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Journal Name:	International Journal of Biochemistry Research & Review
Manuscript Number:	Ms_IJBCRR_23824
Title of the Manuscript:	Adipokines, Receptor activator of nuclear factor- κ B ligand, And Midkine: An Intricate biomarkers Network Involved In Pathogenesis And Activity Of Rheumatoid Arthritis in Egyptians
Type of the Article	Research article

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This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty**', provided the manuscript is scientifically robust and technically sound.

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SDI Review Form 1.6

PART 1: Review Comments

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
<u>Compulsory</u> REVISION comments	In this study serum concentration of TNF-alpha, adiponectin, visfatin and RANKL as well as the expression of midkine in peripheral blood cells was measured in 40 newly diagnosed patients with rheumatoid arthritis and 20 matched control subjects. It is demonstrated that these cyto- and adipokines were elevated in RA patients, were higher in active vs. inactive RA subgroup, and were positively correlated with DAS-28. The study is well-performed and the manuscript is in general well-written. However, there are also some important concerns: 1) The results are not entirely innovative since at least some of these factors have been previously measured in RA. 2) Adiponectin is mentioned as the proinflammatory adipokine in several places in the manuscript. Although adiponectin is proinflammatory in some systems, it reduced inflammation in the majority of studies. Thus, it should not be classified as "proinflammatory". 3) It is suggested that adipokines of interest could be useful in diagnosis and/or monitoring of RA. This is the over-interpretation of results. Diagnostic value of adipokines was not compared to traditional criteria in this study. In addition, as all patients were with recently diagnosed RA, nothing about monitoring could	We appreciated your constructive criticisms and the valuable comments that have helped us greatly to improve our manuscript. We have addressed each of their concerns as outlined below. 1) As using monoclonal antibodies or soluble receptors to neutralize cytokines as TNF-α have been developed as treatments for RA but they are not curative with failure of response being common. So that, other pro-inflammatory cytokines may play a role in the pathophysiology of inflammation in RA patients our aim was to identified the combined role of adipocytokines, RANKL and MDK axis in RA, thus this study aimed to unravel their roles in RA pathogenesis, early diagnosis and activity, which may open new avenues for developing preventive and therapeutic strategies for RA. 2) The word (pro-inflammatory) was removed 3) This is our conclusion: Adipocytokines, RANKL and MDK axis has a role in pathogenesis, early diagnosis and disease activity in patients with RA. These results may open new avenues for



SDI Review Form 1.6

	be concluded. 4) What kind of adiponectin (total or HMW) was measured? 5) Some details about ELISA kits should be provided such as detection limit, intra- and interassay coefficients of variation. 6) Correlations between adipo- and cytokines measured in this study should be analysed. In addition, some multivariate analysis would be interesting, for example to establish which of adipo- and cytokines of interest are the strongest and independent predictors of RA severity.	developing preventive and therapeutic strategies for RA. We did not study their role in the follow up or its prognostic role, only we studied their role in early diagnosis of RA and monitoring RA activity if it is active or not according to DAS-28 on our ongoing research we test the relationship between this axis and disease progression and prognosis as completion of this study in our Egyptian population 4)Total adiponectin was measured 5) I checked them in the kits those are the values you asked about. Serum levels of TNF-α was determined using a highly sensitive sandwich enzyme linked immunosorbent assay (ELISA) technique using commercial kits (Affymetrix eBioscience, USA) according to the manufacturer's protocol (intra-assay co-efficient of variation (CV)< 6%; interassay CV < 7.4%). The detection limit of this assay is 2.3 pg/ml. Serum RANKL was determined using a highly sensitive sandwich ELISA technique using commercial kits (Sunred Biological Technology Co. Shanghai, PRC) according to the manufacturer's protocol (intra-assay CV < 9%; interassay CV < 11%). The detection limit of this assay is 0.072 pmol/l. Serum adiponectin was determined using a highly sensitive sandwich ELISA technique using commercial kits (Ani Biotech Oy,
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SDI Review Form 1.6

		Organium Laboratories Business Unit, Finland) according to the manufacturer's protocol (intra-assay CV < 10%; interassay CV<15%). The detection limit of this assay is <0.3 ng/ml. Serum visfatin was determined using competitive sandwich ELISA technique using commercial kits (Ray Biotech, Inc. USA) according to the manufacturer's protocol (intra-assay CV < 10%; interassay CV<15%). The detection limit of this assay is <0.778 ng/ml 6)Correlation study was performed for all studied biochemical and molecular biomarkers in table 5 in manuscript.
<u>Minor</u> REVISION comments	1) It should be specified in the Abstract that MDK mRNA was measured in peripheral blood cells. 2) Page 1: TNF-alpha is classified as the adipokine which is not strictly correct. Although TNF-alpha is produced by adipose tissues, there are other sources of it such as inflammatory cells. Thus, especially if measured only in serum, TNF-alpha should not be classified as the adipokine because the source of its elevation is not clear.	1)This was done 2) We changed adipokine to adipocytokines in the whole manuscript.
<u>Optional/General</u> comments		