion and forces may be applied as a single uniform force or increase / decrease incrementally. This provides information regarding different tissue components. In this study it is important to select a method that can be used to measure the same biomechanical property in all three tissues (joints, skin and arteries). A very simple assessment of elasticity is to measure the amount of displacement (stress) in response to a force e.g. the increase in length in response to a stretching (tensile) force known as "Strain". The ratio of stress to strain is known as the elastic modulus, in this case since the strain is tension it is also known as tensile modulus.

A. STANDARD CLINICAL ASSESSMENTS FOR ARTICULAR HYPERMOBILITY

BEIGHTON SCORE

The standard clinical assessment for articular hypermobility is the Beighton Score (1). This score is based upon the clinician's assessment of passive joint range of movement (performed by an examiner while the subject is relaxed) of extension and flexion at 9 locations:

1. Extension of the right and left 5th finger metacarpophalangeal joint (bending the 5th finger backwards). If the finger can be extended beyond 90 degrees without causing pain the joint is consider hypermobile.
2. Volar flexion of the thumb. If the thumb can be flexed forwards so that it touches the forearm without causing pain the joint is considered hypermobile.
3. Extension of the elbow. If the elbow can be extended (straightened) beyond 180 degrees (i.e. bent backwards) without causing pain the joint is considered hypermobile.
4. Extension of the knees. If the knees can be extended (straightened) beyond 180 degrees (i.e. bent backwards) without causing pain the joint is considered hypermobile.
5. Flexion of the spine. If the study participant can place their palms flat on the floor without bending their knees their spine is considered to be hypermobile.

This standard assessment of joint mobility has been developed by an expert consensus group for the purpose of conducting epidemiological research. Individuals are considered to be hypermobile if they have a score greater than 3/9. However, this method is limited several of ways.

1. It dichotomises assessments at each joint and then again in summing the scores from the different joints to categorise an individual as hypermobile or not hypermobile.
2. It assumes the existence of a discreet hypermobility state rather than a continuum of joint stiffness
3. Beighton scores may be confounded by ageing. Degenerative arthritis (osteoarthritis) preferentially affects the thumbs, spine and knees reducing range of motion. These joints which are key components of the Beighton score.

BEIGHTON QUESTIONNAIRE

In response to these limitations, efforts have been made to develop assessments of hypermobility free of the confounding effects of ageing and osteoarthritis. A questionnaire based upon the Beighton score (3) is described below.

1. Can you now (or could you ever) place your hands flat on the floor without bending your knees?
2. Can you now (or could you ever) bend your thumbs to touch your forearm?
3. As a child did you amuse your friends by contorting your body into strange shapes or could you do the splits?
4. As a child or teenager did your shoulder or kneecap dislocate on more than one occasion?
5. Do you consider yourself to be double-jointed?

The principle limitation of the questionnaire is that it is subject to recall bias rand is based upon dichotomised assessments.

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B. ARTICULAR BIOMECHANICAL ASSESSMENT: THE HUNTER HYPEREXTENSOMETER (HHEM)

The principle limitations of clinical Beighton score and questionnaire are that they are based upon dichotomised assessments (a joint either is, or is not hypermobile) and that most of the joints assessed are frequently affected by degenerative arthritis (osteoarthritis). The 5th finger meta-carpo-phalangeal (MCP) joint is the only joint in the Beighton scores that is rarely affected by osteoarthritis. Early research (1979) in the field of hypermobility focused on quantitative biomechanical assessments at the index finger MCP joint using a device (the Leeds finger HyperExtensometer - LHEM) shown in Figure 3 below) (1).

The LHEM measured the angular displacement of the 2nd finger meta-carpo-phalangeal (MCP) joint in extension (how far the finger could be bent backwards) in response to a torque applied to extend the joint. The term torque describes rotational force taking into account the length of the length of the lever arm (in this case the finger). If the same force of extension is applied to the tip of two fingers with the same “intrinsic articular stiffness” the laws of physics dictate that it will be easier to extend a longer finger and it will be bent further backwards than a shorter finger in response to the same force. This is overcome by extending the finger using a lever with the fulcrum located directly beneath the MCP joint.

The LHEM has been used to apply a range of torques to produce standard stress-strain curves. The stress strain curves of participants who were clinically hypermobile exhibited differences in the "toe region" with lower torques required to extend the MCP. The "toe region describes the junction between the initial flatter part of the curve where little resistance is met and the second steeper linear part of the stress-strain curve. It is though that the initial minimal resistance represents the initial alignment of collagen fibres in the direction of tissue displacement. At this point the collagen fibres engage tension in the direction of force. As collagen is less elastic, much larger increases in torque are required to produce the same increases in displacement and the curve becomes linear. The key assessment is therefore the torque required to extend the MCP beyond the junction between the "toe" and "linear" regions. This work (1) identified a torque of 2.6 $kgcm^{-1}$ as the minimum to extend the finger into the linear phase of the curve and most practical single measurement for the purpose of quantifying stiffness of this joint.

A similar device, the Hunter Hyperextensometer (HHEM) shown in Figures 4 and 5 below, has been designed, constructed from Meccanno© and tested at the John Hunter Hospital. Subjects are assessed seated in a chair with their wrist and finger strapped to this device mounted on the right arm of the chair. A pulley attached through an axle to a lever arm passively extends the finger. Two-hundred gram weights can be added incrementally to a cradle suspended to the pulley wheel to deliver a range of torques extending the 5th finger MCP. Preliminary studies of the HHEM (2,3) found that three 200 gram weights resting in the 155 gram cradle delivered the torque required to extend the joint to the junction of the "toe" and linear regions and provided the most practical single measurement for the purpose of quantifying stiffness of this joint

The torque delivered with this weight is 0.0259 Nm (2.59 N cm) is remarkably close to the threshold identified using the Leeds device (LHEM). These assessments were well tolerated, highly reproducible and correlate with Beighton scores and CSES skin assessments described below (4).

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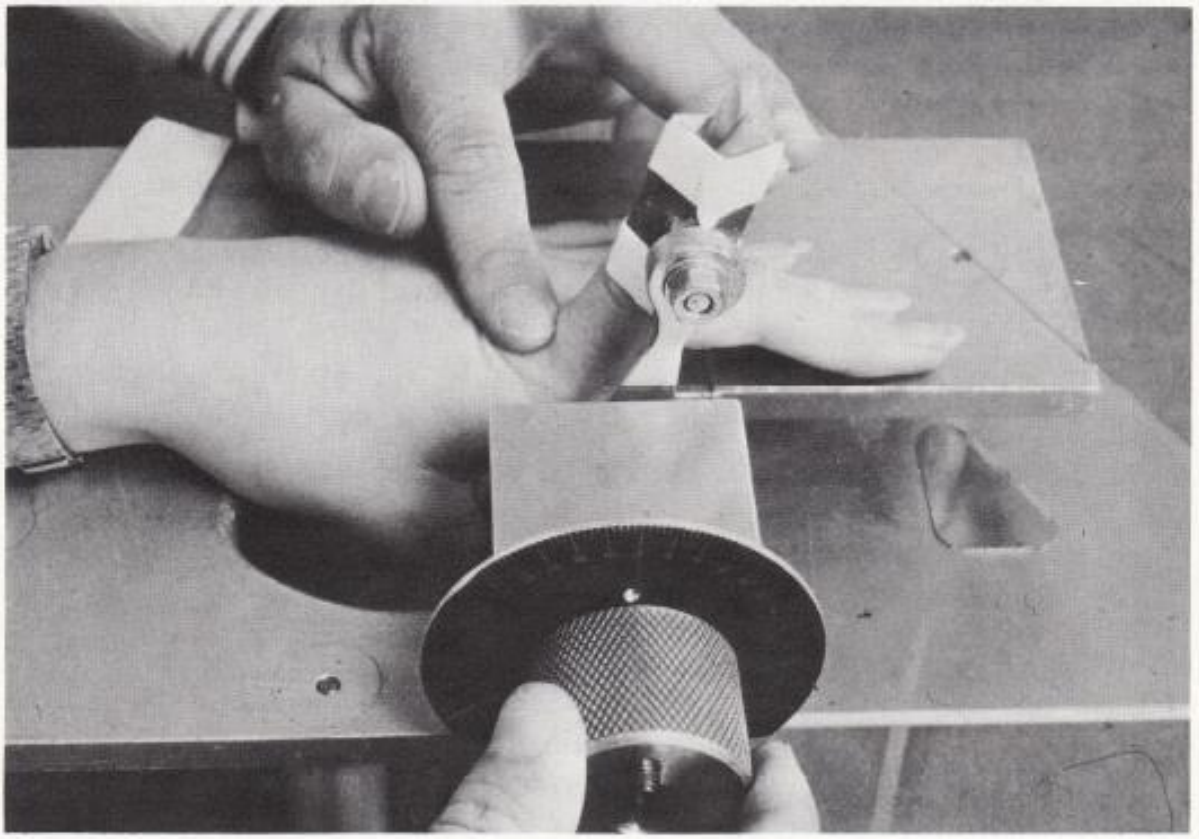
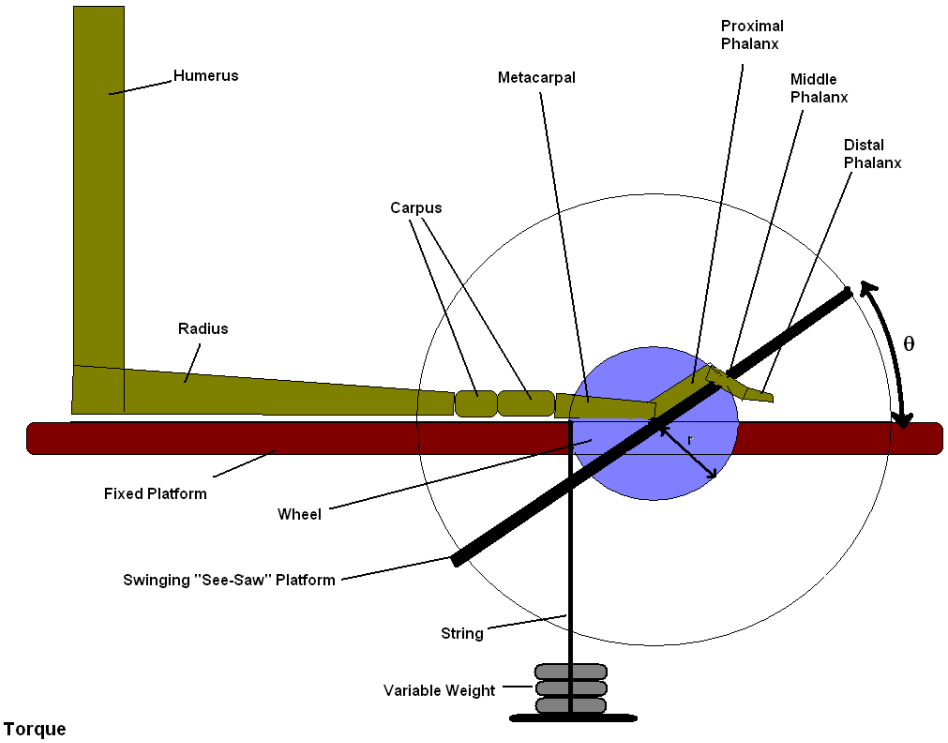


Fig. 2.3. A finger hyperextensometer for the quantification of joint laxity. The finger of the subject is hyperextended at the metacarpophalangeal joint by the application of a pre–set fixed torque. The resultant angle of hyperextension is read off on the dial.

Figure 3 The Leeds Finger Hyper Extensometer (LHEM). The finger of the subject is hyperextended at the 2nd metacarpophalangeal joint by application of a pre-selected fixed torque.



Torque

$\tau = r.F$

r = Wheel Radius

F = downward force on string
= mass (kg) x 9.8 metres /sec ^{2}

θ = the angle between "See-Saw" and the Fixed Platform

r = 0.04 metres
a = 9.8 m/sec ^{2}

To achieve a torque of 2.6kg / cm????

τ

Figure 4: Design for the Hunter Hyperextensometer (HHEM). The upper limb skeleton is represented in green. The wrist (carpus) is held firmly in apposition to the base of the device (brown) with a Velcroe strap. The 5th MCP positioned directly over the rotational axis of a lever arm (black). The lever arm is attached to a pulley wheel (purple) with a radius of 35 millimetres (0.035 metres) from which a fixed weight (755 grams – 0.750 kg) is suspended delivering a standardised torque (T = Force x wheel radius) to extend the finger. The force delivered to the wheel = mass x acceleration dues to gravity (9.82 m^2). The torque delivered to extend the 5th finger MCP using this system is 0.755 x 0.035 x 9.81 = 0.0259 Nm (Newton metres) = 2.59 Ncm regardless of finger length. The angle to which the finger is extended measures the torque required to produce angular displacement to the junction of the "toe" and "linear regions of the stress strain curve for this joint.

Figure 5: The Hunter Hyperextensometer in use. The device has been constructed from Meccanno. The participant's wrist and metacarpophalangeal joints are secured in apposition to the platform. A fixed torque is applied to passively extend the 5th metacarpophalangeal joint by placing 600 grams of weights in the Meccanno cradle suspended from the pulley wheel (radius 35 mm) to deliver a torque of 2.59 N cm. The angular displacement in response to this standard torque is measured in degrees of extension after 60 seconds.

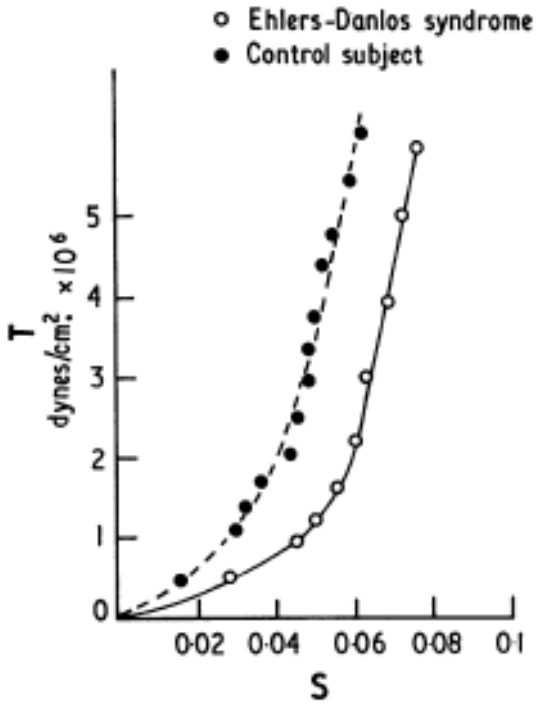
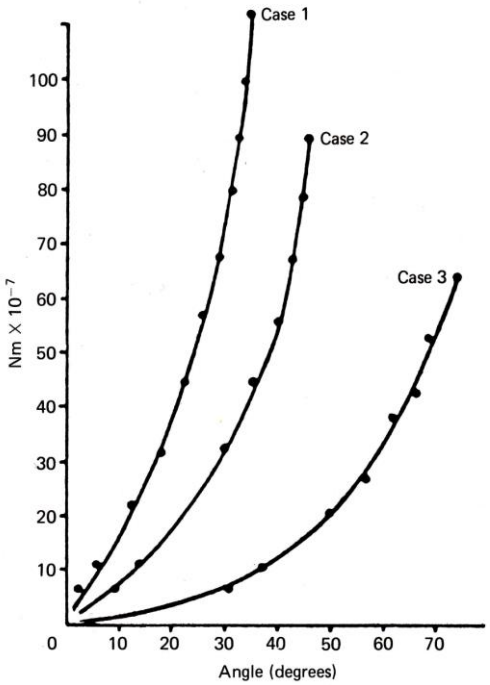


Fig. 5.—Stress/strain curve for intact skin in Ehlers-Danlos syndrome.



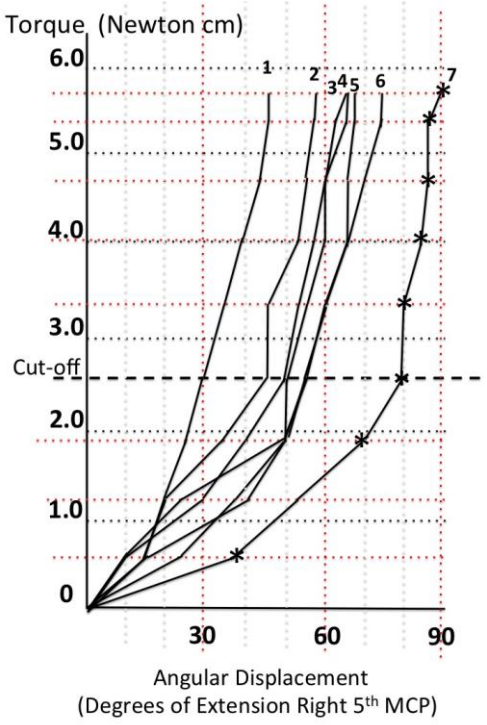


Figure 3 Stress Strain Curves for the Skin from Graham R et al (upper left) and the two Hyperextensometers – Leeds (lower left) and Hunter (lower right). The stress strain curves are all characteristically biphasic with a flat "toe region" and steeper "linear" region. In the toe region the connective tissues deform easily in response to low tensile forces as collagen fibres align in the direction of tension. As the collagen fibres become engaged greater resistance is encountered and the curve becomes linear. The differences between hypermobile and control subjects lie in the "toe region". For the HHEM the limit of the toe region is encountered with an applied torque of 2.59 Newton cm (0.0259 Nm) and provides a single quantitative assessment that discriminates between hypermobile (indicated with *) and control subjects.

C. BIOMECHANICAL ASSESSMENT OF THE SKIN

I. CLINICAL SKIN EXTENSIBILITY SCORE – CSES

While the skin has long been described as being "softer" in BJH a simple method for quantifying this in biomechanical terms was described recently. Farmer et al (1) developed a simple Clinical Skin Extensibility Score (CSES) to quantify skin elasticity using methods analogous to tensile modulus. The displacement described as the increase in distance between two dots drawn on the skin on the back of the hand in response to a tensile force applied by the examiner simply by stretching the skin manually. This is adjusted for skin thickness measured as the thickness of a fold of skin measured using Harpenden skin-fold calipers. CSES measures the displacement when tension is applied to stretch the skin to the junction of the "toe" and "linear" regions of the stress-strain curve and is therefore comparable with measurements using the Hunter Hyperextensometer. CSES have been found to be highly reproducible at our centre and correlate with clinical Beighton scores and measurements of articular stiffness using the hyperextensometer (2).

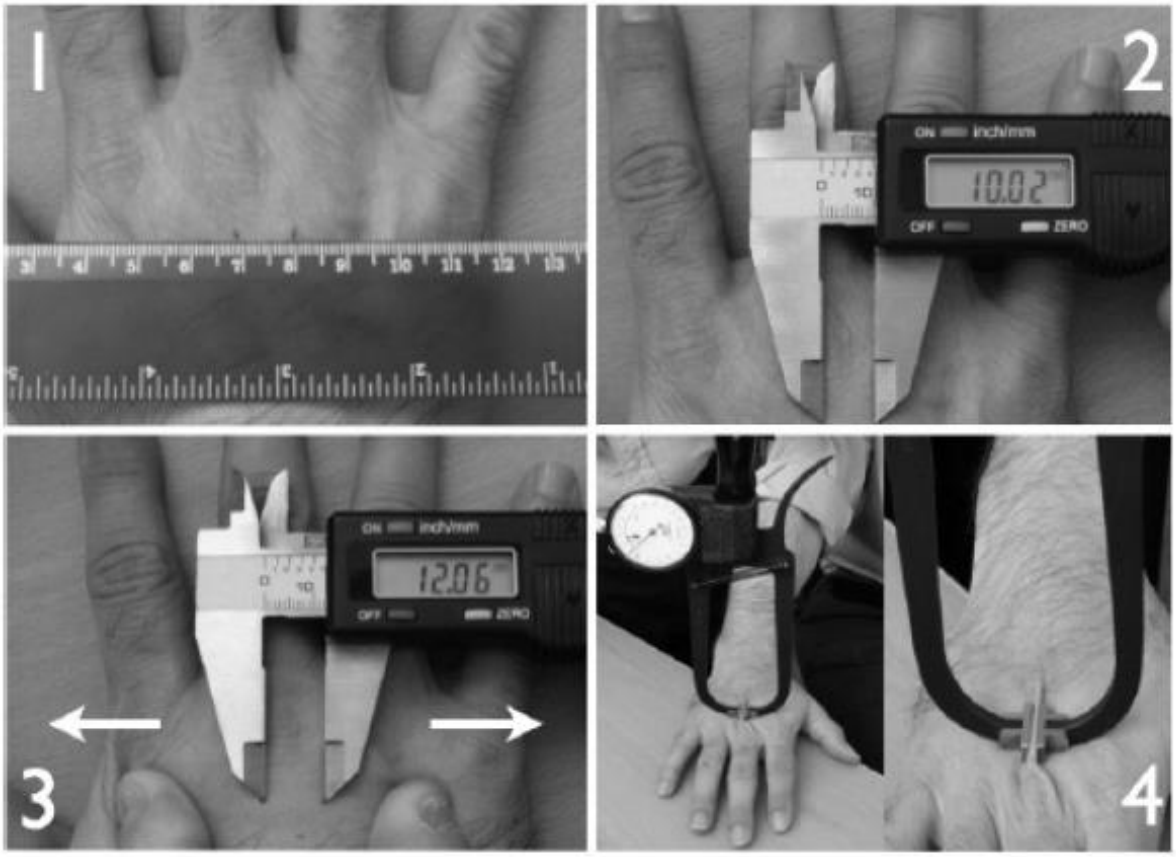


Figure 1. Skin extensibility measurements used to derive the corrected skin extensibility score. 1. On the dorsum of the right hand positioned on a flat surface, using a simple ruler, 2 dots are marked between the middle third of the second and third metacarpals 10 mm apart. 2. The distance between the inner aspects of the 2 dots is measured accurately using an electronic caliper (± 0.01 mm). 3. A maximal lateral stretching force is applied in a perpendicular fashion (arrows) to the metacarpals until the skin is taut and the increment is measured. A percentage increment can be calculated from the measurements derived in panels 2 and 3. 4. Skin-fold thickness is measured between the 2 dots using a Harpenden caliper. Skin thickness is skin-fold thickness/2.

Figure 6 Clinical Skin Extensibility Scores (CSES) using the method described by Farmer et al.

II. QUANTIFICATION OF SKIN STIFFNESS

Elastic Modulus – The Method of Grahame et al

In 1970 Rodney Grahame described a more detailed method to quantify skin elasticity (3) using a suction cup applied to the forearm, with negative pressure (suction) generated by a syringe and quantified using a mercury manometer. He described stress-strain curves using a range of suction cup sizes and then used the device to quantify effects of age, gender and pregnancy upon skin elasticity. This method was capable of providing quantitative measurements to produce Stress Strain curves and calculate Elastic Modulus. However, the method required specialised equipment.

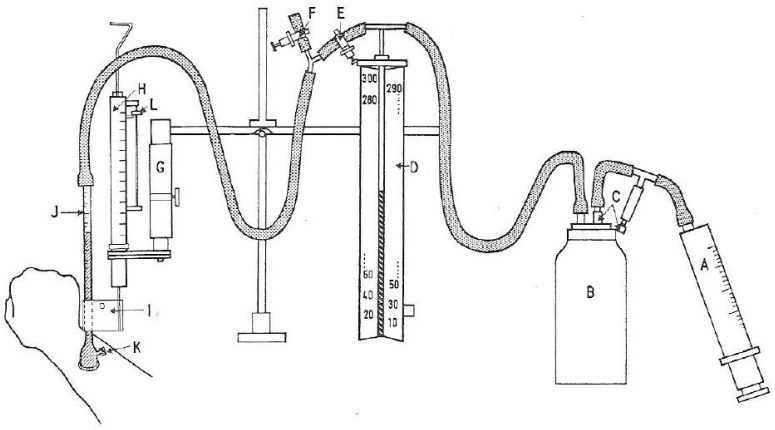
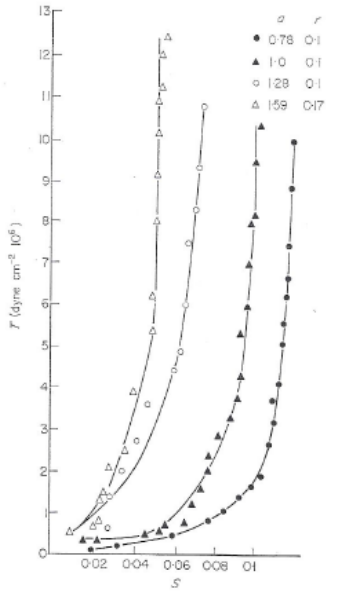
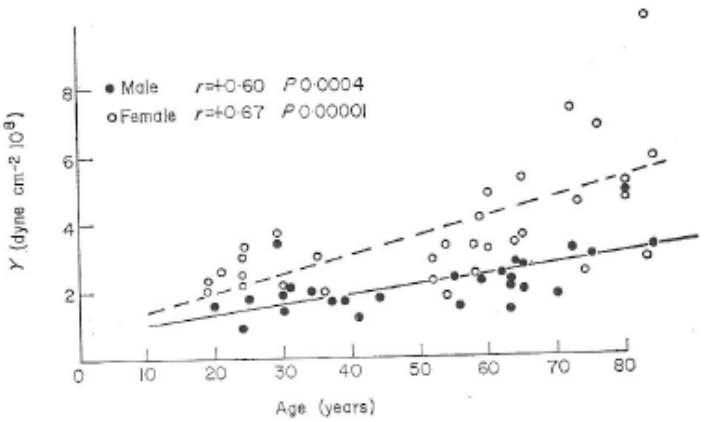


FIG. 2. Diagrammatic representation of the apparatus for measuring skin elasticity *in vivo* (see text).





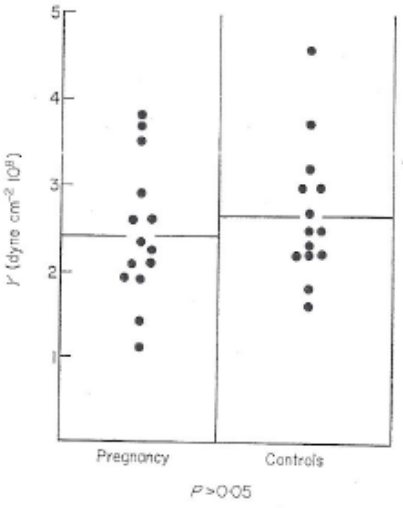


Figure 7 Figures from Grahame R at al showing the device for quantifying skin elastic modulus (top left), preliminary work evaluating different sized suction cups (top right), gender differences (bottom left) and effects of pregnancy (bottom right).

Elastic Modulus: The "Syringe Test"

A simplified method has been developed to quantify skin elastic modulus in this study and is illustrated in the Figure 8 below. Two syringes will be connected by pneumatic tubing (oxygen tubing). Syringe 1 has the plunger removed so that the barrel can be applied to the skin. The site selected is the ventral aspect of the dominant forearm in the supinated position at the mid-point between the biceps tendon and distal radius. Syringe 2 contains the plunger lubricated internally with olive oil to reduce friction and held vertically with a weight attached to the plunger to generate a negative pressure drawing the skin into the barrel of Syringe 1. The Syringe and weights are held thus for 5 seconds. The same cradle and weights that are used for the HHEM will be used for this assessment. Strain will be quantified simply as the volume of air drawn into Syringe 2 measured using the calibrations on side of the syringe. Elastic modulus calculated as the displacement (volume of air drawn into syringe 2) divided by the negative pressure applied to the syringe. Corrected elastic modulus will be calculated by dividing the raw elastic modulus by the skin thickness calculated as half the skin-fold thickness measured with Harpenden calipers.

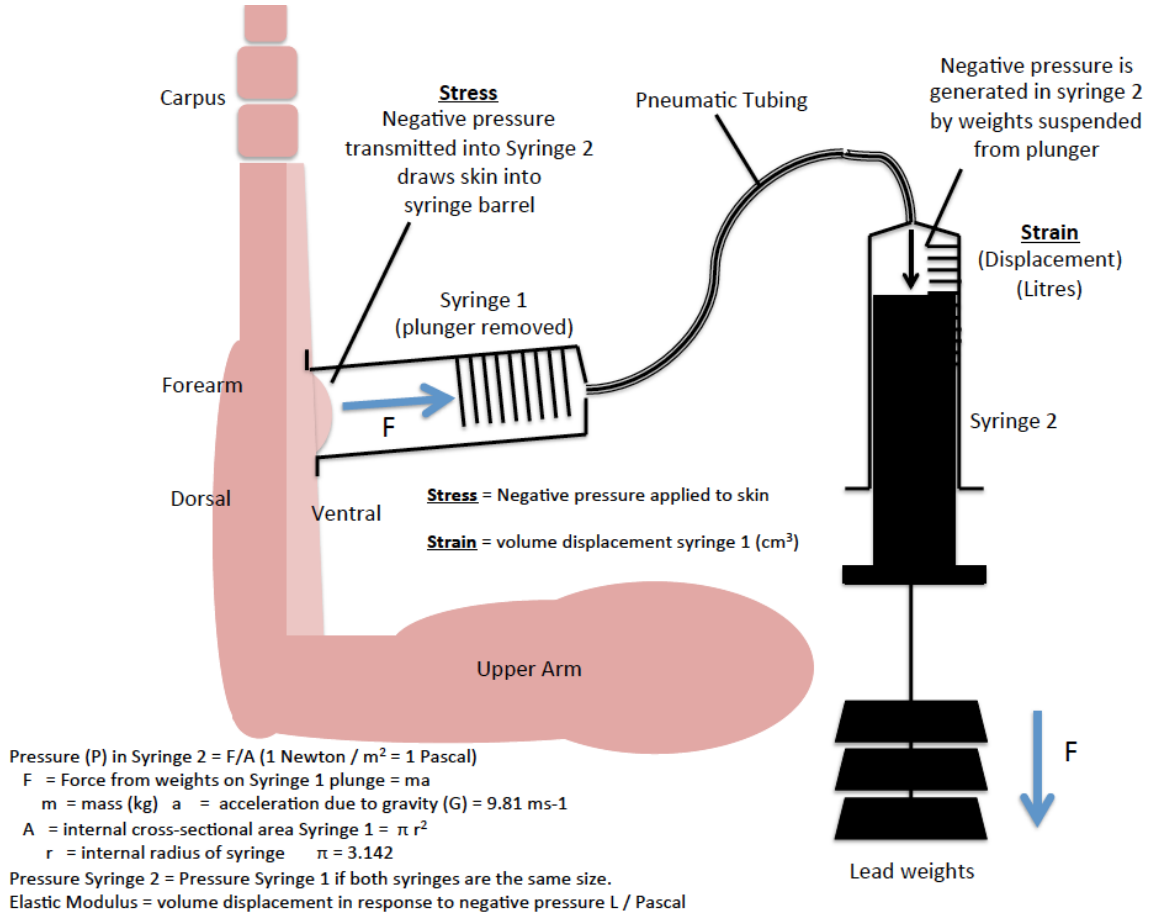


Figure 8 Skin Elastic Modulus - the Simplified Method used to Quantify Skin Stiffness (Elastic Modulus) described as volume displacement in response to a negative pressure (suction) applied to the ventral aspect of the forearm.

While previous studies have evaluated the skin on the dorsum of the hand this is not feasible using this method as air-tight seals cannot be reliably obtained at this site due to the boney architecture. The ventral aspect of the forearm has been selected as a site easily accessible, with no issues regarding boney contour. The method has been tested at this site in a single participant (the Chief investigator), is well-tolerated and produces the expected stress-strain curve. In this study 10 participants with and without clinical hypermobility will be more fully assessed with a range of Stresses (weights) and syringe combinations. This data will be used to generate stress-strain curves for the method and used as the basis for decisions regarding feasibility and discriminant validity of a single measurement. Assessments will be performed twice by

two observers to calculate intra- and inter-observer reproducibility. The potential effect of corticosteroids will be evaluated in the Syringe Test Sub-Study described above.

References

1. Farmer A et al J Rheumatol 2010, 37 (7) 1513-1518.
2. Oakley SP and Tsai J. Australian Rheumatology Association Annual Scientific Meeting, 2012
3. Grahame R Clin Sci 1970: 39; 223-8. A Method for measuring Skin Elasticity in vivo with Observations of the Effects of Age, Sex and Pregnancy.

D. VASCULAR BIOMECHANICAL ASSESSMENTS

The platform of vascular assessments employed in these studies is described in detail in the protocols for Hunter HEART-2. These assessments include Endothelial function measured by EndoPAT and aortic stiffness measured using the SphygmoCor system. Both assessments are non-invasive, completely safe and well tolerated.

ENDOPAT

EndoPAT measures the magnitude of the pulse in the index finger. The increase in the magnitude of the pulse after a period of complete occlusion of blood flow to the arm is a measure of the increased dilation in the arteries and expressed as a ratio or index (pulse magnitude after occlusion / pulse magnitude prior to occlusion). While it is considered to principally reflect vascular smooth muscle relaxation in response to endothelial cell nitric oxide production it is also influenced by stiffness of the connective tissue scaffold that encases the blood vessel and is thus a measurement of the displacement (dilation) in response to a tensile force (luminal distension pressure) i.e. tensile modulus of the arterial wall. It is thus analogous to the CSES and HHEM measurements (described above).

SPHYGMOCOR

Aortic Stiffness measured as Carotid-to-Femoral Pulse Wave Velocity (SphygmoCor system). This system simply measures the velocity of the transmitted pulse down the aorta. It is mathematically related to the stiffness of the vessel wall. While it is a valuable composite assessment of the combined effects of all cardiovascular risk factors it is conceptually a very different and indirect method of measuring arterial stiffness.

E. RHEUMATOID AND PSORIATIC ARTHRITIS DISEASE SEVERITY

Participants with Rheumatoid Arthritis or Psoriatic Arthritis will have data collected regarding:

- Disease duration (years);
- Clinical Disease Activity Scores (DAS28): composite disease activity measures based upon tender and swollen joint counts in 28 joints, ESR and CRP blood tests and patient global score for pain (detailed in the Appendices). These are standard assessments of rheumatoid and psoriatic arthritis in clinics and clinical trials. No additional blood will be drawn for the purpose of this study.
- Psoriasis Non-articular manifestations): assessment for enthesitis (inflammation of tendon attachments), skin and nail involvement are standard assessments in patients with Psoriatic Arthritis patients.
- Joint damage (X ray evidence) of articular damage and severity and X rays are a routine part of clinical care. Modified Sharp van der Heidje radiographic scores are the standard radiographic outcome assessments in clinical trail and are described fully in the Appendices.
  Reference: Van der Heidje D et al J Rheumatol 1999; 26: 743-5.
- Anti-Rheumatic Medications
  - Conventional Disease-Modifying Anti-Rheumatic Drugs (cDMARDs) including methotrexate, leflunomide, sulfasalazine, hydroxychloroquine.
  - Biologic DMARDS (bDMARDs) including TNF inhibitors (etanercept, adalimumab, golimumab, certolizumab, infliximab), Interleukin-6 blockade (tocilizumab), lymphocyte depletion (rituximab), cell-signalling blockage (abatacept), interleukin 12 and 23 blocka=de (ustekinemab) and interleukin-17 blockade (secukinemab)
  - Small Molecules: the JAK Inhibitor tofacitinib
  - Corticosteroids
  - Non-Steroidal Anti-inflammatory Drugs

An overall summary of Disease Severity will be based upon disease activity and treatment intensity to generate a grade on a scale of 0-5:

1. No Disease: No evidence of inflammatory arthritis and not taking anti-rheumatic medications (excluding NSAIDs). This will include ACPA-positive participants with no evidence of RA – the so-called "Pre-RA" group
2. Mild Disease Severity: Currently in remission using cDMARDs alone for greater than 6 months;
3. Moderate Disease Severity: Currently not in remission and receiving conventional DMARDs only for greater than 6 months;
4. High Disease Severity: Currently in remission with bDMARDs or small molecules for greater than 6 months.
5. Extreme Disease Severity: Currently not in remission and receiving bDMARDs or "small molecules" for greater than 6 months.

ACR / EULAR Definition of Remission for Rheumatoid Arthritis

- Tender joint count ≤1 and
- Swollen joint count ≤1 and
- C-reactive protein ≤1 mg/dL and
- Patient global assessment ≤1 (on a 0–10 scale)

Reference: Felson DT et al Arthritis Rheumatism 2011: 63; 573-586

INCLUSION CRITERIA

The study will include:

- 100 people with ACPA-positive RA as defined by 2010 ACR EULAR Criteria (1) (see appendix) including but nor restricted to participants in Hunter HEART-RA-2.1, Hunter HEART-RA-1.
- Participants in the Hunter HEART-RA-2.2 Study. This includes:
    - 50 First Degree Relatives of People with Rheumatoid Arthritis
    - 50 Healthy Controls
    - 50 people with anti-CCP antibodies by blood test without RA or first degree relative with RA
- Patients with Psoriatic Arthritis

Case Groups

1. ACPA-positive Rheumatoid Arthritis (RA) (N=100);
2. People at risk of developing ACPA-positive RA;
    a. First Degree Relatives of people with ACPA-Positive RA (N=50);
    b. People with a positive ACPA blood test who do not have RA (N=50);
3. Psoriatic Arthritis (PsA) as defined by the CASPAR Criteria (2) (N=25) (see appendix)
4. N=25 Cutaneous Psoriasis without psoriatic arthritis (N=25)

Control Groups

1. Healthy Controls Unrelated to people with RA (N=50);
2. Benign Joint Hypermobility defined as a Beighton Score > 4 (BJH) (N=25)

References:

1. Aletaha D et al Arthritis Rheumatism 2010; 62: 2569-81.
2. Taylor W, Gladman D, Helliwell P, et al. Arthritis Rheum. 2006;54:2665-2673

EXCLUSION CRITERIA

1. Pain / Discomfort. Assessments of Articular Elasticity will only be performed in participants without causing pain or discomfort. By way of screening participants will first have the assessment fully explained to them and then be asked to demonstrate 5th finger passive extension on themselves (i.e. they will bend back the 5th finger themselves).
2. Other hypermobility states. Benign Joint Hypermobility is the most common form of hypermobility. Other more serious forms of hypermobility include Marfan Syndrome, Ehler's Danlos Types 1, 2 and 4 are all rare conditions and have well understood collagen gene mutations. They can be identified clinically excluded from this study and directed to appropriate medical care.
3. Neurological disorders and conditions including but not restricted to cerebrovascular accident, multiple sclerosis, motor neurone disease, spinal cord injury. These conditions influence muscle tone and will impact upon assessments of articular mobility.

METHODOLOGICAL ISSUES

1. Confounding

As the study is observational in design the most significant challenge will confounding from joint destruction due arthritis and the effects corticosteroid exposure. These may differentially affect biomechanical properties in different tissues. While corticosteroids reduce inflammation they can cause skin thinning and fragility and are associated with elevated CV risk. Therefore corticosteroid exposure will be calculated in terms analogous to smoking exposure ("prednisone years" = average daily dose in mg x duration of therapy as estimated by the patient). RA can result in diminished range or increased range of joint motion depending upon the type of articular damage incurred. Radiographic damage will be evaluated from clinical images and graded using the methods described in the appendix. Other potential confounders including alcohol and tobacco exposure will be noted. The stiffness of all connective tissues increases with age. Arterial stiffness as evaluated by carotid-femoral pulse wave velocity is strongly influenced by ageing. However, assessments using EndoPAT are not significantly affected by ageing (1).

2. Selection Bias

The study is cross-sectional case (several groups) versus control (several groups) and as such there is potential for selection bias.

Blinding

The key assessments to this study are the evaluation of the skin. These will be performed by an assessor blind to the results of assessments of articular and arterial stiffness. The key arterial assessment of stiffness is the EndoPAT is completely automated.

References

1. Hamburg NM, Palmisano J, Larson MG, Sullivan LM, Lehman BT, Vasan RS, Levy D, Mitchell GF, Vita JA, Benjamin EJ. Hypertension. 2011 Mar;57(3):390-6

STATISTICAL ANALYSIS

The study is entirely exploratory and there is no data upon which to base estimates of sample size. This study will co-recruit from the Hunter HEART-RA-2 study, which has been powered to test a different hypothesis. In total there will be:

- 100 people with RA (from Hunter HEART-RA 2 and outpatients);
- 50 healthy control subjects (from Hunter HEART-RA 2);
- 50 first-degree relatives of people with RA (from Hunter HEART-RA 2);
- 50 people who have a positive ACPA blood test but no signs RA (from Hunter HEART-RA 2);
- 25 Psoriatic arthritis (outpatients)
- 25 Cutaneous psoriasis
- 25 Benign Joint Hypermobility defined as a Beighton Score > 4

A. PRELIMINARY ANALYSIS

The distribution of the data will be evaluated to determine whether biomechanical properties are distributed normally, skewed or bi-modal. The "Syringe Test" will be performed twice by two different assessors in the first 10 participants to determine the intra- and inter-observer reproducibility. The Syringe Test Sub-Study will be performed in 10 additional participants at 2 time points to evaluate the possible effect of corticosteroids upon skin stiffness. Paired t test will be used to determine whether significant change has occurred during 3 months treatment with corticosteroids.

B. RELATIONSHIP BETWEEN ARTICULAR, ARTERIAL AND CUTANEOUS BIOMECHANICAL ASSESSMENTS

Direct comparison will be made between articular (Hyperextensometer) assessments, skin (CSES) and vascular (EndoPAT) assessments using appropriate statistical methods determined by the distribution of the data.

C. COMPARISON OF BIOMECHANICAL PROPERTIES BETWEEN GROUPS

Biomechanical assessments will be compared between the various Case and Control groups using appropriate statistical methods determined by the distribution of the data.

D. RELATIONSHIP BETWEEN BIOMECHANICAL ASSESSMENTS AND ARTHRITIS SEVERITY

Within RA and PsA groups biomechanical assessments will be compared with arthritis severity as defined above using methods determined by the data.

INTERIM ANALYSES

Interim analyses will be performed within each group upon :

1. 20% recruitment within each group;
2. 50% recruitment within each group;
3. 100% recruitment within each group.

APPENDICES

APPENDIX I: BEIGHTON CRITERIA FOR HYPERMOBILITY AND DIAGNOSTIC CRITERIA FOR BENIGN JOINT HYPERMOBILITY SYNDROME

Table 1. Nine-Point Beighton hypermobility score[14].

	R	L
The ability to		
(1) Passively dorsiflex the 5th metacarpophalangeal joint to ≥ 90°	1	1
(2) Oppose the thumb to the volar aspect of the ipsilateral forearm	1	1
(3) Hyperextend the elbow to ≥ 10°	1	1
(4) Hyperextend the knee to ≥ 10°	1	1
(5) Place hands flat on the floor without bending the knees	1	
Maximum total	9	

One point may be gained for each side for maneuvers 1–4 so that the hypermobility score will have a maximum of 9 points if all are positive.

Table 3. Revised diagnostic criteria for the benign joint hypermobility syndrome (BJHS). The BJHS is diagnosed in the presence of 2 major criteria, or one major and 2 minor criteria, or 4 minor criteria. Two minor criteria will suffice where there is an unequivocally affected first-degree relative. BJHS is excluded by presence of Marfan or Ehlers-Danlos syndrome [other than the EDS Hypermobility type (formerly EDS III) as defined by the Ghent 1996[8] and the Villefranche 1998[9] criteria, respectively]. Criteria Major 1 and Minor 1 are mutually exclusive, as are Major 2 and Minor 2.

Major criteria

1. A Beighton score of 4/9 or greater (either currently or historically)
2. Arthralgia for longer than 3 months in 4 or more joints

Minor criteria

1. A Beighton score of 1,2, or 3/9 (0, 1, 2, or 3 if aged 50+)
2. Arthralgia (≥ 3 mo) in 1–3 joints, or back pain (≥ 3 mo), spondylosis, spondylolysis/spondylolisthesis
3. Dislocation/subluxation in more than one joint, or in one joint on more than one occasion.
4. Soft tissue rheumatism ≥ 3 lesions (e.g., epicondylitis, tenosynovitis, bursitis).
5. Marfanoid habitus (tall, slim, span/height ratio > 1.03, upper:lower segment ratio < 0.89, arachnodactyly [+ Steinberg/wrist signs].
6. Abnormal skin: striae, hyperextensibility, thin skin, papyraceous scarring.
7. Eye signs: drooping eyelids or myopia or antimongoloid slant.
8. Varicose veins or hernia or uterine/rectal prolapse.

Reference

Grahame R et al J Rheumatol 2000: 27(7); 1777-9. Classification Criteria. The Revised (Brighton 1998) Criteria for the Diagnosis of Benign Joint Hyper Mobility Syndrome.

APPENDIX II: HYPERMOBILITY – DATA ENTRY SHEET

Date: ID Sticker:

Age (years):

Gender: Male / Female

Group RA / Healthy Control / FDR of RA / Incidental ACPA positive / PsA / Psoriasis / BJHS

Height (cm) Arm Span (cm) Weight (kg)

Questionnaire

1. Can you now (or could you ever) place your hands flat on the floor without bending your knees? ☐
2. Can you now (or could you ever) bend your thumb to touch your forearm? _____. ☐
3. As a child did you amuse your friends by contorting your body into strange shapes or could you do the splits? ☐
4. As a child or teenager did your shoulder or kneecap dislocate on more than one occasion? _____. ☐
5. Do you consider yourself to be double-jointed? _____. ☐

Questionnaire score / 5 _____.

Beighton Score

	Right	Left
5th Finger Hyperextension	☐	☐
Finger PIP hyperextension	☐	☐
Thumb Abducts to Forearm	☐	☐
Elbows Hyperextend	☐	☐
Knees Hyperextend	☐	☐
Lumbar Spine Flexion	☐	

Beighton Score _____ /9

Benign Joint Hypermobility (Please tick)

Major Criteria BJHS

- Beighton > 4/9 (Current or Historical) …… ☐
- Arthralgia > 3 months in ≥4 joints…….. ☐

Minor Criteria BJHS

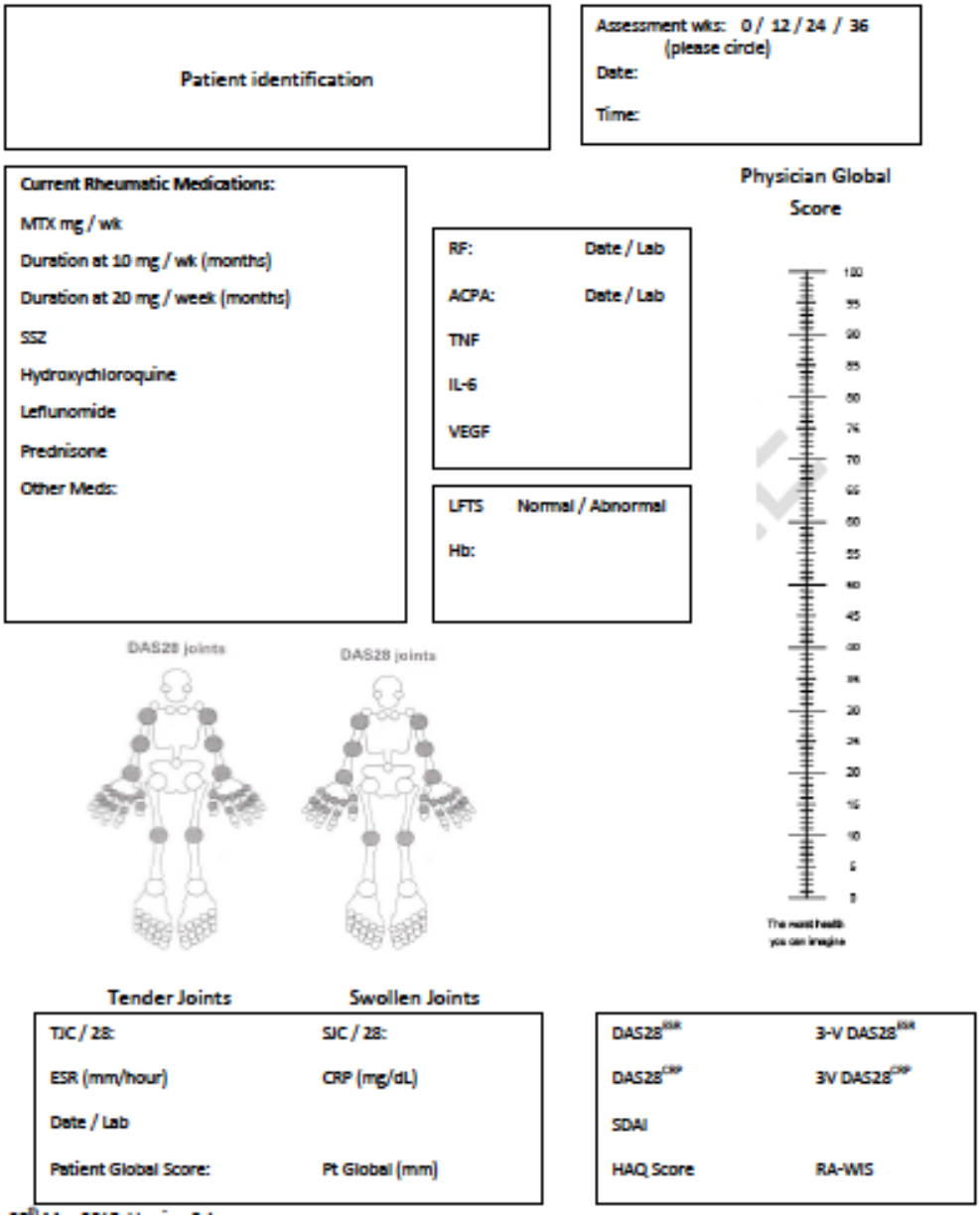
- Beighton 1,2 or 3 (0 if over 50)…….. ☐
- Arthralgia > 3 mo (>4 jts) or back pain…….. ☐
- Dislocation > 1 joint > 1 occasion…….. ☐
- Soft tissue rheumatism (enthesitis, bursitis)……. ☐
- Marfanoid Habitus…….. ☐
- Abnormal Skin…….. ☐
- Eye signs…… ☐
- Varicose veins…….. ☐

BJHS Yes / No (please circle)

Biomechanical Assessment

Skin Stretch (Increase 0.1 mm)	Skin fold thickness (0.1 mm)	CSES	HHEM Angular Displacement (Degrees)

APPENDIX III: RHEUMATOID AND PSORIATIC ARTHRITIS DISEASE ACTIVITY



ARTHRITIS SEVERITY	
Arthritis Disease Duration at time of assessment (years)	
Arthritis in Remission	YES / NO
Treatment	cDMARDs / bDMARDs
Modified van der Heidje Sharpe Score Hands	
Feet	
Total	
Corticosteroid exposure (average daily prednisone dose x yrs exposures)	
Arthritis Severity Grade (please tick below)	
1. Mild Disease Severity: In remission on cDMARDs	
2. Moderate Disease Severity: Not in remission on cDMARDs	
3. High Disease Severity: In remission with bDMARDs	
4. Extreme Disease Severity: Not in remission on bDMARDs	
Anti-CCP (date:) Rheumatoid Factor (date:)	

APPENDIX IV: EULAR / ACR 2010 DIAGNOSTIC CRITERIA FOR RHEUMATOID ARTHRITIS

Table 3. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis

	Score
Target population (Who should be tested?): Patients who	
1) have at least 1 joint with definite clinical synovitis (swelling)*	
2) with the synovitis not better explained by another disease†	
Classification criteria for RA (score-based algorithm: add score of categories A–D; a score of ≥6/10 is needed for classification of a patient as having definite RA)‡	
A. Joint involvement§	
1 large joint¶	0
2–10 large joints	1
1–3 small joints (with or without involvement of large joints)#	2
4–10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)**	5
B. Serology (at least 1 test result is needed for classification)††	
Negative RF *and* negative ACPA	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)‡‡	
Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1
D. Duration of symptoms§§	
<6 weeks	0
≥6 weeks	1

From Aletaha D et al Arthritis Rheumatism 2010; 62: 2569-81.

A score > 6 is sufficient for a diagnosis of rheumatoid arthritis.

Low positive Anti-CCP is > the upper limit of normal and < 3 times the upper limit of normal

High positive Anti-CCP is > 3 times the upper limit of normal

Hunter Area Pathology Service Reference Ranges:

Negative	<20 EU / mL
Low Positive	21-60 EU / mL
High Positive	>60 EU / mL

APPENDIX V: 28 JOINT DISEASE ACTIVITY SCORE FOR RHEUMATOID ARTHRITIS AND PSORIATIC ARTHRITIS

DAS28 = 0.56. (√28 TJC) + 0.28.(√SJC) + 0.70.ln (ESR) + 0.014. (PGA)

TJC 28 Tender joint count

SJC 28 swollen joint count

ESR Erythrocyte Sedimentation Rate (mm/hour)

PGA Patient Global Assessment by Visual Analogue Scale

Reference:

SDAI Smolen JS, Breedveld FC, Schiff MH, *et al.* Rheumatology (Oxford) 2003; 42: 244-57.

APPENDIX VI: MODIFIED SHARPE VAN DER HEIDJE SCORE FOR RADIOLOGICAL DAMAGE IN RHEUMATOID ARTHRITIS AND PSORIATIC ARTHRITIS

Initials of the patient's name : _____ Date : _____ Visit : 1 2 3 4 5

File CHUS : _____

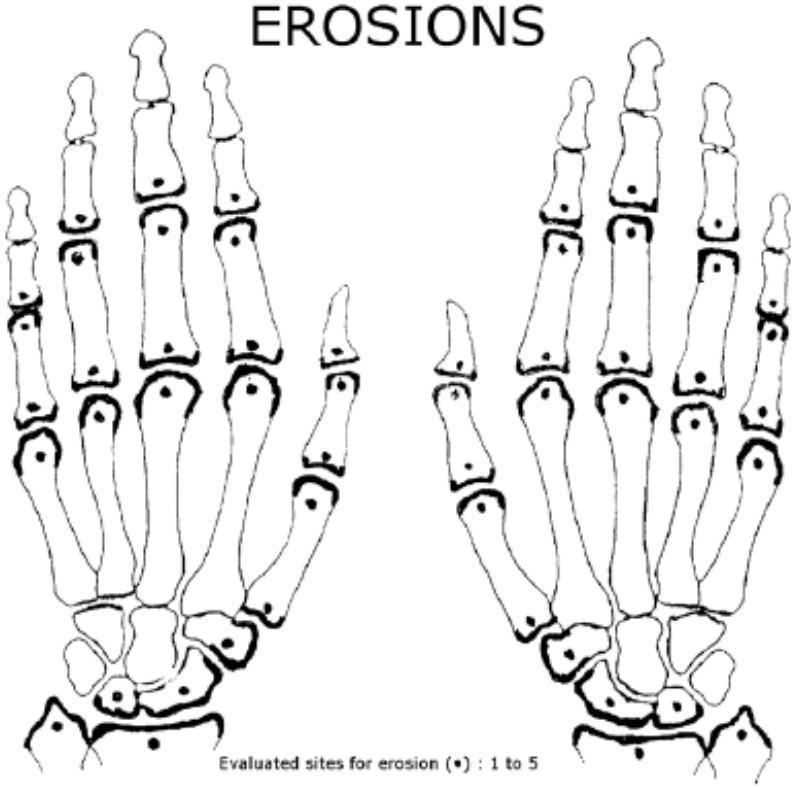
EROSIONS

Score

Hands : _____

Feet : _____

Total : _____

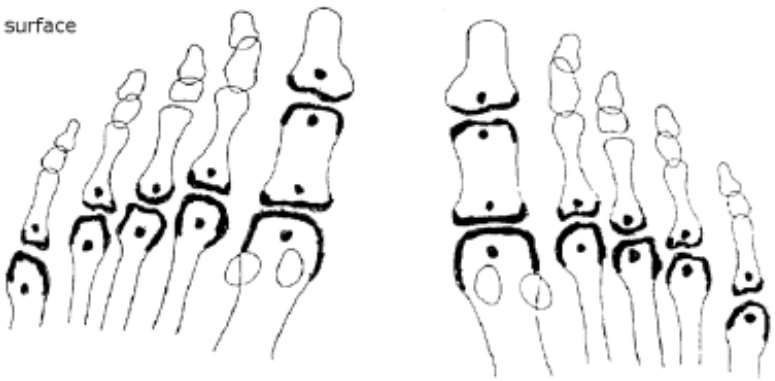


Evaluated sites for erosion (•) : 1 to 5

SCORE

1 = Discreet lesion
2 to 4 = Surface dependant
3 = Reaches >50% of the joint surface
5 = Bone collapsus

P.S. The erosion noted can be caused by R.A. and arthrosis.



Evaluated sites for erosion (•) :
1 to 10 (5 for each side of the joint)

_____ Signature of the evaluator

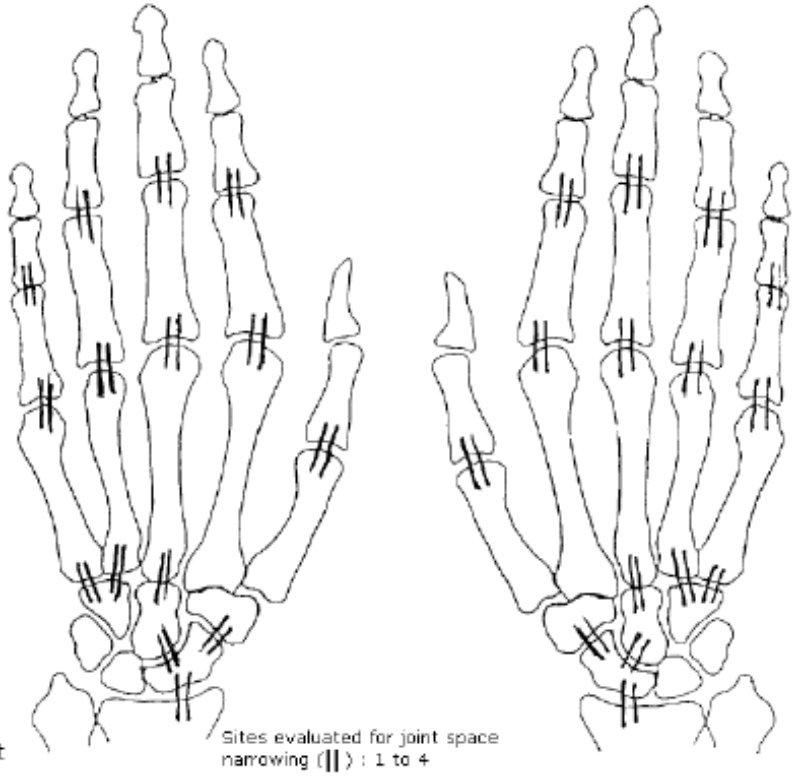
_____ Date of the evaluation

Initials of the patient's name : _____ Date : _____ Visit : 1 2 3 4 5

File CHUS : _____

JOINT SPACE NARROWING

Defined periarticular osteopenia ☐



Sites evaluated for joint space narrowing (||) : 1 to 4

Score

Hands : _____

Feet : _____

Total : _____

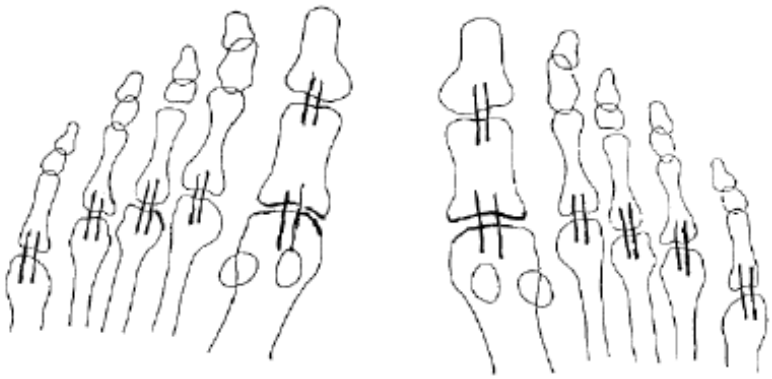
Score

1 = Focal or not important enough to quote 2

2 = >50% space left (generalized narrowing)

3 = <50% space left or subluxation

4 = Complete ankylosis or luxation



Sites evaluated for joint space narrowing (||) : 1 to 4

_____ Signature of the evaluator

_____ Date of the evaluation

APPENDIX VII: DIAGNOSTIC CRITERIA FOR PSORIATIC ARTHRITIS

Table. The CASPAR classification criteria for PsA

To be classified as having PsA, a patient must have inflammatory articular disease (joint, spine, entheseal) with ≥ 3 of the following 5 points:

Criterion	Description
1. Evidence of psoriasis (one of a, b, c):	
(a) Current psoriasis[a]	Psoriatic skin or scalp disease currently present, as judged by a rheumatologist or a dermatologist
(b) Personal history of psoriasis	A history of psoriasis obtained from patient or family physician, dermatologist, rheumatologist, or other qualified health care professional
(c) Family history of psoriasis	A history of psoriasis in a first- or second-degree relative by patient report
2. Psoriatic nail dystrophy	Typical psoriatic nail dystrophy, including onycholysis, pitting, and hyperkeratosis observed on current physical examination
3. Negative test result for RF	By any method except latex but preferably by ELISA or nephelometry, according to the local laboratory reference range
4. Dactylitis (one of a, b):	
(a) Current	Swelling of an entire digit
(b) History	A history of dactylitis recorded by a rheumatologist
5. Radiological evidence of juxta-articular new bone formation	Ill-defined ossification near joint margins (excluding osteophyte formation) on plain x-ray films of hand or foot

CASPAR, CIASsification criteria for Psoriatic ARthritis; PsA, psoriatic arthritis; RF, rheumatoid factor; ELISA, enzyme-linked immunosorbent assay.

[a] Current psoriasis scores 2; all other items score 1.

Reference

Taylor W, Gladman D, Helliwell P, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006;54:2665-2673

APPENDIX VIII: ENTHESITIS SCORE IN PSORIATIC ARTHRITIS

Attachment 7: LEI Worksheet

Patient ID: _____ Date: _____

Please indicate whether pain or tenderness is absent or present at the following sites:

Site	Pain Absent	Pain Present
Lateral elbow epicondyle		
Left	☐ (0)	☐ (1)
Right	☐ (0)	☐ (1)
Medial femoral condyle		
Left	☐ (0)	☐ (1)
Right	☐ (0)	☐ (1)
Achilles tendon insertion		
Left	☐ (0)	☐ (1)
Right	☐ (0)	☐ (1)
TOTAL SCORE *Sum the number of ticks in 'pain present' column*		☐ / 6

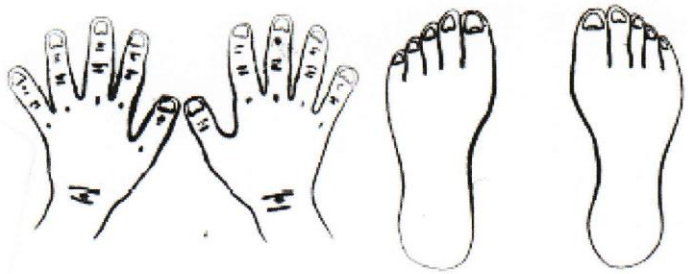
APPENDIX IX: DACTYLITIS SCORES IN PSORIATIC ARTHRITIS

Attachment 5: Dactylitis assessment

DACTYLITIS WORKSHEET

Protocol No. CNTO148PSA4001	Date (DD MM YY)	Country ID	Site ID	Patient No.

Please indicate dactylitic joints



Finger or Toe	Tenderness Score: response to squeeze *0 no tenderness* *1 tender* *2 tender and wince* *3 tender and withdraw*
TOTAL SCORE	

Version 3.0 dated 28th July 2014

APPENDIX X: PASI SCORE FOR SEVERITY OF PSORIATIC ARTHRITIS

PSORIASIS AREA AND SEVERITY INDEX (PASI) WORKSHEET

HOSPITAL NO.: .....

PATIENT NAME: .....

DATE OF VISIT: .....

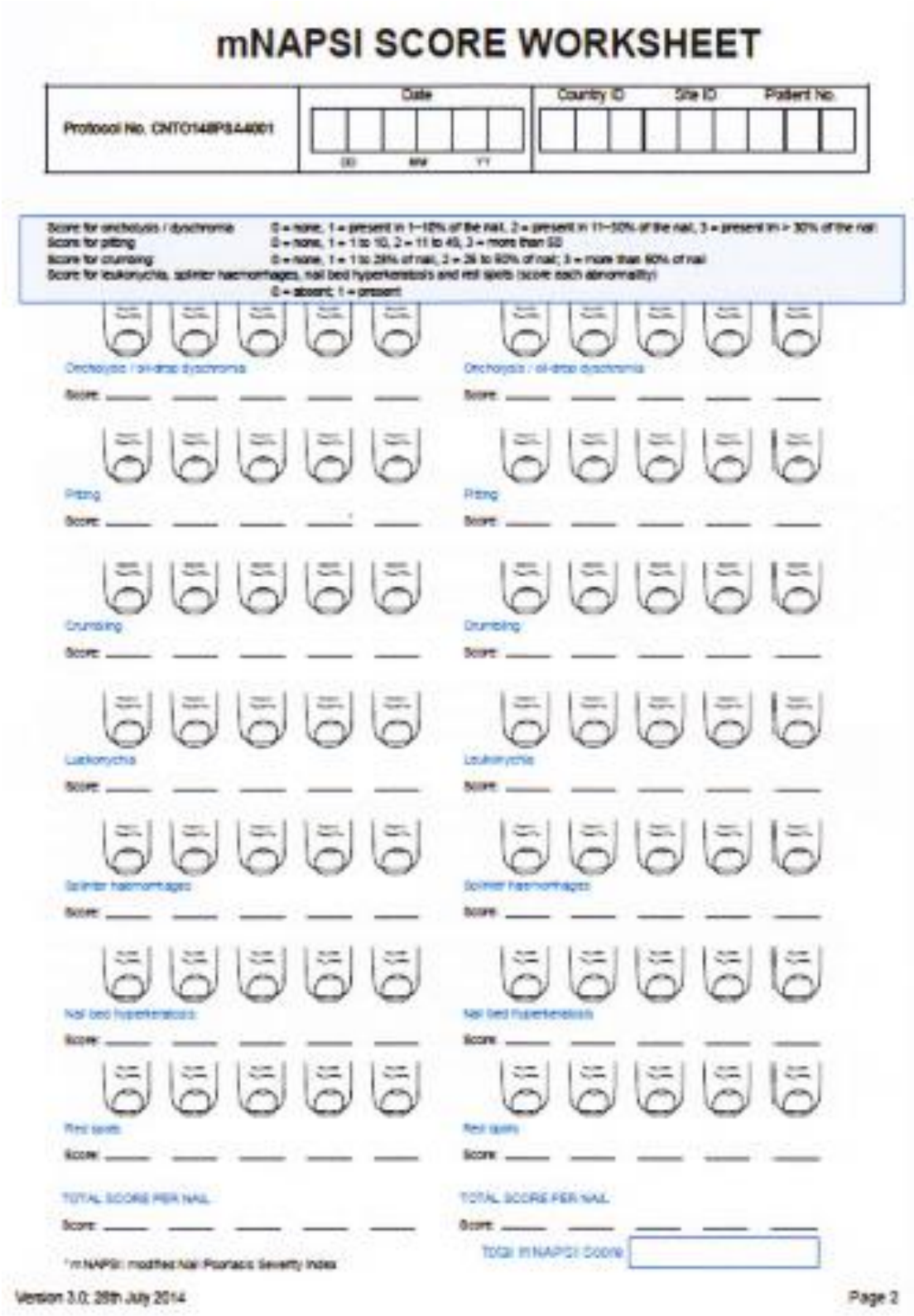
The Psoriasis Area and Severity Index (PASI) is a quantitative rating score for measuring the severity of psoriatic lesions based on area coverage and plaque appearance.

Plaque characteristic	Lesion score	Head	Upper Limbs	Trunk	Lower Limbs
Erythema	0 = None 1 = Slight 2 = Moderate 3 = Severe 4 = Very severe				
Induration/Thickness					
Scaling					
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) *Degree of involvement as a percentage for each body region affected (score each region with score between 0-6)*	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 XI: NAPSI SCORE FOR SEVERITY OF NAIL CHANGES IN PSORIATIC ARTHRITIS



mNAPSI SCORE WORKSHEET

Protocol No. CNTO148PSA4001 | Date (DD MM YY) | Country ID | Site ID | Patient No.

Score for onycholysis / dyschromia: 0 = none, 1 = present in 1–10% of the nail, 2 = present in 11–50% of the nail, 3 = present in > 50% of the nail
Score for pitting: 0 = none, 1 = 1 to 10, 2 = 11 to 49, 3 = more than 50
Score for crumbling: 0 = none, 1 = 1 to 25% of nail, 2 = 26 to 50% of nail; 3 = more than 50% of nail
Score for leukonychia, splinter haemorrhages, nail bed hyperkeratosis and red spots (score each abnormality):
0 = absent; 1 = present

Onycholysis / oil-drop dyschromia — Score: ____ ____ ____ ____ ____ | Onycholysis / oil-drop dyschromia — Score: ____ ____ ____ ____ ____

Pitting — Score: ____ ____ ____ ____ ____ | Pitting — Score: ____ ____ ____ ____ ____

Crumbling — Score: ____ ____ ____ ____ ____ | Crumbling — Score: ____ ____ ____ ____ ____

Leukonychia — Score: ____ ____ ____ ____ ____ | Leukonychia — Score: ____ ____ ____ ____ ____

Splinter haemorrhages — Score: ____ ____ ____ ____ ____ | Splinter haemorrhages — Score: ____ ____ ____ ____ ____

Nail bed hyperkeratosis — Score: ____ ____ ____ ____ ____ | Nail bed hyperkeratosis — Score: ____ ____ ____ ____ ____

Red spots — Score: ____ ____ ____ ____ ____ | Red spots — Score: ____ ____ ____ ____ ____

TOTAL SCORE PER NAIL — Score: ____ ____ ____ ____ ____ | TOTAL SCORE PER NAIL — Score: ____ ____ ____ ____ ____

TOTAL mNAPSI Score: ____

*mNAPSI: modified Nail Psoriasis Severity Index

Version 3.0, 28th July 2014 — Page 2

APPENDIX XII: CALCULATION OF PRESSURES GENERATED IN SYRINGE 2

Assumptions

1. Volume of the gas remains constant at this range of pressures
2. There is negligible friction between the tubing and the gas within it.
3. There is negligible friction between the syringe and the plunger lubricated with olive oil.

Pressure (P) in Syringe 2 = F/A (1 Newton / m^2 = 1 Pascal)
F = Force from weights on Syringe 1 plunge = ma
m = mass (kg) a = acceleration due to gravity (G) = 9.81 ms-1
A = internal cross-sectional area Syringe 1 = πr^2
r = internal radius of syringe $\pi = 3.142$
Pressure Syringe 2 = Pressure Syringe 1 if both syringes are the same size.
Elastic Modulus = volume displacement in response to negative pressure L / Pascal

30 ml Syringe

- Diameter 30cc syringe plunger = 20 mm = 0.020 m
- Radius (r) = 0.0100 m
- Cross Sectional Area (A) = $\pi \times r^2$ = 3.142 x 0.010 0 x 0.0100 =**3.142** x 10^{-4} m^2
- Negative pressure delivered =Force / Area Nm^{-2} (Pa)
- 1 Pascal (Pa) = 1 N/m^2

60 mL syringe

- Diameter 60 cc syringe plunger = 27 mm = 0.027 mm
- Radius (r) = 0.0135
- Area = $\pi \times r^2$ = 3.142 x 0.0135 x 0.0135 = **5.726** x 10^{-4} m^2

Mass Description	Mass (kg)	Accel-eration Gravity (ms^{-2})	Force (N)	Syringe Internal Cross-Sectional Area 30cc Syringe (x 10^{-4} m^2)	Syringe Internal Cross-Sectional Area 60 cc Syringe (x 10^{-4} m^2)	Negative Pressure Delivered by 30 cc Syringe To 30 cc Syringe (x 10^{-4}) Pa	Negative Pressure Delivered by 60 cc Syringe to 60 cc Syringe (x 10^{-4}) Pa
	a	b	c = a x b	d	e	f = c x d	g = c x e
Cradle	0.155	9.82	1.5221	3.142	5.726	4.78	8.72
Cradle + 0.100 kg	0.255	9.82	2.5041	3.142	5.726	7.88	14.34
Cradle + 0.200 kg	0.355	9.82	3.4861	3.142	5.726	10.95	19.96
Cradle + 0.300 kg	0.455	9.82	4.4681	3.142	5.726	14.04	25.58
Cradle + 0.400 kg	0.555	9.82	5.4501	3.142	5.726	17.12	31.21
Cradle + 0.500 kg	0.655	9.82	6.4321	3.142	5.726	20.20	36.83
Cradle + 0.600 kg	0.755	9.82	7.4141	3.142	5.726	23.30	42.45
Cradle + 0.700 kg	0.855	9.82	8.3961	3.142	5.726	26.38	48.07