Demographic and Clinical characteristics of children with Juvenile Dermatomyositis in Cape Town

by

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Declaration

I, **Dr. Lawrence Owino Okong'o**, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Abstract

Study rationale: Juvenile dermatomyositis (JDM) is a rare idiopathic inflammatory myopathy of childhood with an incidence of 1.9-3.2 per million. The aetiology of JDM is uncertain but may result from immune dysregulation triggered by environmental factors in genetically susceptible children. The demographic and clinical characteristics of JDM may thus differ by race and geographic regions. Few studies have described the characteristics of JDM patients from Africa. There is need for further studies for better understanding of the epidemiology, clinical characteristics and outcome of patients with JDM from the continent.

Methods: We conducted a retrospective observational study to determine clinical characteristics and outcomes of patients satisfying the Bohan and Peter criteria for probable JDM seen between 2004-2013 in Red Cross, Groote Schuur and Tygerberg hospitals in Cape Town. Data was analyzed using R version 3.1.0 (2014-04-10).

Results: Twenty five cases were identified: 16 female and 9 male. Thirteen (52%) of the cases were of indigenous African, eleven (44%) mixed and one (4%) European ancestry. The median ages at disease onset and diagnosis were 6.75 (range 2.0-9.7) and 7.9 (range 3.4-9.75) years respectively. Muscle weakness and characteristic cutaneous manifestations occurred in all the 25 patients while 24 had elevated muscle enzymes. All the patients received corticosteroids, seventeen (73.9%) received methotrexate and four received rituximab. Eleven patients had calcinosis during the disease course [median follow up period of 50 (range 0.5-159) months]. The mortality was 2/25 (8%) while only 40% of the patients had clinically inactive disease by PRINTO criteria. There was no difference in racial distribution (p-value

= 1), age at disease onset (p-value = 0.87) and disease duration prior to treatment initiation (p-value = 0.75) between patients who had clinically active and inactive disease.

Discussion: The demographic characteristics of children with JDM were similar to that from most other regions of the world with female predominance and similar age at onset. The median delay in diagnosis (4 months) was not longer than that reported in most other studies. However, some children had prolonged delay of up to 7 years due to misdiagnosis that denied them appropriate treatment in a timely manner. Majority (60%) of the patients also remained with clinically active disease, which put them at risk of further disease complications including calcinosis. Even though the mortality rate was low (8%) this was still more than double that reported in most recent large studies especially from the resource rich countries.

Conclusions: Long term follow up of JDM patients is advisable since majority of patients seem to have clinically active disease many years after disease onset despite treatment. Formulation and use of appropriate treatment guidelines and protocols may aid in the early diagnosis and appropriate management for optimum outcomes.

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AST	Aspartate transaminase
CMAS	Childhood Myositis Assessment Scale
CRP	C-Reactive Protein
CT Scan	Computerised Tomography Scan
CK	Creatine Kinase
EMG	Electromyography
ESR	Erythrocyte Sedimentation Rate
GSH	Groote Schuur Hospital
HREC	Human Research Ethics Committee
IMACS	International Myositis And Clinical Studies
IVIG	Intra-Venous Immune Globulin
JDM	Juvenile Dermatomyositis
LDH	Lactate Dehydrogenase
MAA	Myositis Associated Antibodies
MDI	Myositis Damage Index
MHC	Major Histocompatibility Complex
MMT	Manual Muscle Testing
MRI	Magnetic Resonance Imaging
MSA	Myositis Specific Antibodies
PRINTO	Paediatric Rheumatology International Trials Organization
RCWMCH	Red Cross War Memorial Children's Hospital.
TBH	Tygerberg Hospital
vWF	Von Willebrand Factor

Section I: Dissertation (publication format)

1 Chapter 1: Introduction

1.1 Context

1.1.1 Historical perspective

Juvenile dermatomyositis (JDM) is an immune mediated vasculopathic disease of childhood characterized by inflammation of the striated muscles, skin and internal organs. The descriptions of patients presenting with muscle damage and skin lesions were first given by Wagner in 1863[1]. Hans Unverritch later described a case of a man who presented with systemic symptoms, muscle weakness, periorbital discolorations and degenerative muscle changes on histology. This patient later died of respiratory failure. In 1891, Unverritch reported a second case and used for the first time, the term dermatomyositis to describe these cases.

1.1.2 Aetiopathogenesis of juvenile dermatomyositis

JDM probably arises as a result of immune dysregulation in genetically susceptible individuals following exposure to some as yet incompletely described environmental triggers. The role of genetic factors in the aetiology and pathogenesis of JDM has been backed by reports of familial clustering of JDM with other autoimmune diseases such as SLE, rheumatoid arthritis and type-1 Diabetes [2].

Several HLA haplotypes such as HLA DRB1*0301, DQA1*0301, HLA-DQA1*0501 and HLA-B8 occur more frequently in patients with JDM than in the general population and may thus confer risk for JDM. Conversely, HLA DQA1*0201 and DQA1*0101 alleles have been associated with lower risk of JDM in Caucasians [3,4]. Other gene loci that appear to confer risk of JDM include genes for the inflammatory cytokines TNFα, IL-1α and IL-1β; as well as the lymphocyte

signaling gene PTPN22. The TNF308A and IL1 polymorphisms are associated with higher risk of ulcerative disease and calcifications in JDM patients [4,5].

Environmental exposures such as infections, exposure to sunlight, vaccination and drugs have been reported as possible triggers [5-7] that may induce or worsen symptoms of JDM. Seasonal clustering of cases of JDM has further added to the speculation about the role of infections in the pathogenesis of JDM [8].

JDM is associated with a broad range of immune aberrations involving autoantibody production; complement mediated endothelial damage; aberrations in innate immunity and T-cell dysfunction. Increased levels of inflammatory cytokines including type I interferon stimulate up-regulation of MHC I expression on muscle. Expression of MHC I in myofibrils is associated with development of myositis with perivascular inflammatory cell (T cells, B cells, Macrophages and plasmacytoid dendritic cell) infiltration of muscle fibres [6].

Autoantibodies are identifiable in most cases of JDM. These can be classified either as myositis specific antibodies (MSA) or myositis associated antibodies (MAA). The MAA also occur in autoimmune diseases other than JDM. The MSAs include: anti Jo-1, anti-SRP and anti-Mi2. The more recently described MSAs such as anti-TIF1 (anti p155/140) and anti-NXP (anti p140) are more prevalent in JDM than the previously described autoantibodies and occur in upto 40% of JDM patients [4,9]. These newer MSAs are also associated with specific disease phenotypes with anti-p140 being associated with calcinosis.

1.1.3 Demographic characteristics

Dermatomyositis affects people of all ages though two peaks at onset have been described: 5-14 years and 45-64 years. The bimodal distribution demonstrates the uniqueness of the childhood [Juvenile Dermatomyositis (JDM)] form as a distinct disease from the adult form. JDM is the most common of the idiopathic inflammatory myopathies of childhood with incidence of 1.9-3.2 per a million [8,10].

Data from large patient registries indicate that the average age of onset of JDM is seven years (ranges from 5.7-8.7 years) with greater incidence in girls than boys (ratio of 1.9-4.2:1)[11-14]. However, regional differences exist and studies from India and Saudi Arabia have reported higher incidence rates in male children [15,16]. JDM occurs in all regions of the world though some studies suggest that there could be differences in incidence rates among different racial groups. Mendez *et al* found a lower incidence rate among children of Hispanic ancestry compared to those of African and Caucasian ancestry in the USA [10]. Racial differences have been noted in the incidence rates of certain disease manifestations with much higher incidence of calcinosis among children of African ancestry compared to other racial groups [12,17,18].

1.1.4 Clinical characteristics, investigations and diagnosis

JDM is a multisystem disease and manifests with symptoms in the skin, muscles as well as other organs including the lungs, gut, joints, heart and kidneys. Even though there are no validated criteria for the diagnosis and classification of JDM, the Bohan and Peter criteria which were initially proposed in 1975 for the diagnosis of inflammatory myositis in adults [19,20] are often applied for this purpose. The Bohan and Peter criteria are a set of five clinical and laboratory features that include characteristic cutaneous features, proximal muscle weakness, raised muscle enzymes,

characteristic muscle biopsy and suggestive electromyographic (EMG) findings. Presence of the characteristic cutaneous features with three of the other four criteria is necessary for a diagnosis of definite JDM while presence of the characteristic rash with two other features denotes Probable JDM.

However, in current paediatric practice, muscle biopsy and EMG are rarely performed due to their invasive nature. Instead, Magnetic Resonance Imaging (MRI) of muscle has gained popularity and has been proposed as a non-invasive alternative to muscle biopsy and EMG for assessing muscle inflammation [21,22]. Further, whole body muscle MRI has been found to perform well in identifying areas of muscle inflammation, identifying areas of active inflammation to biopsy and in quantifying the inflammatory burden in JDM [23].

Other non-invasive modalities for the evaluation of muscle inflammation for diagnosing dermatomyositis that have been explored include PET scans [24,25], Ultrasound Scan (MSUS)[26,27], and Scintigraphy (bone scans) [28-30]. Even though MRI is increasingly being used in the diagnosis and monitoring of JDM, it is still relatively expensive and inaccessible in most resource limited settings like Sub-Saharan Africa. Ultrasound is cheaper and more widely available compared to MRI. Further, MSUS is not associated with exposure to radiation just like with MRI. Bone scans are another alternative that is cheaper than MRI and may be less affected by operator (subjective) factors compared to MSUS.

1.1.5 Management

Steroids have been used empirically as the mainstay and first line of management of JDM even though there had been no Randomized Controlled Trials (RCTs) supporting their use and efficacy until recently. A multinational prospective cohort

study on the treatment modalities employed by clinicians confirmed steroids as being the most common drugs used in JDM treatment [33]. In addition to steroids, immunosuppressive and immune modulating drugs such as methotrexate, intravenous immunoglobulin (IVIG), azathioprine, cyclosporine, mycophenolate mofetil and cyclophosphamide have traditionally been used to induce remission in severe disease and as steroid sparing agents.

In response to the lack of evidence based standardized guidelines, the Childhood Arthritis & Rheumatology Research Alliance (CARRA) proposed consensus treatment guidelines for the management of moderately severe JDM [31,32]. Three consensus treatment guidelines were proposed: Prednisone and methotrexate, Prednisone with methotrexate and pulse methyl prednisone; and Prednisone, methotrexate, pulse methyl prednisone and Intravenous Immunoglobulin. Ruperto *et a*l [33] recently published the results of their RCT which showed that combination of prednisone with methotrexate or with cyclosporine was more effective than prednisone alone in the management of JDM. Further, the prednisone methotrexate combination had less adverse effects than the prednisone cyclosporine combination.

Few studies have looked at the efficacy of biological agents in JDM and therefore there are currently insufficient data to recommend use of biologic agents for the treatment of JDM. Oddis *et al* conducted an RCT on the efficacy of rituximab in refractory adult and Juvenile Dermatomyositis and noted that rituximab was efficacious in management of refractory JDM to achieve the IMACS definition of improvement [34]. A small study looking at the efficacy of infliximab for the treatment of refractory JDM in 5 patients demonstrated clinical benefit in muscle strength, patient global wellbeing, physician global assessment of improvement and even calcinosis in all the patients [35]. However, some studies have reported

unfavourable results with use of anti-TNF biologics in dermatomyositis and inflammatory myositis [36]. Generally, caution is advised in the use of anti-TNF biologics due to reports of TNF inhibitor induced dermatomyositis in patients receiving adalimumab and eternacept for the treatment of arthritis [37,38].

1.1.6 Treatment Outcome

The outcome of JDM has markedly improved over the years. In the years before the introduction of steroids for the treatment of JDM (before 1960s), the mortality rates were about 30% and a further 30% of the patients survived with major sequelae [14]. With the use of modern diagnostic and therapeutic strategies, JDM mortality rate has reduced to less than 5% [14,39-41]. Despite the improvement in mortality rates among JDM patients, disease and treatment related damage such as calcinosis, interstitial lung disease, residual muscle weakness, lipodystrophy and steroid toxicity remain major challenges and significantly affect the quality of life of affected individuals.

However, data on the characteristics and treatment outcome of JDM patients from Africa is scarce and only one study has been published that specifically described a series of JDM patients from the continent [12]. In that study, a higher rate of calcinosis and vasculitis compared to that from other regions was reported suggesting that the clinical manifestations and outcome of JDM in African patients could be different. There is need of further studies for a better understanding of the epidemiology, clinical manifestations and treatment outcomes of JDM in patients from Africa. We therefore carried out a study to review and describe the clinical features and treatment outcomes of JDM patients from Cape Town, South Africa.

1.2 Ethical considerations

The study was approved by the Human Research Ethics Committees (HREC) of the Universities of Cape Town (HREC/REF: 062/2014, **appendix 5**) and Stellenbosch (Ref: S14/04/080, **appendix 6**). Permission to carry out the study and access patient records was sought from the respective hospital administrators. Consent from patients or their parents was not obtained since this was a retrospective case note review and did not involve direct patient contact. Patient confidentiality was observed and information collected was kept anonymous. The study was conducted in observance of the principles of Helsinki (2008) and Good Clinical Practice (GCP).

1.3 Author guidelines Paediatric rheumatology journal

The manuscript will be submitted to the journal Paediatric Rheumatology for publication. Paediatric Rheumatology is the official journal of the Paediatric Rheumatology European Society (PReS) and the premier journal specifically dedicated to paediatric rheumatology. It is an online open access journal and thus shall provide the maximum reach among the paediatric rheumatology community and to any other interested scientist, clinician or researcher. The journal does not limit the length of the manuscripts submitted for publication though authors are encouraged to be concise. The journal is listed in the citation index of the Institute for Scientific Information (ISI) and is accredited by the South African Department of Education.

The full author guidelines for paediatric rheumatology journal is included as **appendix 7**. The author instructions can be accessed at "http://www.ped-rheum.com/authors/instructions."

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2 Chapter 2: Publication--ready manuscript

Characteristics and outcome of children with Juvenile Dermatomyositis in Cape Town: A cross-sectional study.

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2.1 Abstract

Background: Juvenile dermatomyositis (JDM) is a rare idiopathic inflammatory myopathy of childhood with an incidence of 1.9-3.2 per million. The aetiology of JDM is uncertain but may result from immune dysregulation triggered by environmental factors in genetically susceptible children. The demographic and clinical characteristics of JDM may thus differ by race and geographic regions. Few studies have described the characteristics of JDM patients from Africa. There is need for further studies for better understanding of the epidemiology, clinical characteristics and outcome of patients with JDM from the continent.

Methods: We conducted a retrospective observational study to determine clinical characteristics and outcomes of patients satisfying the Bohan and Peter criteria for probable JDM seen between 2004-2013 in Red Cross, Groote Schuur and Tygerberg hospitals in Cape Town. Data was analyzed using R version 3.1.0 (2014-04-10].

Results: Twenty five cases were identified: 16 female and 9 male. Thirteen (52%) of the cases were of indigenous African, eleven (44%) mixed and one (4%) European ancestry. The median ages at disease onset and diagnosis were 6.75 (range 2.0-9.7) and 7.9 (range 3.4-9.75) years respectively. Muscle weakness and characteristic cutaneous manifestations occurred in all the 25 patients while 24 had elevated muscle enzymes. All the patients received corticosteroids, seventeen (73.9%) received methotrexate and four received rituximab. Eleven patients had calcinosis during the disease course [median follow up period of 50 (range 0.5-159) months]. The mortality was 2/25 (8%) while only 40% of the patients had clinically inactive disease by PRINTO criteria. There was no difference in racial distribution (p-value = 1), age at disease onset (p-value = 0.87) and disease duration prior to treatment

initiation (p-value = 0.75) between patients who had clinically active and inactive disease.

Conclusion: The demographic characteristics of children with JDM were similar to that from most other regions of the world with female predominance and similar age at onset. However, majority of the patients remained with clinically active disease, which put them at risk of further disease complications including calcinosis. Long term follow up of JDM patients and use of appropriate treatment guidelines and protocols may guide appropriate management for optimum outcomes.

Keywords

Juvenile dermatomyositis, JDM, Outcome, Africa.

2.2 Background

Juvenile dermatomyositis (JDM) is an immune mediated vasculopathic disease of childhood characterized by inflammation of the striated muscles, skin and internal organs. The most common clinical manifestations are proximal muscle weakness and characteristic cutaneous lesions such as heliotrope rash, Gottron's papules and calcinosis. However, disease manifestations may occur in the lungs, heart, gastrointestinal tract and other organs. The pathogenesis of JDM is not fully understood but environmental factors are thought to trigger the disease in genetically predisposed children [1-4].

JDM is most commonly diagnosed and classified using the Bohan and Peter criteria published in 1975 [5,6]. Though initially proposed for use in adults, these criteria are also widely used for diagnosis of myositis in the paediatric age group. The criteria include presence of a characteristic rash, symmetrical proximal muscle weakness, elevated muscle enzymes in serum, electromyographic changes and muscle biopsy features of inflammatory myositis. The presence of the skin manifestations is mandatory for diagnosis while presence of three of the other features is necessary for classification as definite JDM and of two other features as probable JDM. Presence of characteristic skin lesions without apparent muscle involvement may be seen in about 1.0% of cases and is referred to as amyopathic dermatomyositis [7].

Data from multicenter patient registries indicate that the average age of onset of JDM is seven years with greater incidence in girls than boys (ratio of 2:1) [8-11]. However, regional differences exist and studies from India and Saudi Arabia have reported higher incidence rates in male children [12,13]. JDM occurs in all regions of the world though some studies suggest that there could be differences in incidence rates among different racial groups. Mendez *et al* reported a lower incidence rate

among children of Hispanic ancestry compared to those of African and Caucasian ancestry in the USA [14]. Racial differences have also been noted in the incidence rates of certain disease manifestations with much higher incidence of calcinosis being reported among children of African ancestry compared to other racial groups [9,15,16].

The reported treatment outcome of JDM has improved over the years. The mortality rate has significantly reduced from more than 30% before routine use of steroids [17], to less than 5% reported in most recent studies [11,18-20]. Despite the improvement in mortality rates among JDM patients, disease and treatment related damage remains a major challenge and significantly affect the quality of life of affected individuals. However, data on the characteristics and treatment outcome of JDM patients from Africa is scarce and only one study has been published that specifically described a series of JDM patients from the continent [9]. In that study, a higher rate of calcinosis and vasculitis compared to that from other regions was reported suggesting that the clinical manifestations and outcome of JDM in African patients could be different.

There is need of further studies for a better understanding of the epidemiology and treatment outcomes of JDM in patients from Africa. We therefore carried out a study to review and describe the clinical features and treatment outcomes of patients seen with JDM from Cape Town, South Africa.

2.3 Methods

2.3.1 Study design, study setting and patients

We carried out a retrospective folder review of JDM patients seen between January 2004 and December 2013 in three tertiary care hospitals [Tygerberg, Groote Schuur and Red Cross War Memorial Children's Hospital) in Cape Town, South Africa. These three hospitals are the main tertiary referral hospitals for the Western Cape Province and also serve the surrounding regions of the Eastern and Northern Cape provinces of South Africa. Patients from this catchment area diagnosed with JDM were likely to have been referred to one of these centres for evaluation and treatment. The approximate population in the primary catchment area was 4.6 Million in 2004 and 6.1 million in mid-2014 with children (people aged <15 years) constituting 35% and 26.5% of the population respectively [21]. The province populace is composed of people of diverse ancestral backgrounds with the most populous groups being, in descending order, people of mixed, indigenous African and European ancestries [21].

Only patients who were seen between January 2004 and December 2013 and satisfied the Bohan and Peter criteria for classification as probable JDM were included. Data was extracted from the patient records as at the last review prior to 31st December 2014 to allow for a follow up period of one year for each patient. Data was abstracted onto case record forms (CRF) and later transcribed onto an excel spreadsheet. Information collected included: demographics, clinical and laboratory features, radiological investigation results, treatment given and treatment outcomes.

The primary outcome variable was disease activity at last review. Patients were classified as having clinically active disease or inactive disease. A modification of the PRINTO criteria for inactive disease [22] was used. The PRINTO criteria include CK<150 U/L, CMAS>48, MMT>78 and Physician global (VAS) <0.2. Patients

satisfying any three of these criteria are classified as having clinically inactive disease. We used a modification of these criteria due to difficulties with direct comparisons since this was a retrospective study and data on some of the PRINTO criteria items was not available. Therefore for this study we modified the criteria as follows (modification in brackets):

- CK<150 U/L (No modification),
- CMAS>48 (No modification),
- MMT>78 (or documented full muscle strength using any muscle strength assessment scale by the attending physician) and
- Physician global (VAS) <0.2 (or documentation of absence of symptoms and signs of active disease by the clinician).

Patients were classified as having inactive disease if they satisfied any three of these criteria.

Secondary outcome measure was damage defined as persistent changes in anatomy, physiology or function present for at least 6 months at the last review (IMACS definitions of damage and specific damage items) [23,24]. Damage was assessed as being present or absent by systems and patients classified as either exhibiting damage (any) or none at last follow up.

2.3.2 Data analysis

Data was analysed using R i386 3.1.0 (The R Foundation for Statistical Computing, Vienna, Austria) software. Median and interquartile ranges were used for descriptive statistics for quantitative variables (non-normally distributed data). Frequencies were computed for qualitative variables. Non-parametric tests (Wilcoxon rank sum tests)

were used for comparison of medians across groups. For comparison between categorical variables, cross-tabulation was used with formulation of Fisher's exact (chi square) statistic. The two sided p-values <0.05 were considered to be statistically significant.

The study was approved by the human research ethics committees of Cape Town (HREC/REF: 062/2014) and Stellenbosch universities (S14/04/080).

2.4 Results

2.4.1 Patient characteristics

Twenty seven cases with a diagnosis of JDM seen between 2004 and 2013 were identified. Two had amyopathic JDM and were excluded as they did not meet the inclusion criteria of probable JDM. Of the other twenty five, twelve satisfied the criteria for definite JDM. Six of the probable JDM cases were reclassified as definite JDM when muscle MRI findings were considered. Thus in total, eighteen (72%) were classified as definite and seven (28%) probable JDM. Sixteen of the patients were female (F:M 1.8:1). Thirteen (52%) of the cases were of indigenous African, eleven (44%) mixed and one (4%) European ancestry. The median age at disease onset was 6.75 (range 2.0-9.7) years and at diagnosis 7.9 (range 3.4-9.75) years. The median duration from symptom onset to diagnosis was 4 (range 0.5-84) months. One patient was retrospectively diagnosed with JDM after a period of 84 months having previously been labelled as discoid lupus. The median duration of follow up was 50 (range 0.5-159) months. Some of the findings are presented graphically in **figure 1.**

Figure 1: Box and whisker plot illustrating delay in diagnosis (months). The median period from disease onset to diagnosis (delay) was 4 (range 0.5-84) months with maximum of 84 months for a patient initially diagnosed as discoid lupus before the final diagnosis of JDM was made seven years later.

2.4.2 Diagnostic features and characteristics

Muscle weakness and characteristic cutaneous manifestations were documented in all the 25 patients with heliotrope rash occurring in 20 and Gottron's papules in 19 patients. Muscle enzymes were elevated in all but one patient. This patient however, had suggestive muscle biopsy changes and satisfied the criteria for classification as probable JDM. Creatine phosphokinase (CK) was elevated in 22 of 24 cases. The two patients with normal CK had elevated AST and ALT and in addition one had elevated aldolase and the other had elevated lactose dehydrogenase (LDH). Aldolase was only determined in five patients and was elevated in three of them. **Figure 2** summarizes results of the diagnostic procedures and criteria.

Figure 2: Bar graph illustrating results of diagnostic investigations

Present: *features supportive of myositis****; Absent:*** *not supportive of myositis****; Not available:*** *Not done or results not accessible****.*** Muscle enzymes were elevated in 24 of the 25 patients. Biopsy was done in 12 and showed features consistent with JDM in 11. Other investigations done were EMG in 5 and MRI in 9 patients.

Muscle biopsy was performed in twelve (48%) of the patients and showed characteristic features including perifascicular atrophy, fibre degeneration and regeneration and perivascular inflammation consistent with JDM in 11 (91.7%) of the cases. **Figure 3** demonstrates some of the characteristic muscle biopsy changes of perifascicular atrophy (3**a** and **b**) and perivascular inflammation (3**c** and **d**) seen in one of our patients. Five of the patients had documented EMG results showing features consistent with myositis.

Figure 3a-d clockwise from top. Haematoxyllin and Eosin sections showing (**a** & **b**) perifascicular fibre atrophy (**b** high power); and **c** & **d** perivascular inflammation (**c** high power). Note the atrophic myofibres at the periphery of the fascicles (a & b) and the abundant perivascular mononuclear inflammatory cell infiltrates (c & d). These features are typical of dermatomyositis with accompanying vasculitis.

Muscle MRI for initial diagnostic work-up was done in nine patients and demonstrated active inflammation in eight of the patients. **Figure 4** shows the characteristic diffuse edema on MRI of the thigh muscles of one of the patients. All the patients in whom MRI was done were diagnosed in the latter half of the period under review (2009-2013).

Figure 4: Saggital (STIR) and Coronal MRI images showing diffuse edema in the thigh muscles characteristic of JDM.

2.4.3 Clinical characteristics

There was no documented family history of neuromuscular or autoimmune diseases among the cases. However, history of preceding infection was reported in 6 cases: upper respiratory tract infection (URTI) in 4 cases and dental or skin abscesses in 2 cases with a median time to onset of JDM symptoms of 1 month. One patient had a traumatic event (sexual abuse) one month prior to onset of JDM symptoms.

Pulmonary involvement was reported in four patients and two of them died; one with suspected severe interstitial lung disease and the other with pulmonary hemorrhage

and sepsis. The third patient had clinical as well as HRCT features of interstitial lung disease (ILD) and restrictive pattern on pulmonary function tests (PFTs). One other patient had deranged spirometry results, which normalized with treatment. In total, PFT results were available for six patients (done after mean of 4.4 years from diagnosis) and only two of the patients had deranged lung function parameters (restrictive pattern).

Cardiovascular involvement was observed in one patient who presented with generalized oedema and heart failure. Echocardiography showed mildly dilated chambers with reduced ejection fractions of <55%. Echocardiography however, was not routinely done to document baseline state or monitor cardiac function of JDM patients in the three centres. Neurological manifestations were seen in two cases; one had convulsions thought to be due to cerebral vasculitis and the other had localized sensory neuropathy.

Cutaneous and musculoskeletal manifestations were the most common and are summarized together with other clinical features in **Table 1**. Of note, three patients had calcinosis at diagnosis, 8 others developed calcinosis and three had resolution of calcinosis during follow up. **Figure 5** shows a radiograph of one of the patients showing tumoural and planar calcinosis in the forearm. There was no statistically significant difference in the age at onset, age at diagnosis and duration of follow up among patients who developed calcinosis and those who did not have calcinosis. The median time to diagnosis from symptom onset was longer in children who had calcinosis (6 months) than in those who did not have calcinosis (3 months). The difference was however not statistically significant ($p = 0.13$). In addition, even though there was a tendency towards a higher prevalence of calcinosis among

indigenous African children (8/13) compared to children of other racial backgrounds (3/12), the difference was not statistically significant (p=0.11).

Figure 5: Forearm radiograph showing mixed tumoural and planar calcinosis in one of the JDM patients.

2.4.4 Laboratory investigations

Autoantibodies [Myositis associated (MAA) and myositis specific antibodies (MSA)] were only tested in a few patients. Among the MSAs, only anti-Jo1 was tested and was negative in all the six patients tested. ANA results were available in 19 patients and was low positive in seven (three had Hep-2 titres of 40, 40 and 100; and four had composite ANA ratio of 8, 2.2 4.6 and 32 U/L). The results of the laboratory investigations are summarized in **table 2.**

2.4.5 Treatment

Information on treatment was available for 23 of the 25 patients. We could not locate treatment records in two cases. The most common drugs used were oral prednisone (100%), methotrexate (74%), intravenous methylprednisolone (39%) and intravenous immunoglobulin (IVIG). Prednisone alone was used in five patients, prednisone and methotrexate without another agent in nine patients and various other drugs were added as second line drugs to the main treatment modality (prednisone and methotrexate) in poor responders as summarized in **figure 6** below.

Figure 6: Treatment modalities in Cape Town JDM patients. All the patients received corticosteroids during the course of their treatment. Biologics were used in

6 patients (rituximab in 5 and infliximab in 1). **Abbreviations:- Cyclophos:** cyclophosphamide; **Medrol:** intravenous methylprednisolone; **Pred:** Prednisone **PredMTX:** Prednisone and methotrexate; **IVIG:** Intravenous immunoglobulin.

2.4.6 Treatment outcome: diseases activity, mortality and damage

Of the 25 patients, 10 were still in care, 8 were discharged, 2 transferred to other centres, 3 were lost to follow up and 2 patients died. Ten (40%) of the patients had clinically inactive disease. Patients who had clinically inactive disease had significantly lower CK levels (mean 105.5 U/L) than those with clinically active disease at their last review (mean CK 203.5 U/L) (***p=0.02***). There was no statistically significant difference in the median duration of follow up (p = 0.28), age of onset, race, diagnostic delay, disease category (probable or definite) and disease type (chronic/polycyclic or monocyclic) between those who had clinically inactive and active disease.

The mortality rate was 2/25 (8%) over a median follow-up period of 50 months. Death resulted from respiratory failure in the setting of global weakness (and possible interstitial lung disease) in one patient and from sepsis, GI bleed and pulmonary hemorrhage (at autopsy) in the other.

Overall, 18 (72%) of the patients had some documented damage though a full damage assessment was hampered by missing data occasioned by the retrospective nature of the study. The most common systems in which disease damage was reported were: endocrine (9 cases), skin (8 cases), musculoskeletal (7 cases) and respiratory (3 cases) systems. Endocrine damage was mainly as a result of growth failure **(figure 7)** though one patient developed diabetes mellitus and another,

adrenal insufficiency. Growth failure occurred in a high proportion of patients (36%). Growth failure was defined by the IMACS criteria as presence of two of the following three features:

a. Less than 3 percentile height for age.

b. Growth velocity over 6 months less than 3 percentile for age.

c. Crossing at least 2 centiles (5%, 10%, 25%, 50%, 75%, 95%) on growth chart.

Musculoskeletal damage included one patient who had osteoporosis with vertebral fracture that was demonstrated using bone scans (scintigraphy). One patient, who had suffered from suppurative otitis media during follow up, developed sensorineural hearing loss. Three patients had calcinosis at diagnosis, 8 developed calcinosis and three had resolution of the calcinosis during follow up.

Figure 7: growth chart for one of the patients with growth failure. Note stature for age line crosses from above 50th centile to below 3rd centile and remains below 3rd centile line for >3 years.

2.5 Discussion

A better understanding of the epidemiology and clinical outcomes of JDM has been enhanced by the establishment of multicenter and multinational collaborations such as the paediatric rheumatology international trials organization (PRINTO) and international myositis assessment and clinical studies group (IMACS). However, data from Africa has been scarce and the epidemiology of JDM from the continent has been based on extrapolation of data collected from other populations and regions. The mean age at disease onset in most of these registries has been reported to be about seven years with a female predominance of about 2:1 [10,11,20]. The median age of onset (6.75 years) and gender composition (female: male 1.9:1) among the JDM patients in our series was similar to that of most studies from other regions.

In the current study, we also found a relatively high rate of calcinosis (44% of the cases). Even though children of indigenous African ancestry appeared to have a higher prevalence of calcinosis (61.5%) compared to patients of other ancestral background (25%), the difference was not statistically significant (p=0.11). Higher rates of dystrophic calcinosis have been reported among indigenous African compared to JDM patients of other ancestral backgrounds [16]. It is not clear why indigenous African patients appear to have higher risk of calcinosis. Certain immune phenotypes have been associated with higher risk of occurrence of calcinosis. It is not known if black African children have higher prevalence of these immune phenotypes thus putting them at greater risk for calcinosis. The immune phenotype was not determined for our patients and published studies are not available on the comparative prevalence of autoantibody and other associated risk factor profiles among indigenous African compared to children of other ancestral backgrounds.

Increased risk of calcinosis and other disease damage could also be related to poor access to care with subsequent inappropriate and delay in instituting treatment. Delay in diagnosis may be the consequence of lack of access to clinicians skilled in diagnosing and managing dermatomyositis and similar conditions; and lack of access to diagnostic facilities such as EMG and muscle biopsy. However, there was no significant difference in the delay in making a diagnosis between the patients of indigenous African and patients of other ancestral origins ($p = 0.27$).

As the search for better and more acceptable diagnostic procedures and tools continues, MRI is gradually being used in the three centres instead of or in addition to EMG and muscle biopsy for diagnosis of JDM. Eleven muscle MRIs were done as part of the diagnostic evaluation of children; all in the latter half of the period under review. Thus MRI seems to have gained prominence as a diagnostic tool for JDM consistent with findings from other studies [19,25,26]. However, in Africa and many other resource constrained economies, MRI may not be available in many centres and even where it is available, long waiting times, technical issues with reporting and cost implications may prove prohibitive. Thus additional diagnostic modalities such as muscle ultrasound and Bone scintigraphy that may provide cheaper and more convenient alternatives for demonstrating evidence of muscle inflammation may be welcome [27-29].

The mortality rate (8%, 1 death per 52 patient years) in our series appears higher than the 2-4% reported in most recent studies from other regions [11,18-20]. This finding was consistent with that by Faller *et al* [9] who reported a mortality of 9.5% (1 death per 27.3 patient years) among indigenous African children with JDM from Johannesburg, South Africa. These two studies were small and it's not possible to draw generalizable conclusions. They however provide some insight into possible

treatment outcomes of JDM in Africa. Two deaths were reported in our study as well as in the study by Faller *et al* and all the four deaths resulted from respiratory (involvement) disease which has been identified as an early disease feature predictive of mortality [18].

Juvenile dermatomyositis is a chronic disease and many patients may never achieve a clinically inactive disease state. After a median follow up time of 50 months, only ten (40 %) of the 25 patients had clinically inactive disease (PRINTO criteria) at their last follow up. Sanner *et al* studied the long-term outcome of JDM and after 16.8 years, 59% of the patients still had clinically active disease [30]. Other authors have similarly reported a relatively high level of disease activity, with only 33% among a cohort of 39 JDM patients being disease free at last review over a ten year period [31]. It is thus clear that most children with JDM have long-term inflammation and disease activity that linger long after initiation of treatment. Formulation of appropriate guidelines and standard of care protocols to guide short-term and long-term management of JDM could enable appropriate timely interventions for better treatment outcomes.

2.6 Conclusion

The demographic characteristics of JDM patients from Cape Town (median disease onset age of 6.75 years and Female to male ration of 1.9:1) was similar to that reported from most regions of the world. It is probable that there was unnecessary delay in the diagnosis of cases. One patient was diagnosed retrospectively seven years after disease onset. There was however a relatively high rate of calcinosis (44%) and mortality (8%).

Further, there was persistent clinically active disease in a large proportion of this cohort (60%), putting them at risk of further disease complications. This could be a reflection of inadequate or less aggressive treatment. The study adds to the available literature on JDM in Africa and demonstrates a need for a defined standard of care package to ensure adequate access to skilled multidisciplinary teams, essential diagnostic facilities and therapeutic resources for better treatment outcomes.

The study limitations included missing values and the relatively small number of cases identified. Establishment of a prospective cohort in future could be useful in providing better quality data for better outcome assessments in line with currently accepted international guidelines.

2.7 List of abbreviations

AST	Aspartate transaminase
CMAS	Childhood Myositis Assessment Scale
CRP	C-Reactive Protein
CT Scan	Computerised Tomography Scan
CK	Creatine Kinase
EMG	Electromyography
ESR	Erythrocyte Sedimentation Rate
IMACS	International Myositis And Clinical Studies
IVIG	Intra-Venous Immune Globulin
JDM	Juvenile Dermatomyositis
LDH	Lactate Dehydrogenase
MAA	Myositis Associated Antibodies
MDI	Myositis Damage Index
MMT	Manual Muscle Testing
MRI	Magnetic Resonance Imaging
MSA	Myositis Specific Antibodies
PRINTO	Paediatric Rheumatology International Trials Organization
vWF	Von Willebrand Factor

2.8 Competing interests

We declare that there are no financial competing interests. This study was undertaken as a thesis component of an MPhil (Paediatric Rheumatology) degree for Lawrence Owino Okong'o.

2.9 Authors' contributions

LO drafted the protocol, analysed the data and drafted the manuscript. ME provided the data on the cases from one of the three centres and reviewed the protocol and manuscript. JW participated in the design of the study, provided data on the cases from one of the three study centres and reviewed the protocol and manuscript. CS conceived of the study, and participated in its design and coordination, helped to draft the manuscript and provided general supervision.

All authors read and approved the final manuscript.

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Other members of the paediatric rheumatology teams including Dr. Nicky Brice and Dr. Kate Webb who were involved in managing the patients and documented the findings that have formed part of the study source documents.

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2.12 Tables and figures

Table 1: Disease manifestations and organ damage among the JDM cases

	Cumulative clinical manifestations (%)	**Clinical manifestations at last review**
Skin		8 (32)
Calcinosis, scarring, atrophy	11 (44)	8 (32)
Skin ulcers	11 (44)	1
Oedema (Generalized, Periorbital or limb)	11 (44)	0
Alopecia	3 (12)	3 (12)
Lipodystrophy	1 (4)	1 (4)
Musculoskeletal	7(28)	7 (28)
Muscle tenderness	13 (52)	0
Arthritis	7 (28)	2 (8)
Contractures	5(20)	5 (20)
Muscle wasting	4 (16)	4 (16)
Osteoporosis with fracture	1(4)	1 (4)
Endocrine	9 (36)	9 (36)
Growth failure	8 (32)	8 (32)
Diabetes mellitus	1 (4)	1 (4)
Adrenal insufficiency	1 (4)	1 (4)
Respiratory	3 (12)	3 (12)
Interstitial lung disease (ILD)	2 (8)	2 (8)
Dysphonia	2 (8)	0
Hemorrhagic pneumonitis	1 (4)	1 (4)
Gastrointestinal		
Dysphagia	5 (20)	0
Abdominal pain or bleeding	3 (12)	0
Ocular	2 (8)	2 (8)
Cataracts	2 (8	2 (8)
Cardiovascular		
Abnormal capillaroscopy	15 (60)	NA
Raynaud's phenomenon	6 (24)	NA
Cardiomyopathy	1 (4)	0
Nervous system		
Seizures; neuropathy	2 (8)	0
Sensorineural hearing loss	1 (4)	1 (4)
Infections		
Fungal (skin)	7 (28)	NA
Bacterial (staph aureus 2, gram neg 1)	3 (12)	NA
TB	2 (8)	NA

Table 2: Laboratory investigation results

Investigation	Ref	Median (IQR)	Results No. positive	Percentage
Enzymes				
CK	26 - 145 U/L	1074.0 (222.8-3397.5)	22/24	91.7
Aldolase	3.0 - 12.0U/L	12.6 (7.7-15.9)	3/5	60
LDH	142 - 261U/L	445.0 (277.0- 493.5)	14/19	73.7
AST	0 - 41 U/L	74.0 (35.25-140.5)	16/22	72.7
ALT	5 - 25 U/L	48.0 (26.5-82.0)	18/23	78.3
Autoantibody				
Anti-Jo1	<7 EliA U/ml	0.3 (0.3 - 0.45)	0/6	0
Anti-p155/140	NA	NA	0	0
Anti-p140	NA	NA	0	0
Anti-RNP	<7 EliA U/ml	0.3 (0.3 - 0.5)	0/9	0
Inflammatory markers				
ESR		20 (12 - 35)	11/19	57.9
CRP		2.6 (<1- 6)	2/10	20
vWF activity		77 (62-112%)	2/4	50

Table 3: Determinants of disease activity

	Clinically inactive disease	**Clinically active disease**	**p-value**
Number	10	15	
Sex (F/M)	8/2	8/7	p = 0.228‡
Race (Indigenous African/other)	5/5	8/7	P = 1
Age at onset (Median) years	7.8	6.0	p = 0.868‡
Time to diagnosis (Median) months	3.5	4.5	p = 0.745‡
Duration follow up (Median) months	55.5	49.1	p = 0.21‡
Calcinosis (Yes/No)	4/6	6/9	p = 1†
CK (Median)	105.5	203.5	W = 109, ***p = 0.02***‡
Disease type: Chronic/poly- vs Mono			p = 0.35†

†Fisher exact ‡ Wilcoxon rank sum test

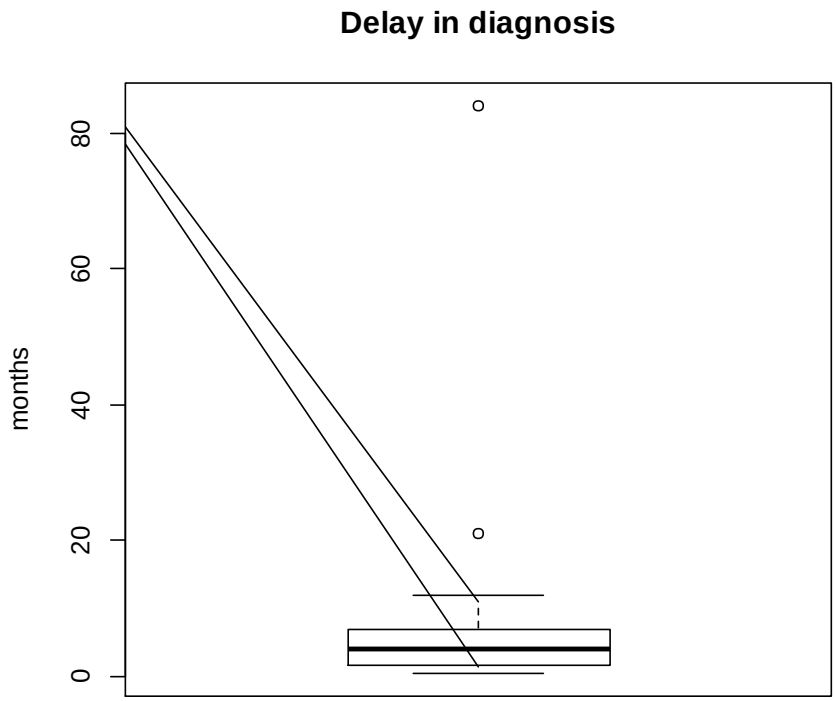

Figure 1: Box and whisker plot illustrating age of patients (years) and delay in diagnosis (months). The median age at onset was 6.75 years and at diagnosis 7.9 years. The median period from disease onset to diagnosis (delay) was 4 months with maximum of 84 months (the extreme outlier) for a patient initially diagnosed as discoid lupus before the final diagnosis was made.

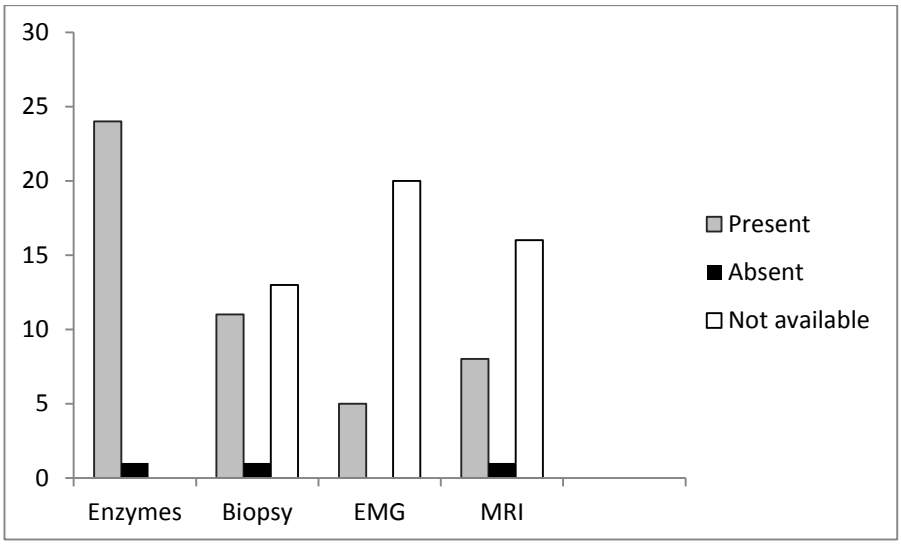

Figure 2: Bar graph illustrating results of diagnostic investigations

Present: *features supportive of myositis****; Absent:*** *not supportive of myositis****; Not available:*** *Not done or results not accessible****.*** Muscle enzymes were elevated in 24 of the 25 patients. Biopsy was done in 12 and showed features consistent with JDM in 11. Other investigations done were EMG in 5 and MRI in 9 patients.

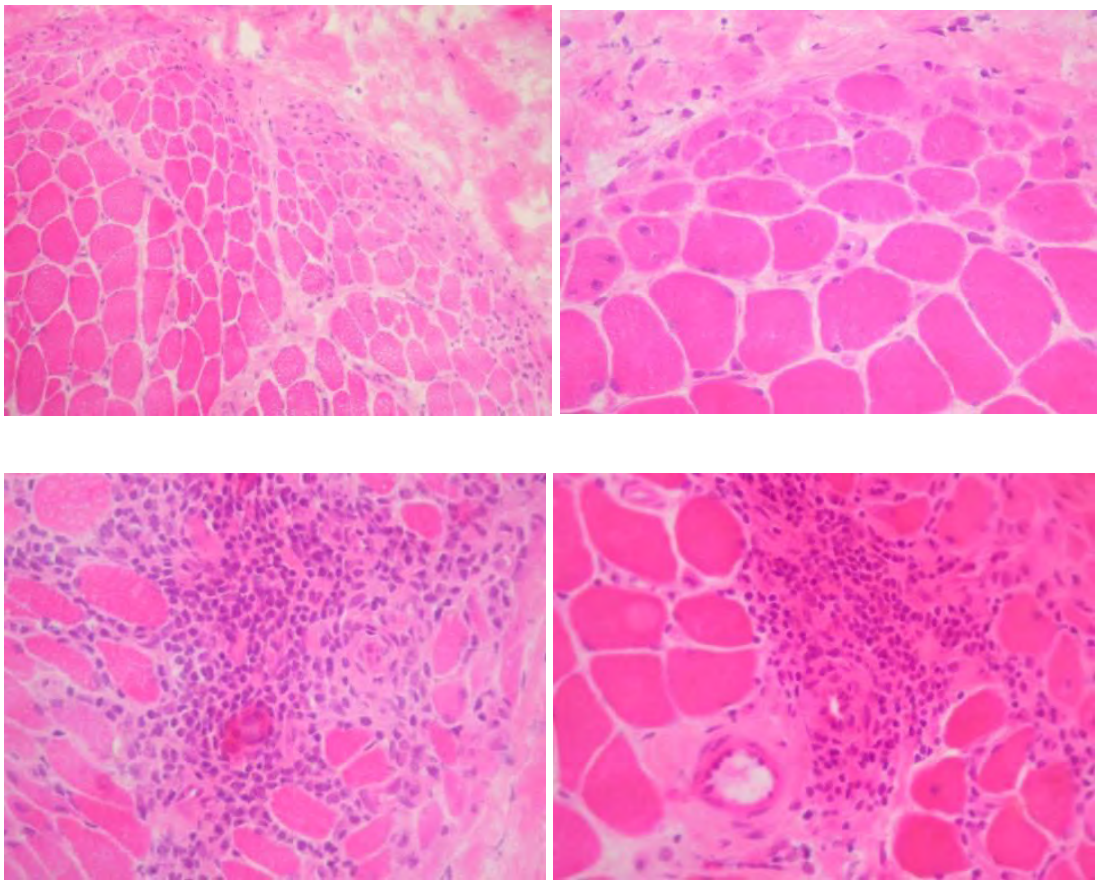

Figure 3a-3d clockwise from the top. Haematoxyllin and Eosin sections showing (**a** & **b**) perifascicular fibre atrophy (**b** high power); and **c** & **d** perivascular inflammation (**c** high power). Note the atrophic myofibres at the periphery of the fascicles (a & b) and the abundant perivascular mononuclear inflammatory cell infiltrates (c & d). These features are typical of dermatomyositis with the accompanying vasculitis.

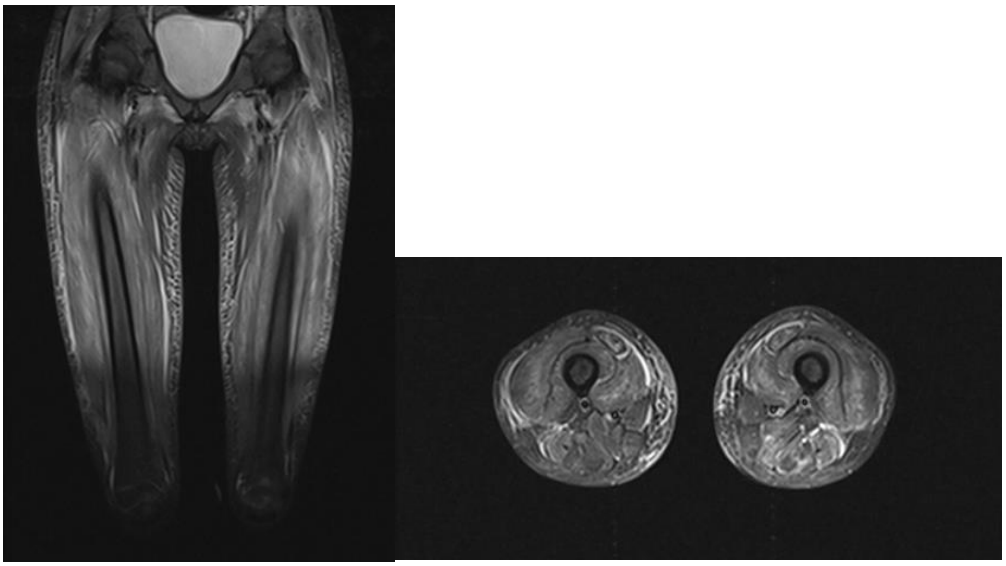

Figure 4: Saggital (STIR) and Coronal MRI images showing diffuse edema in the thigh muscles characteristic of JDM.

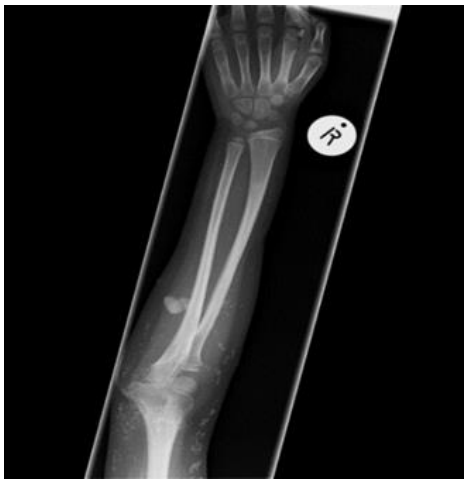

Figure 5: Forearm radiograph showing mixed tumoural and planar calcinosis in one of the JDM patients.

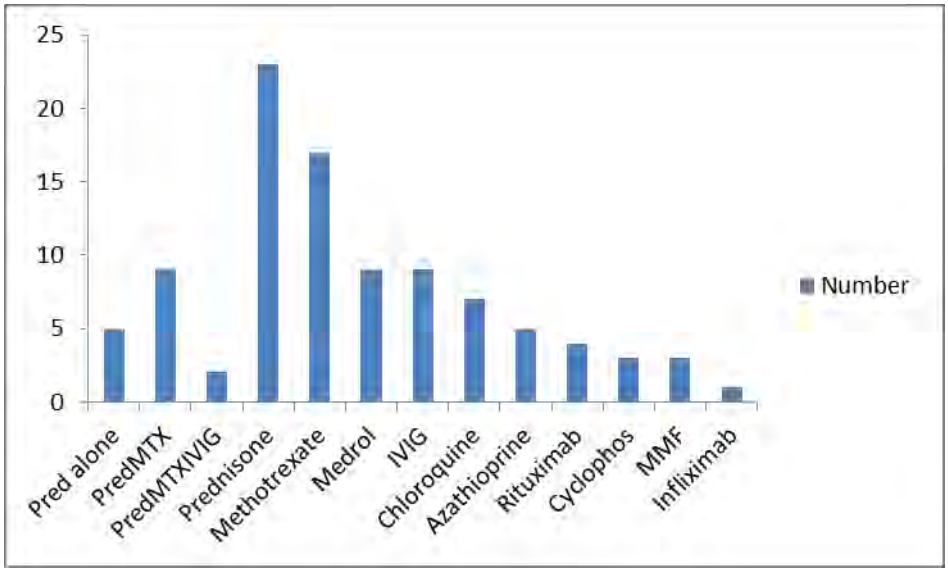

Figure 6: Treatment modalities in Cape Town JDM patients. All the patients received corticosteroids during the course of their treatment. Biologics were used in 6 patients (rituximab in 5 and infliximab in 1).

Abbreviations. Cyclophos: cyclophosphamide; **Medrol:** intravenous methylprednisolone; **Pred:** Prednisone **PredMTX:** Prednisone and methotrexate; **IVIG:** Intravenous immunoglobulin.

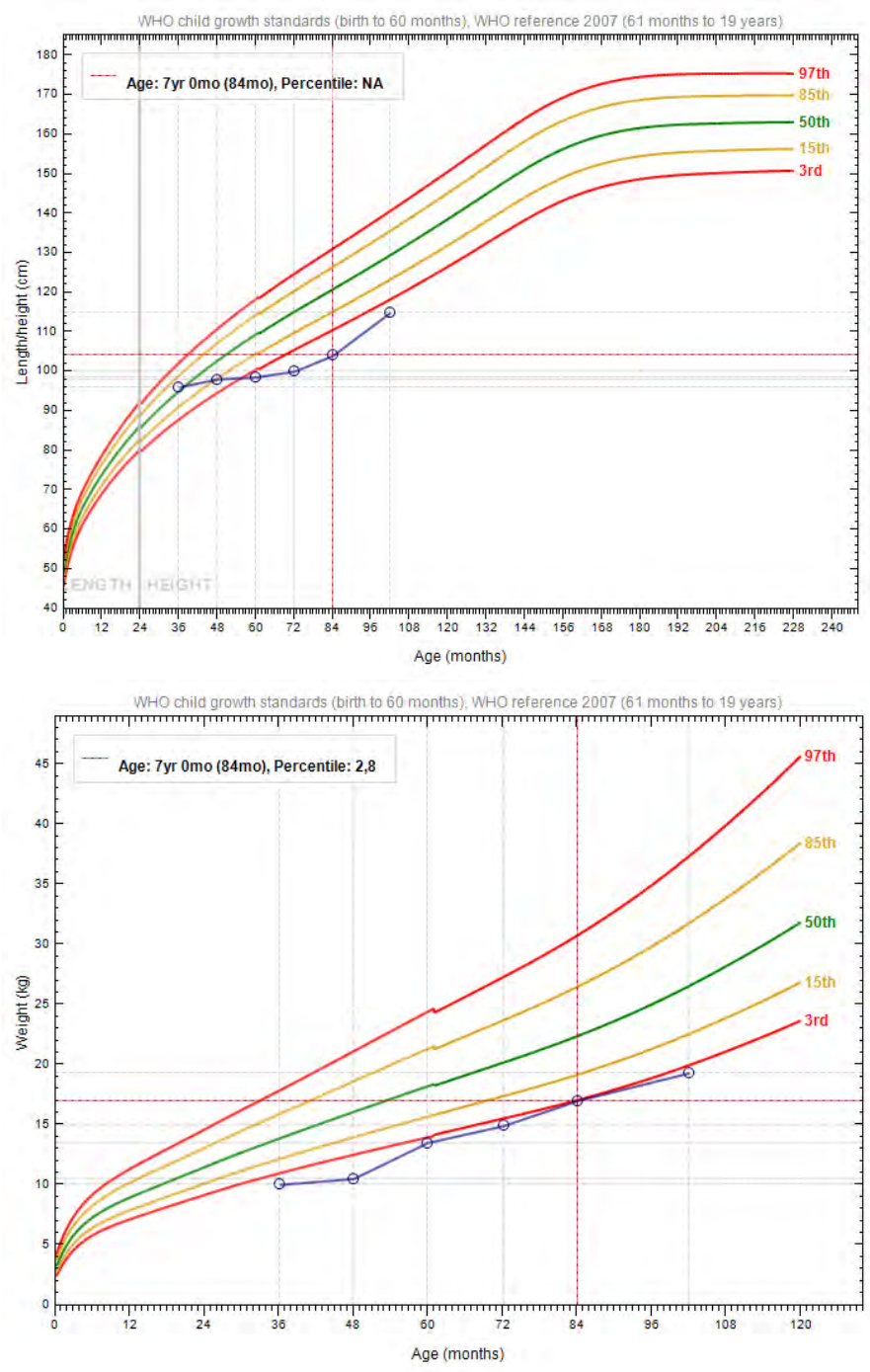

Figure 7: growth chart for one of the patients with growth failure. Note stature for age line crosses from above 50th centile to below 3rd centile and remains below 3rd centile line for >3 years.

Graph produced by replotting the child growth indices on the WHO AnthroPlus v1.0.4 software (http://www.who.int/growthref/tools/en/).

2.13 Appendices

2.13.1 Appendix 1: Case record form

Section A: Demographic data and disease classification

Sex	1.	Male	2.	Female
Birth Date				
Race	1.	Indigenous African	2.	European Caucasian
	3.	Cape coloured	4.	Other
Residential address	Province/Municipality……..			
Date of onset	Date of first visit		Date of diagnosis	
Outcome: 1. Ongoing care 2. Discharged 3. Lost to follow up 4. Death			Last Date of Visit	
Family history of autoimmune disease (1= Yes; 2= No; 3=Unknown)		If Yes, Specify disease and relationship		

Diagnostic criteria	0 = Not present 1 = Present NA = Cannot be assessed
1. Heliotrope rash OR Gottron's papules/sign	
2. Proximal Muscle Weakness	
3. Muscle Biopsy Changes	
4. Electromyographic changes	
5. Muscle MRI changes	
6. Elevated Muscle Enzymes	
Classification (1. Definite JDM; 2. Probable JDM; 3. Amyopathic 4. Mixed Connective Tissue Disease 5. Does not satisfy criteria for probable JDM)	
Comorbid conditions (specify)	

Section B: Clinical manifestations

A modified Myositis Disease Activity Assessment Tool **(MDAAT)** shall be used to document the clinical features that were present at diagnosis (or first visit) and cumulatively upto the last documented visit.

Constitutional Activity NA = Cannot be assessed 0 = Not present 1 = Present		
	At diagnosis	Cumulatively
Pyrexia (fever > 38° Celsius)		
Weight loss		
Fatigue, malaise, lethargy		
Cutaneous Activity NA = Can't be assessed 0 = Not present 1 = Present		
	At diagnosis	Cumulatively
Cutaneous ulceration		

Panniculitis		
Erythematous rashes		
Heliotrope rash		
Gottron's papules/sign		
Nailfold capillary changes		
Alopecia, diffuse hair loss		
Alopecia, patchy		
Mechanics hands		
Skeletal Disease Activity NA = Can't be assessed 0 = Not present 1 = Present		
	At diagnosis	Cumulatively
Moderate/severe arthritis		
Mild arthritis		
Arthralgia		

Gastrointestinal Disease Activity		
	At diagnosis	Cumulatively
Dysphagia		
Moderate/severe abdominal pain		
Mild abdominal pain		

Pulmonary Disease Activity		
	At diagnosis	Cumulatively
Dyspnoea		
Dysphonia		

Cardiovascular Disease Activity		
	At diagnosis	Cumulatively
Pericarditis		
Myocarditis		
Arrhythmia		
Sinus tarchycardia		

Muscle Disease Activity NA = Cannot be assessed 0 = Not present 1 = Present		
Myalgia		
Muscle weakness		
Other disease activity		

25. Relapses

Manifestation	Time from remission	Cause	Action

26. Disease activity core set measures:

Core set	Diagnosis	Review 1	Review 2	Other reviews
CMAS				
MMT8				
VAS Physician				
VAS Patient global				

CHAQ				

Section C: Drugs and other therapeutic modalities

		At diagnosis	during disease
		Dose and Duration	Dose and Duration
1.	Prednisone (Medrol I.V)		
2.	Prednisone (Oral)		
3.	Methotrexate		
4.	Chloroquine		
5.	Mycophenolate		
6.	Ciclosporin		
7.	Azathioprim		
8.	Cyclophosphamide		
9.	Infliximab		
10.	Rituximab		
11.	Immunoglobulin (IVIG)		
12.	Surgery		
13.	Physiotherapy		
14.	Other		

Section D: Diagnostic work up

Laboratory work up					
Reference range		Value at assessment			
		1st	2nd	3rd	4th
ESR					
CRP					
ANA					
dsDNA					
Anti-Ro/SSA					
Anti-La/SSB					
Anti-RNP					
Anti-Scl 70					
Anti-PMScl					
Anti-Jo1					
pANCA					
cANCA					
Other antibody					
CK					
Aldolase					
AST					
LDH					
Triglycerides					

Results of Radiological and other Diagnostic investigations

	Modality	Assessment		
		First	Second	Third
1.	Muscle MRI			
2.	Chest CT			
3.	Barium swallow			
4.	Muscle biopsy			
5.	EMG			
6.	Spectroscopy			
7.	Nailfold Capillaroscopy			
8.	ECG			
9.	Echocardiogram			
10.	FEV1			
12.	FVC			
13.	DLCO			
14.	Ophthalmology			

Section E: Damage Assessment

A modified Myositis Damage Index (MDI) tool shall be used to document organ damage cumulatively over the entire period of care till the last documented visit. The items are scored as present (1), absent (0) or Cannot be assessed (NA).

MUSCLE DAMAGE NA = Cannot be assessed 0 = Not present 1 = Present			
1. Muscle atrophy (clinical)	0	1	NA
2. Muscle weakness not attributable to active muscle disease	0	1	NA
3. Muscle dysfunction: decrease in aerobic exercise capacity	0	1	NA
4. Muscle atrophy assessed by radiographic methods	*0*	*1*	*NA*
5. Low serum creatinine (Value……..)	*0*	*1*	*NA*

SKELETAL DAMAGE NA = Cannot be assessed 0 = Not present 1 = Present			
6. Joint contractures	0	1	NA
7. Osteoporosis with fracture / vertebral collapse	0	1	NA
8. Avascular necrosis	0	1	NA
9. Deforming arthropathy (excluding contractures)	0	1	NA
10. Osteoporosis without clinical fracture,	*0*	*1*	*NA*
11. Limitation of motion (Passive Joint ROM in degrees):			
a. Elbow extension (degrees): R_____L_____	*0*	*1*	*NA*
b. Hip flexion (degrees): R_____L_____	*0*	*1*	*NA*
c. Knee extension (degrees): R_____L_____	*0*	*1*	*NA*

d. Ankle dorsiflesion (degrees) R_____L_____ *0* *1* *NA*

CUTANEOUS DAMAGE NA = Cannot be assessed 0 = Not present 1 = Present

12. Calcinosis:	0	1	NA
a. Calcinosis, superficial plaques or nodules	*0*	*1*	*NA*
b. *Calcinosis, tumoral*	*0*	*1*	*NA*
c. Calcinosis, planar	*0*	*1*	*NA*
d. Calcinosis, exoskeleton/calcinosis universalis	*0*	*1*	*NA*
13. Alopecia	0	1	NA
14. Cutaneous scarring or atrophy	0	1	NA
15. Poikiloderma	0	1	NA
16. Lipodystrophy	0	1	NA

GASTROINTESTINAL (GI) DAMAGE

17. Dysphagia	0	1	NA
18. GI dysmotility, constipation, diarrhea or abdominal pain	0	1	NA
19. Infarction or resection of bowel or other GI	0	1	NA
20. Steatosis	*0*	*1*	*NA*

PULMONARY DAMAGE NA = Cannot be assessed 0 = Not present 1= Present

21. Dysphonia	0	1	NA
22. Impaired lung function due to respiratory muscle damage	0	1	NA
23. Pulmonary fibrosis	0	1	NA
24. Pulmonary hypertension	0	1	NA

25. Diminished lung function:

a. DL-CO/Va (Carbon monoxide diffusing capacity corrected for alveolar volume) (% Predicted =_____%)	*0*	*1*	*NA*
b. FEV1 (% predicted =_____%)	*0*	*1*	*NA*

CARDIOVASCULAR DAMAGE NA=Can't be assessed 0=Not present 1=Present

26. Hypertension requiring treatment > 6 months	0	1	NA
27. Ventricular dysfunction / cardiomyopathy	0	1	NA

PERIPHERAL VASCULAR DAMAGE

30. Tissue or pulp loss	0	1	NA
31. Digit or limb loss or resection	0	1	NA

32. Venous or arterial thrombosis with swelling, ulceration or venous stasis

	0	1	NA
ENDOCRINE DAMAGE NA = Cannot be assessed 0 = Not present 1 = Present			
34. Growth failure	0	1	NA
35. Delay in development of secondary sexual characteristics	0	1	NA
36. Hirsutism or Hypertrichosis	0	1	NA
37. Irregular menses	0	1	NA
38. Primary or Secondary Amenorrhea	0	1	NA
39. Diabetes	0	1	NA
40. Hyperlipidemia (regardless of treatment)	*0*	*1*	*NA*
41. Infertility (female or male)	0	1	NA
42. Sexual dysfunction	0	1	NA
OCULAR DAMAGE NA = Cannot be assessed 0 = Not present 1 = Present			
43. Cataract resulting in visual loss	0	1	NA
44. Visual loss, other, not secondary to cataracts	0	1	NA
INFECTION NA = Cannot be assessed 0 = Not present 1 = Present			
45. Chronic infections:_____	0	1	NA
46. Multiple infections Specify:_____	0	1	NA
MALIGNANCY NA = Cannot be assessed 0 = Not present 1 = Present			
47. Any form of cancer, Specify type, grade and stage:_____	0	1	NA
OTHER DAMAGE, specify NA = Cannot be assessed 0 = Not present 1 = Present			
48. *Death: Cause and date*_____	*0*	*1*	*NA*
49. Other (specify):_____			

2.13.2 Appendix 2: Confidential log of JDM study patients.

Participant ID	Folder number
JDM1	
JDM2	
JDM3	
JDM4	
JDM5	
JDM6	
JDM7	
JDM8	
JDM9	
JDM10	
JDM11	
JDM12	
JDM13	
JDM14	
JDM15	
JDM16	
JDM17	
JDM18	
JDM19	
JDM20	
JDM21	
JDM22	
JDM23	
JDM24	
JDM25	
JDM26	
JDM27	
JDM28	

2.13.3 Appendix 3: Budget

The principal investigator shall do the data collection and analysis.

The budget is self-funded.

ITEM	**COST**
Telephone, cell phone & fax	R – 100
Internet & email	R – 0
Office supplies	R – 100
Courier & postage	R – 200
Printing & copying	R – 200
Ethics committee fee	R – 0
Transport	R – 300
Total direct costs	R – 900
Indirect costs (12%)	R – 108
GRAND TOTAL	R–1008

2.13.4 Appendix 4: Timelines

	Activity	**Proposed Start Date**	**Proposed end date**
1.	Proposal preparation	October 2013	December 2013
2.	Proposal submission for review and ethical approval	December 2013	April 2014
3.	Data collection	April 2014	May 2014
4.	Dissertation write up	October 2014	February 2015
5.	Dissertation submission	March 2015.	April 2015
6.	Submission of articles for publication	April 2014	August 2014

2.13.5 Appendix 5: Ethics committee approval University of Cape Town

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492 • **Facsimile** [021] 406 6411
Email: Sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/research/humanethics/forms

14 March 2014

HREC/REF: 062/2014

Dr C Scott
Paediatric Rheumatology
Room 5.16-ICH Building
Red Cross War Memorial Children's Hospital
Rondebosch

Dear Dr Scott

Project Title: DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF CHILDREN WITH JUVENILE DERMATOLYOSISTIS IN CAPE TOWN-Mphil Dr L Okong'o

Thank you for your letter dated 03rd March 2014, addressing the issues raised by the Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above mentioned study.

Approval is granted for one year until the 28 March 2015.

Please submit a progress form, using the standardised Annual Report Form, if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

We acknowledge that the following student:- Dr L O Okong'o is also involved in this study.

Please note that the on-going ethical conduct of the study remains the responsibility of the principal investigator

Please quote the HREC REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Hrec/ref:062/2014

2.13.6 Appendix 6: Ethics committee approval University of Stellenbosch

UNIVERSITEIT·STELLENBOSCH·UNIVERSITY
jou kennisvennoot · your knowledge partner

Ethics Letter

24-Jun-2014

Ethics Reference #: S14/04/080
Clinical Trial Reference #:
Title: Demographic and clinical characteristics of children with juvenile dermatomyosistis in Cape Town.

Dear Dr Lawrence Owino Okong'o,

We acknowledge receipt of documents pertaining to the above study and the approval letter from the UCT Human Research Ethics Committee, for this project.

The approval of the UCT HREC is recognised by the Stellenbosch University Health Research Ethics Committee for this particular project. However please continue to keep us informed of the progress of the project, by submitting annual progress reports.

Please note that research that will be conducted at any tertiary academic institution also requires approval from the relevant hospital manager.

If you have any queries or need further assistance, please contact the HREC Office 0219389156.

Sincerely,

REC Coordinator signature removed
Franklin Weber
Health Research Ethics Committee 1

2.13.7 Appendix 7: Paediatric rheumatology Instructions for authors

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Presubmission enquiries: If you wish to make a presubmission enquiry about the suitability of your manuscript, please email the editors who will respond to your enquiry as soon as possible.

Submission process: Manuscripts must be submitted by one of the authors of the manuscript, and should not be submitted by anyone on their behalf. The submitting author takes responsibility for the article during submission and peer review.

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- Microsoft word (DOC, DOCX)
- Rich text format (RTF)
- Portable document format (PDF)
- TeX/LaTeX (use BioMed Central's TeX template)
- DeVice Independent format (DVI)

TeX/LaTeX users: Please use BioMed Central's TeX template and BibTeX stylefile if you use TeX format. During the TeX submission process, please submit your TeX file as the main manuscript file and your bib/bbl file as a dependent file. Please also convert your TeX file into a PDF and submit this PDF as an additional file with the name 'Reference PDF'. This PDF will be used by internal staff as a reference point to check the layout of the article as the author intended. Please also note that all figures must be coded at the end of the TeX file and not inline.

If you have used another template for your manuscript, or if you do not wish to use BibTeX, then please submit your manuscript as a DVI file. We do not recommend converting to RTF. For all TeX submissions, all relevant editable source must be submitted during the submission process. Failing to submit these source files will cause unnecessary delays in the publication procedures.

Preparing main manuscript text

General guidelines of the journal's style and language are given below.

Overview of manuscript sections for Research Articles

Manuscripts for Research Articles submitted to *Pediatric Rheumatology* should be divided into the following sections (in this order):

- Title page
- Abstract
- Keywords
- Background
- Methods

- Results and discussion
- Conclusions
- List of abbreviations used (if any)
- Competing interests
- Authors' contributions
- Authors' information
- Acknowledgements
- Endnotes
- References
- Illustrations and figures (if any)
- Tables and captions
- Preparing additional files

The **Accession Numbers** of any nucleic acid sequences, protein sequences or atomic coordinates cited in the manuscript should be provided, in square brackets and include the corresponding database name; for example, [EMBL:AB026295, EMBL:AC137000, DDBJ:AE000812, GenBank:U49845, PDB:1BFM, Swiss-Prot:Q96KQ7, PIR:S66116].

The databases for which we can provide direct links are: EMBL Nucleotide Sequence Database (EMBL), DNA Data Bank of Japan (DDBJ), GenBank at the NCBI (GenBank), Protein Data Bank (PDB), Protein Information Resource (PIR) and the Swiss-Prot Protein Database (Swiss-Prot).

You can download a template (Mac and Windows compatible; Microsoft Word 98/2000) for your article.

For reporting standards please see the information in the About section.

Title page

The title page should:

- provide the title of the article
- list the full names, institutional addresses and email addresses for all authors
- indicate the corresponding author

Please note:

- the title should include the study design, for example "A versus B in the treatment of C: a randomized controlled trial X is a risk factor for Y: a case control study"
- abbreviations within the title should be avoided

Abstract

The Abstract of the manuscript should not exceed 350 words and must be structured into separate sections: **Background,** the context and purpose of the study; **Methods**, how the study was performed and statistical tests used; **Results**, the main findings; **Conclusions**, brief summary and potential implications. Please minimize the use of abbreviations and do not cite references in the abstract. **Trial registration**, if your research reports the results of a controlled health care intervention, please list your trial registry, along with the unique identifying number (e.g. **Trial registration**: Current Controlled Trials ISRCTN73824458). Please note that there should be no

space between the letters and numbers of your trial registration number. We recommend manuscripts that report randomized controlled trials follow the CONSORT extension for abstracts.

Keywords

Three to ten keywords representing the main content of the article.

Background

The Background section should be written in a way that is accessible to researchers without specialist knowledge in that area and must clearly state - and, if helpful, illustrate - the background to the research and its aims. Reports of clinical research should, where appropriate, include a summary of a search of the literature to indicate why this study was necessary and what it aimed to contribute to the field. The section should end with a brief statement of what is being reported in the article.

Methods

The methods section should include the design of the study, the setting, the type of participants or materials involved, a clear description of all interventions and comparisons, and the type of analysis used, including a power calculation if appropriate. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses in the Methods section.

For studies involving human participants a statement detailing ethical approval and consent should be included in the methods section. For further details of the journal's editorial policies and ethical guidelines see 'About this journal'.

For further details of the journal's data-release policy, see the policy section in 'About this journal'.

Results and discussion

The Results and discussion may be combined into a single section or presented separately. Results of statistical analysis should include, where appropriate, relative and absolute risks or risk reductions, and confidence intervals. The Results and discussion sections may also be broken into subsections with short, informative headings.

Conclusions

This should state clearly the main conclusions of the research and give a clear explanation of their importance and relevance. Summary illustrations may be included.

List of abbreviations

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations can be provided, which should precede the competing interests and authors' contributions.

Competing interests

A competing interest exists when your interpretation of data or presentation of information may be influenced by your personal or financial relationship with other people or organizations. Authors must disclose any financial competing interests; they should also reveal any non-financial competing interests that may cause them embarrassment were they to become public after the publication of the manuscript.

Authors are required to complete a declaration of competing interests. All competing interests that are declared will be listed at the end of published articles. Where an author gives no competing interests, the listing will read 'The author(s) declare that they have no competing interests'.

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- In the past three years have you received reimbursements, fees, funding, or salary from an organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future? Is such an organization financing this manuscript (including the article-processing charge)? If so, please specify.
- Do you hold any stocks or shares in an organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future? If so, please specify.
- Do you hold or are you currently applying for any patents relating to the content of the manuscript? Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript? If so, please specify.

- Do you have any other financial competing interests? If so, please specify.

Non-financial competing interests

Are there any non-financial competing interests (political, personal, religious, ideological, academic, intellectual, commercial or any other) to declare in relation to this manuscript? If so, please specify.

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Authors' contributions

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OnlineFirst chapter in a series (without a volume designation but with a DOI)

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Online document

Doe J. Title of subordinate document. In: The dictionary of substances and their effects. Royal Society of Chemistry. 1999. http://www.rsc.org/dose/title of subordinate document. Accessed 15 Jan 1999.

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Doe J. Title of supplementary material. 2000. http://www.privatehomepage.com. Accessed 22 Feb 2000.

University site

Doe, J: Title of preprint. http://www.uni-heidelberg.de/mydata.html (1999). Accessed 25 Dec 1999.

FTP site

Doe, J: Trivial HTTP, RFC2169. ftp://ftp.isi.edu/in-notes/rfc2169.txt (1999). Accessed 12 Nov 1999.

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