Author's response to reviews

Title: Metabolic Syndrome in Rheumatoid Arthritis: case control study.

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Author's response to reviews: see over
Dear Sir,

We wish to thank you and the reviewers for your interest in our manuscript. Please find attached the revised version of an article we have proposed for publication, entitled “Prevalence of Metabolic Syndrome in patients with Rheumatoid Arthritis and its determinants”.

Authors Rostom S et al, Editorial manuscript number: Ref.: Ms. 1161719207809910

We hereby confirm that the article has not been published and is not under consideration for publication elsewhere. There were no financial support or other benefits from commercial sources for the work reported on in the manuscript, or any other financial interests that any of the authors may have, which could create a potential conflict of interest or the appearance of a conflict of interest with regard to the work.

The manuscript has been read and approved by all authors.

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Reviewer's report:

Reviewers N 1 report:

Dr Rostom and colleagues described the frequency of metabolic syndrome in RA patients and also evaluated the association between MetS and RA. The result of this study is valuable because it is the first study from Morocco.

We wish to thank the reviewer for his interest.

Major compulsory revisions

The authors have shown that the frequency of the MetS in RA patients was significantly higher compared to controls and the presence of MetS in patients with RA was associated with a higher systemic inflammatory marker, and glucocorticoids use. They should clearly describe the novelty of their study and its difference with previous studies.

Morocco is one of the countries of North Africa with unmet need of sustainable healthcare delivery systems. North Africa is a region with challenging political, climatic and geographical conditions. Data from small studies in the region show that RA is frequently diagnosed late and many patients present with active disease and severe disability. Despite this, only a small proportion of patients receive DMARDs particularly biologic DMARDS, and the scarcity of medical and social resources is a barrier to appropriate treatment in many countries [1-6]. Morocco had also participated in two international studies: QUEST RA study [7], which is a successful example of quantitative clinical measuring of RA as part of routine clinical care in a large number of centres across more than 30 countries including countries from Europe (France, Germany, Netherlands,...), USA, Argentina, Brazil, Morocco, and United Arab Emirates. This study has suggested high disease activity in our country. The second study is COMORA study: comorbidities in RA (data not yet published), these two studies suggest a high disease activity in our country (300 patients from 10 centers of the country), the use of high-dose corticoids, and a more frequent association with hypertension, dyslipidemia, overweight and less frequent exposure to tobacco and alcohol. Solomon A et al [8] have assessed the risk factor profiles for atherosclerotic cardiovascular disease in black and other Africans with established rheumatoid arthritis and found that
proportions of individual metabolic syndrome components differed between black and other patients but their total numbers of metabolic risk factors and metabolic syndrome frequencies were similar. From these data from cross-sectional studies in Africa, we can assume that the activity profile and Severity of RA in Africa is quite different from Western countries. Furthermore, metabolic syndrome and activity are intimately linked. Hence, we aimed to assess the frequency of metabolic syndrome and its components and evaluate the supposed association with disease activity and severity of RA.

This has been added in the introduction section page 3 with references.


Minor essential revisions

Introduction

1. Paragraph 3, lines 20-23, “Several studies have examined… in study populations” should be referenced.

The reviewer is right. This has been performed as asked: References [7-8].

Material and Methods

1. Please explain why the number of cases and controls are different?

The reviewer is right. Indeed, the healthy controls are from the families of patients and the medical and paramedical staff of our hospital. They were adjusted for age and sex. For some age groups of 5 years and gender equivalent, we could not find equivalent controls. We discuss this point with a statistician who has not objected statistically.

2. Please describe the setting, locations and period of recruitment of cases and controls.

Indeed, the reviewer is right; this supplementary population description was added in the patients and methods section.

Our study included 120 consecutive patients with RA fulfilling the 1987 revised American College of Rheumatology classification criteria [9] over a period of 13 months (between May
2010 and June 2011) at the department of rheumatology of El Ayachi tertiary university hospital of Rabat-Sale from outpatient and inpatient services. Patients with other inflammatory diseases, malignancies, diseases of the central nervous system, chronic kidney disease, chronic liver disease besides RA, were excluded from the study.

**Healthy controls**

One hundred age-, sex-, and race-matched apparently healthy volunteers’ women and men from urban and rural residences of the Rabat-Sale province in Morocco served as the control group in the present study. Healthy subjects were represented by families of patients or families of medical or paramedical staff of the hospital. Informed consent was obtained from all subjects and the study was approved by the ethics committee Board of Rabat-Salé.

3. **Please provide the eligibility criteria for cases and controls.**
We wish to thank the reviewer; this has been performed as asked in patients and methods section page 4;

**Results**

1. **The tables should be numbered correctly.**
We wish to thank the reviewer; this has been performed as asked.

2. **Please provide which factors were included in the multivariate analysis or adjusted for?**
The factors included in the multivariate analysis were: age, HAQ, ESR, glucorticoides use.

**Discussion**

1. **This is a case-control study not a cross-sectional? Please correct it.**
Indeed, the reviewer is right. This correction has been performed as asked.

**Level of interest:** An article whose findings are important to those with closely related research interests
We wish to thank the reviewer for his interest.

**Quality of written English:** Needs some language corrections. We wish to thank the reviewer; the draft was corrected in term of English language.
Overall comments:
An interesting problem in RA that deserves more study.
We wish to thank the reviewer for his interest.

Major: This is a relatively small study, which is a concern because it is being proposed as a “prevalence” study. However, a study of this kind, at a single center and with a relatively small number of subjects is at risk for selection bias.
Generalizability is also a question, given that the study is performed in Morocco.
In other words, I suspect the prevalence in other countries would be highly variable.
This should be emphasized in the manuscript

The reviewer is absolutely right, we tried to assess the frequency of metabolic syndrome in a population of small sample and in a tertiary center, so there is inevitably a selection bias and it is certainly not representative of the General population in Morocco. This point was addressed in the discussion section. The term prevalence has been changed by frequency.
Please see below the paragraph added to the discussion

“...The limitations of the current study should be addressed. The cross-sectional design and small size of our study limit the ability to describe causal relationships to the associations detected. Furthermore; the small sample size of this study, and recruitment from a single center, which is a tertiary care center with recruitment of the most active and severe disease expose to bias selection and the risk of surestimation of the real frequency of metabolic syndrome. The international COMORA study (comorbidities in RA) to which Morocco has participated with 300 patients across 10 centers in the country (private and public structures) will be interesting, it can given the frequency of metabolic syndrome and its components and compared these data through countries. Moreover, the Moroccan ESPOIR study (Etude et Suivi des POlyarthrites rhumatoïdes et arthrites Indifférenciées Récentes), a prospective multicenter cohort study of 10 years of follow-up will provide some information on the epidemiological profile of the RA in Morocco. Further prospective studies should prove valuable in determining these causal relationships”. 
Methods

Major: Study selection- this could be more clearly defined. How were patients identified? From what practices? Were there exclusion criteria? More information on how the control population was defined would also be helpful. How were they identified? Were there differences in the geography or socioeconomics of the clinics for RA/controls?

We wish to thank the reviewer for his interest. Indeed, the reviewer is right; this supplementary population description was added in the patients and methods section. Please see below

‘patients : Our study included 120 consecutive patients with RA fulfilling the 1987 revised American College of Rheumatology classification criteria [9] over a period of 13 months (between May 2010 and June 2011) at the department of rheumatology of El Ayachi tertiary university hospital of Rabat-Sale from outpatient and inpatient services.

Patients with other inflammatory diseases, malignancies, diseases of the central nervous system, chronic kidney disease, chronic liver disease besides RA, were excluded from the study.

Healthy controls

One hundred age-, sex-, and race-matched apparently healthy volunteers’ women and men from urban and rural residences of the Rabat-Sale province in Morocco served as the control group in the present study. Healthy subjects were represented by families of patients or families of medical or paramedical staff of the hospital.

Informed consent was obtained from all subjects and the study was approved by the ethics committee Board of Rabat.

Major: Metabolic syndrome definition- It’s clear that the authors used a number of methods to define metabolic syndrome. What could be more clearly delineated is how the components were defined. For example- how was “hypertension” defined? What was available in terms of fasting glucose?

The reviewer is right this supplementary data collection was added in the patients and methods section. Please see below.

Body composition
Body mass index (BMI) was calculated from weight/height\(^2\) (kg/m\(^2\)). BMI values < 18.5 kg/m\(^2\) are considered underweight, between 18.5 - 24.9 as normal, 25-29.9 as overweight and values greater than 30 indicate obesity [12]. Waist circumference (WC) was measured ......... BP was measured by a mercury sphygmomanometer in the sitting position after five minutes of rest. Hypertension was defined by blood pressure ≥ 130 mmHg for systolic pressure or ≥85 mmHg diastolic pressure or current treatment for hypertension.

**Biochemical measures**

Biological tests were performed from venous blood samples obtained the morning after an overnight fast. Plasma fasting glucose (FG) levels were measured using the glucose oxidase method. C-reactive protein (CRP), ESR, total cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) were determined by standard laboratory methods. Concentrations of total cholesterol > 5.0 mmol/L, LDL ≥ 3.0 mmol/L, HDL < 1.3 mmol/L were considered pathologic [13]. A renal function assessment was performed by estimation of glomerular filtration rate according to the Modification of Diet in Renal Disease (MDRD) equation.

**Results:**

Overall the results are not particularly novel, although I doubt there is literature in the Moroccan population.

Minor: Frequency of metsyn- concern is selection bias here, though I believe the results. The variation in prevalence based on the definition is interesting however I would avoid the terms “under/over estimation” since we don’t know what is truth.

The reviewer is right. I would like to thank the reviewer for his relevant comments. The terms “under/over estimation” were removed from the drafts.

Minor: It may be interesting to see how the different components of the metabolic syndrome are affected by different exposures. For example, I wonder if prednisone use is primarily associated with glucose or with weight. In addition, it might be interesting to evaluate whether different RA factors are associated with a greater number of components of the metabolic syndrome in ordinal regression. Finally, it would be interesting to know if there is one component driving the difference between RA and controls (ie. weight).
The prednisone use was associated with glucose (p=0.03), with waist circumference (p=0.04), but not statistically significant with weight (p=0.09). Waist circumference was significantly high in RA (p=0.001), weight was also slightly high in RA than controls (p=0.05).

**Major**: The finding that glucose, SBP, and lipids were higher in Metsyn is not important and could be removed from the results (these are characteristics of the metsyn).

The reviewer is right. The components of metabolic syndrome were removed from the results.

**Major**: Linear regression models might help better characterize some of these associations. For example, was the association with ESR independent of age (which is associated with higher ESR)? Same for the HAQ. Is the HAQ score associated with metabolic syndrome simply through an association with BMI? Is the effect of prednisone independent of BMI? A table with the final regression model and some explanation of how that model was developed would be helpful.

Indeed, this is an interesting suggestion but was not performed.

**Discussion**

**Major**: The authors appear to promote their study as a prevalence study. While they appear to be the first to study metsyn in RA among Moroccan subjects, I’m not sure that I would intimate that this is representative of any larger population. I think the “prevalence” data should be downplayed given it is based on 120 clinic patients.

We completely agree with the reviewer. This point is now addressed in the Discussion. We tried to assess the frequency of metabolic syndrome in a population of small sample and in a tertiary center, so there is inevitably a selection bias and it is certainly not representative of the General population in Morocco. This point was addressed in the discussion section. The term prevalence has been changed by frequency.

Please see below the paragraph which was added to the discussion

“"The limitations of the current study should be addressed. The cross-sectional design and small size of our study limit the ability to describe causal relationships to the associations detected. Furthermore; the small sample size of this study, and recruitment from a single center, which is a tertiary care center with recruitment of the most active and severe disease expose to bias selection and the risk of surestimation of the real frequency of metabolic syndrome."
The sentence ‘’In addition to the originality of most of the findings, this study has several other strengths. These include the use of all of the existing MetS criteria for the first time in Morocco patients with RA’’ was removed from discussion.

Major: The associations between ESR and Metsyn are not convincing, given that ESR can be affected by a number of comorbid conditions (renal disease) as well as age. Furthermore, metabolic syndrome is an inflammatory condition, and thus ESR may be elevated to some degree by the presence of Metsyn. I think a greater discussion of this association and the limitations of a cross-sectional analysis should be included.

The reviewer is right; we took these factors into account in the discussion of results in page 9

Major: An expansion of the discussion of the overall limitations is necessary. The authors should acknowledge that they are likely to suffer from selection bias and/or may not be generalizable to the general population, even within Morocco (ie their selected study sample may not be representative of all Moroccan patients with RA).

We agree with the reviewer that this point is interesting and relevant. This has been performed as asked in the discussion section page 10; please see below:

‘’The limitations of the current study should be addressed. The cross-sectional design and small size of our study limit the ability to describe causal relationships to the associations detected. Furthermore; the small sample size of this study, and recruitment from a single center, which is a tertiary care center with recruitment of the most active and severe disease expose to bias selection and the risk of surestimation of the real frequency of metabolic syndrome’’.

We have also changed the title: Metabolic Syndrome in Rheumatoid Arthritis: case control study.

Level of interest: An article of limited interest

We wish to thank the reviewer and we hope that after these relevant revisions, the manuscript will be more interesting. Morocco is one of the countries of North Africa with unmet need of sustainable healthcare delivery systems. North Africa is a region with challenging political, climatic and geographical conditions. Data from small studies in the region show that RA is frequently diagnosed late and many patients present with active disease and severe disability. Despite this, only a small proportion of patients receive DMARDs particularly biologic DMARDS, and the scarcity of medical and social resources is a barrier to appropriate treatment in many countries [1-6]. Morocco had also participated in two international studies: QUEST RA study [7], which is a successful example of quantitative clinical measuring of RA
as part of routine clinical care in a large number of centres across more than 30 countries including countries from Europe (France, Germany, Netherlands....), USA, Argentina, Brazil, Morocco, and United Arab Emirates. This study has suggested high disease activity in our country. The second study is COMORA study: comorbidities in RA (data not yet published), these two studies suggest a high disease activity in our country (300 patients from 10 centers of the country), the use of high-dose corticoids, and a more frequent association with hypertension pressure, dyslipidemia, overweight and less frequent exposure to tobacco and alcohol. Solomon A et al [8] have assessed the risk factor profiles for atherosclerotic cardiovascular disease in black and other Africans with established rheumatoid arthritis and found that proportions of individual metabolic syndrome components differed between black and other patients but their total numbers of metabolic risk factors and metabolic syndrome frequencies were similar. From these data from cross-sectional studies in Africa, we can assume that the activity profile and Severity of RA in Africa is quite different from Western countries. Furthermore, metabolic syndrome and activity are intimately linked. Hence, we aimed to assess the frequency of metabolic syndrome and its components and evaluate the supposed association with disease activity and severity of RA.

Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.

Editor's comments:
1- If you revise the paper addressing the reviewers' comments, please also work to reduce unnecessary abbreviations. For example, I don't believe the abbreviation "MetS" is needed, and its use makes the paper more difficult to read.
We wish to thank the Editor for his interest. This has been performed as asked.

2- Kindly provide name of ethics committee.
The name of ethics committee: The Research and Ethical Review Board of the Avicenne University Hospital, Rabat, Morocco. This has been added in the patients and methods section.

Best regards,

Samira Rostom, corresponding author