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Immunological Investigations
A Journal of Molecular and Cellular Immunology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iimm20

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To cite this article: Zahra Samimi , Arman Izadpanah , Parisa Feizollahi , Seyed Askar Roghani , Shirin Assar , Parisa Zafari & Mahdi Taghadosi (2020): The Association between the Plasma Sugar and Lipid Profile with the Gene Expression of the Regulatory Protein of *mTOR* (Raptor) in Patients with Rheumatoid Arthritis, Immunological Investigations, DOI: 10.1080/08820139.2020.1781160

To link to this article: https://doi.org/10.1080/08820139.2020.1781160

Published online: 24 Jun 2020.

IMMUNOLOGICAL INVESTIGATIONS
https://doi.org/10.1080/08820139.2020.1781160

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The Association between the Plasma Sugar and Lipid Profile with the Gene Expression of the Regulatory Protein of *mTOR* (Raptor) in Patients with Rheumatoid Arthritis

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ABSTRACT

Background: Rheumatoid arthritis (RA) is an autoinflammatory and self-perpetuating disease with both articular and extra-articular manifestations, such as cardiovascular complications, which are the leading cause of mortality and morbidity in RA patients. Impaired sugar and lipid metabolism are considered as the critical risk factors for cardiovascular disease (CVD). Regarding the regulatory function of Raptor in the immunometabolism, in this study, we evaluated the association between plasma sugar and lipid profiles with the gene expression of Raptor and the cytokine tumor necrosis factor-α (TNF-α), as an inflammatory mediator, in peripheral blood leukocyte of RA patients.

Material and methods: Thirty-five RA patients who received combinational disease modified anti-rheumatoid drugs (DMARD) regimen and thirty healthy subjects enrolled in this study. The gene expression of Raptor was assessed by the real-time PCR method, and the Plasma levels of glucose and lipids, as well as TNF-α, were obtained using Hitachi device and enzyme-linked immunosorbent assay (ELISA) technique, respectively.

Results: The gene expression of Raptor was reduced significantly in RA patients compared to the healthy subjects ($p = .001$). The plasma level of HDL was significantly higher in RA patients than the control group ($p = .001$), while the plasma level of LDL was reduced significantly in these patients ($p = .001$).

Conclusion: In our study, the reduced gene expression of Raptor may contribute to the impaired immunometabolism in RA patients, which is independent of plasma sugar and lipid profile.

KEYWORDS
Rheumatoid arthritis; glucose and lipid profiles; TNF-α; Raptor

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease of joint with variable extra-articular manifestation(van der Pouw Kraan et al. 2003). Given the effect of inflammatory mediators on various biochemical parameters, including plasma sugar and lipids, RA patients

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are at high risk for cardiovascular disease (CVD), which is one of the leading causes of mortality and morbidity in these patients (Chavan et al. 2015). Several traditional risk factors, including impaired glucose metabolism, dyslipidemia, low levels of magnesium, increased uric acid, as well as high prevalence of metabolic syndrome, contribute to the development of CVD in RA patients. Regarding the previous studies, the interaction between CVD risk factors and those related to the RA is complicated(Escalante et al. 2005; Solomon et al. 2010). The factors, such as hyperglycemia and dyslipidemia, also confer significant CVD risk in the general population(Azizi et al., 2002). Nonetheless, these risk factors cannot alone describe the excess CVD risk in RA, which may be further exacerbated by the deleterious effect of inflammation and immune reaction on the vessel walls(Symmons and Gabriel 2011). Compelling evidence show that inflammation affects the development of cardiovascular disease(Libby 2006; Willerson and Ridker 2004). Given the inflammatory nature of RA, It is most likely that the mediators of inflammation, like cytokines amplify the impact of traditional risk factors on development CVD (Crowson et al. 2013). Plasma sugars and lipid molecules are among the critical risk factors with a far-reaching effect in the development of CVD (Azizi et al., 2002). Previous systematic review and meta-analysis showed the correlation between RA and the development of diabetes mellitus(Jiang et al. 2015). Although the mechanism related to the development of DM in RA has not yet been fully elucidated, The inflammatory cytokines, including tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), may induce insulin resistance and eventually result in hyperglycemia and DM(Popa et al. 2007). Furthermore, glucocorticoids abundantly used in the treatment of RA worsen glucose tolerance through the induction of gluconeogenesis by the liver and inhibition of glucose uptake by adipocytes(Burt et al. 2011). Different corticosteroids, especially prednisolone may alter plasma lipids levels through modulation of the genes involved in the lipids metabolic pathways(Staels et al. 1991). In the case of lipid molecules, although the findings have been relatively controversial, the lipid profile appears to have a paradoxical effect on the CVD risk in RA(Myasoedova et al. 2011). For instance, previous data showed there is an inverse correlation between serum low-density lipoprotein (LDL) and CVD risk in these patients(Myasoedova et al. 2011). Acute or chronic high-grade inflammation Suppress LDL cholesterol levels in RA patients(Hahn et al. 2007). Given the high prevalence of dyslipidemia (i.e., pathologic changes of plasma lipid molecules, including triglycerides, cholesterol, LDL, and HDL and their ratios) in RA patients and the inflammatory nature of RA, The survey of inflammation-induced plasma lipid alteration in RA patients could be the subject of further investigation(Toms et al. 2010). On the other hand, intact metabolism is a critical factor that guarantees the proper function of the immune cells, and impairment of metabolic reactions in these cells contributes to RA inflammation (Finlay and Cantrell 2011; Samimi et al. 2019). New insights have been gained into the close association between the immune reaction and metabolism. In rheumatic and chronic inflammatory diseases (CIDs), the activation of the immune system needs a considerable amount of energy (Fox et al. 2005). Mammalian Target of Rapamycin (mTOR) is a multi-subunit ubiquitous serine/threonine kinase acting as a metabolic sensor and central regulator of growth, proliferation, cell metabolism, and survival. It is stimulated in response to factors such as glucose, lipid, growth factors, cytokines, hormones, stresses, and inflammation (Gwinn et al. 2008). There are two types of mTOR complexes called mTORC1 and mTORC2 that are involved in different regulatory pathways(Laplante and Sabatini 2009). mTORC1 is a multi-subunit protein with five components, including mammalian target of rapamycin (mTOR), the regulatory-associated

protein of mTOR (Raptor), mammalian lethal with Sec13 protein 8 (mLST8), proline-rich AKT substrate 40 KDa (PRAS40) and DEP-domain-containing mTOR-interacting protein (Deptor) each of which has its functions. mTORC1 positively regulates cell growth and proliferation through enhancing anabolic processes, including biosynthesis of proteins and lipids(Guertin and Sabatini 2007). Raptor is the regulatory subunit of mTORC1, and it has been implicated in its positive regulation by recruiting substrates for this catalytic subunit (Kim and Sabatini, 2004). The mTOR signaling pathway contributes to the regulation of cardiomyocytes and vascular-associated metabolism, and its inappropriate activation can lead to endothelial cells dysfunction, and impaired insulin metabolic signaling (Chong and Maiese 2012). Furthermore, this signaling pathway is also involved in the inflammatory conditions like RA, where it enhances T-cell polarization toward T Helper (Th) type17 and Th1 subsets which promotes the production of TNF-α, the pro-inflammatory product of macrophages(Perl 2016), that plays a fundamental role in articular destruction and joint damage as well as, co-morbidities associated with RA (Brennan and McInnes 2008).

Considering immune-mediated inflammatory response underlying RA pathogenesis, and reciprocal effects of the inflammation and metabolism in these patients, this study was conducted to investigate the association of Raptor, the crucial modulator of immuno-metabolism, gene expression in peripheral leukocytes with plasma sugar and lipids as critical risk factors in the development of CVD in RA patients.

Method and material

We carry out a cross-sectional study with a consecutive sampling of RA patients referring to Helal Ahmar clinic of the Kermanshah University of Medical Sciences (KUMS), between July 2017 and October 2017. Data regarding age, sex, weight, and relevant medical history were collected into a predesigned form, and the entire participant signed informed consent. This study was following the Declaration of Helsinki and was conducted with approval from the Ethics Committee of Kermanshah University of Medical Sciences (KUMS). We recruited Thirty-five RA patients as well as 30 age- and sex-matched healthy subjects in this survey. The patients fulfilling the American College of Rheumatology/European League Against Rheumatism (ACR-EULAR) 2010 criteria irrespective of disease activity were enrolled in this survey. (Kay and Upchurch 2012) The patients and the controls with a previous history of systemic rheumatic disease other than RA, endocrine, and metabolic disorder, including type 1 and type 2 diabetes mellitus, hyper- or hypothyroidism, severe infection, malignancy, CVD, or other forms of atherosclerosis-related diseases such as stroke/transient ischemic attack (TIA) as well as pregnant women were excluded from our investigation. Since anti-lipid medications, including statins, remarkably reduce plasma lipids, the patients or controls who were under treatment with these drug categories were excluded from the present study. Demographic information and Disease modified anti-rheumatoid drugs (DMARD) dosage in study groups were shown in Table 1.

Measurement of the plasma levels of TNF-α

The plasma levels of TNF-α were evaluated by human sandwich Enzyme-linked Immunosorbent Assay (ELISA) (IBL, Hamburg, Germany) according to the manufacturer's instructions.

Table 1. The DMARD dosage and the demographic information of groups study.

Variable	patient	control
Number	35	30
Age	47.51 ± 1.83	47.63 ± 1.91
Sex	6 men 29 women	6 men 24 women
MTX[1](%)	100	0
HCQ2(%)	100	0
PSL[3](%)	100	0
Other DMARDs[4]	0	0

Data are Mean ± SEM; 1-Methotrexate (7.5–25 mg per week), 2-*Hydroxychloroquin (*200 mg per day), 3-*Prednisolone* (5–10 mg per day). 4- Disease Modifying Anti-Rheumatic Drug.

RNA isolation and detection of mRNA

Total RNA was extracted from whole blood samples with an RNX PLUS kit (SinaClon, Tehran Iran). The RNA concentration and its purity were evaluated using NanoDrop 2000 UV–Vis Spectrophotometer (Thermo Scientific, USA) and 1% agarose gel electrophoresis, respectively. Reverse transcription (RT)–polymerase chain reaction (PCR) was performed with 1 µg of total RNA for cDNA synthesis. Primers were as follows: Raptor forward 5′-AGACTGGAACCTACCTTTGGC – 3′and reverse 5′- GCAACACTGACTGTCTTCATCC-3′; GAPDH (as a housekeeping gene): forward 5′- GAAACCTGCCAAGTATGATG-3′and reverse 5′-AGGAAATGAGCTTGACAAAG-3′were designed using online software (Oligocalc and Oligoanalyzer). cDNA synthesis was performed according to the manufacturer's instruction (Roche, Switzerland).

The Real-time PCR analysis was performed in a total volume of 15 µl that consists of 1 µl of cDNA, 0.5 mM of each forward and reverse primer 7.5 µl of SYBR® Premix Ex Taq™ II) Takara, Japan), and 5.5 µl of H2O. The PCR reactions were performed on the Light cycler 96 (Roche) using the universal thermal cycling parameters (95°C 30 s, 40 cycles of 5 s at 95°C, 30 s at 60°C; melting curve: 5 s at 95°C, 60 s at 60°C, 1 s at 95°C, and continues melting) for both gene mTOR and GAPDH. Polymerase chain reaction reactions were performed in triplicates.

The amount of Raptor mRNA expression was normalized to the corresponding GAPDH mRNA transcript level as a housekeeping gene, and the Relative gene expression was calculated based on Pfaffle Formula (Pfaffl 2001).

$$\text{ratio} = \frac{(E_{\text{target}})^{\Delta C_{P\,\text{target}}(\text{control}-\text{sample})}}{(E_{\text{Ref}})^{\Delta C_{P\,\text{Ref}}(\text{control}-\text{sample})}}$$

Measurement of fasting blood sugar (FBS) and lipid profile

Five milliliters of the blood sample were collected after 12 hours fast and was dispensed in two separate ethylene diamine tetra-acetate (EDTA) tube for assessment of mTOR gene expression, and measurement of plasma levels of TNF-α, Fasting blood sugar (FBS), and lipid profile. Plasma Glucose was determined by glucose oxidase-peroxidase method (Biosystems, Barcelona, Spain), the total cholesterol, HDL, and LDL cholesterol, as well as triglyceride were measured via enzymatic reactions using commercial kits according to

manufacturer's instruction (Biosystem, Barcelona Spain), results were read using fully automated 7020 chemistry analyzer (Hitachi, Tokyo, Japan)

Disease activity score-28 (DAS-28)

Based on the formula DAS-28 = 0.56 (TJ) ½ + 0.28 (SJ) ½ + 0.70 ln (ESR) + 0.014 GH, disease activity score was calculated by an expert rheumatologist (Inoue et al. 2007). (TJ: number of tender joints from 28 joints, SJ: number of swollen joints from 28 joints, GH: global health).

The calculation of body mass index (BMI)

The calculation of weight and height were done based on standard protocol and the World Health Organization (WHO). The subject's weight in kilograms was divided by the height in meters squared to calculate BMI. The BMI was classified into three groups: normal weight (NW) range: 18.5–24.9, overweight (OW) 25.0–29.9, and obese (OB) ≥ 30 (kg/m2).

Statistical analysis

SPSS software version 22 (SPSS, Chicago, IL, USA) was used to conduct the analysis and also the graphs were drawn using Microsoft Excel 2010 software. The comparisons in the two groups were performed using a T-test for normal and Mann-Whitney for non-normative data. Correlation analysis for data with normal distribution and the data in which their distribution was not normal was performed using Pearson and Spearman rank correlation, respectively. The statistical significance level was set at 0.05.

Result

The serum levels of FBS, lipids (LDL, HDL, TG and cholesterol) and TNF-α

The mean serum concentration of LDL, HDL, TG, and cholesterol in two groups are given in Table 2.

The comparison of FBS, lipid profile and TNF-α in patients and control group

The serum concentration of FBS, Cholesterol, TG, and TNF-α were not significantly different between the patients and healthy subjects (P = .188, P = .085, P = .974, P = .574, respectively), while the mean serum level of HDL and LDL were substantially different between patients and healthy controls (p = .001, p = .001) (Figure 1).

The gene expression of Raptor in the study groups

The gene expression of Raptor was reduced significantly in RA patients compared to healthy subjects (P = .001) (Figure 2).

Table 2. The mean BMI and plasma levels of TG, LDL, HDL, cholesterol and TNF-α.

Variables	patients (n = 35)	Control (n = 30)
BMI (kg/m^2)	26.82 ± 0.73	25.49 ± 0.84
FBS (mg/dl)	97.91 ± 3.7	94.96 ± 5.6
HDL (mg/dl)	48.58 ± 3.18	32.46 ± 2.42
LDL (mg/dl)	95.13 ± 4.5	124 ± 5.6
TG (mg/dl)	115.25 ± 9.39	157.96 ± 33.3
Cholesterol (mg/dl)	171 ± 6.2	184.03 ± 6.9
TNF-α (pg/ml)	7.78 ± 0.31	7.82 ± 0.35

Data are Mean ± SEM; BMI: Body Mass Index, FBS: Fasting Blood Sugar, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, TG: triglyceride, TNF-α: Tumor Necrosis Factor.

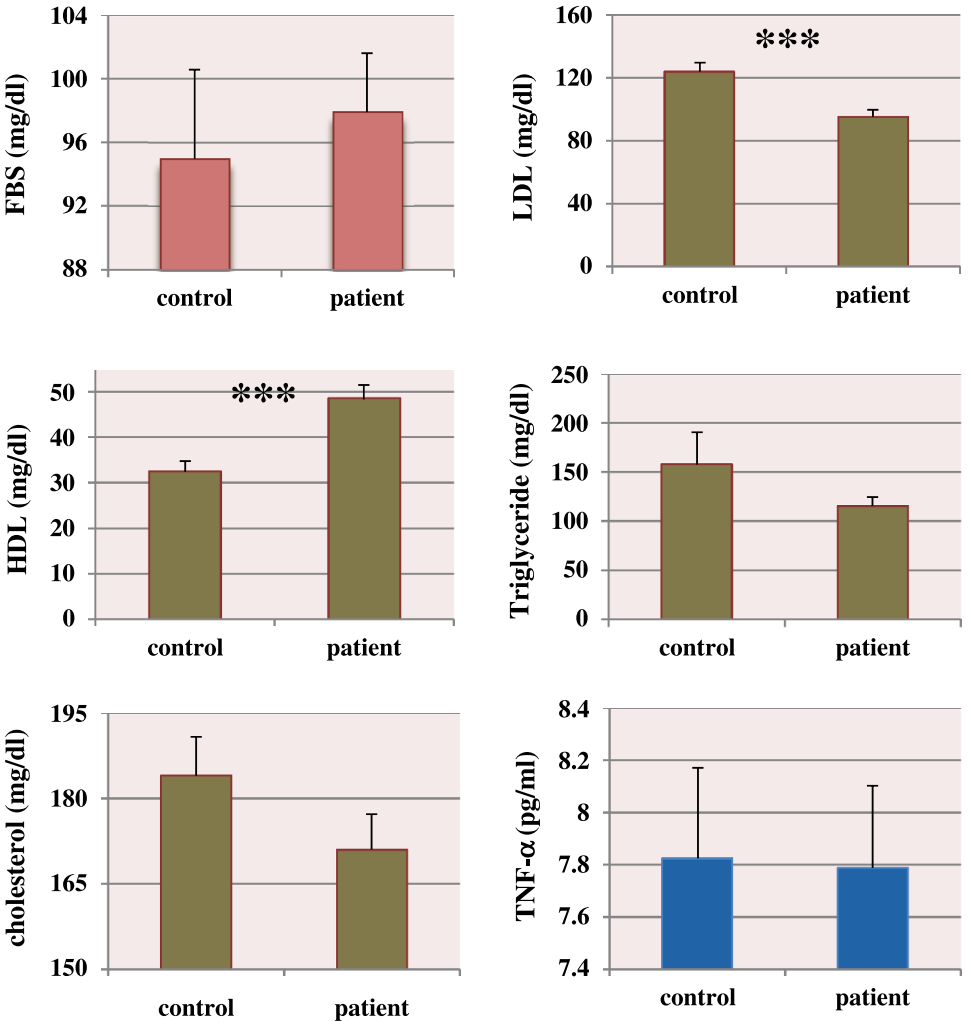

Figure 1. The plasma levels of FBS, lipid profile and TNF-α in RA patients and healthy subjects. FBS: Fasting blood Sugar, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, TNF-α: Tumor Necrosis Factor, ***:P < .001.

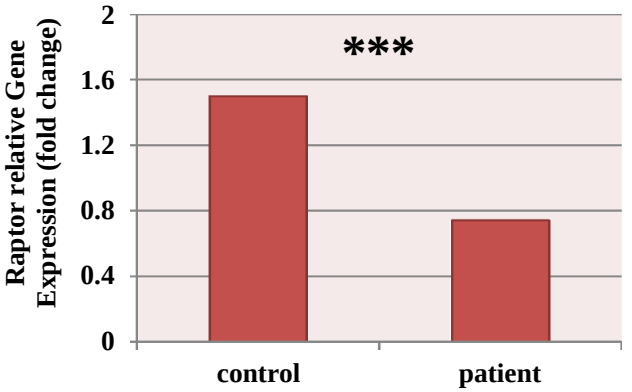

Figure 2. The expression of Raptor mRNA in RA patients and healthy subjects. ***:P < .001 The gene expression of Raptor was significantly lower in RA patients compared to control group.

Assessment of correlation between variables in patients group

The correlation between the serum levels of TNF-α and the gene expression of Raptor with FBS, HDL, LDL, BMI, LDL/HDL, and Cholesterol in the patients group was shown in the Table 3. There was a significantly negative correlation between TG and Raptor gene expression in RA patients (r = −0.431, p = .012). Also, considering Table 4, we did not find a significant association between FBS, lipid profile, Raptor, and TNF-α with DAS-28 in the patient's group.

Discussion

Impaired metabolism, including dyslipidemia, is one of the common underlying complications in RA patients(Erum et al. 2017; Pereira et al. 2009). The role of mTORC1 in both adipose tissue function and control of immune response has been documented recently (Lee et al. 2016; Weichhart and Säemann 2009). Raptor, a regulatory subunit of mTORC1 has a substantial function in the intersection of immunity and metabolism through the

Table 3. The correlation between gene expression of Raptor and TNF-α with FBS and lipid profile.

RA Patients	FBS	HDL	LDL	TG	Chol	BMI	LDL/HDL
TNF-α	r = −0.058	r = 0.271	r = −0.02	r = −0.033	r = −0.109	r = −0.274	p = .160
	p = .740	p = .121	p = .914	p = .852	p = .532	p = .117	r = −0.263
Raptor	r = −0.103	r = 0.119	r = 0.051	r = −0.431	r = 0.005	p = .160	p = .538
	p = .568	p = .516	p = .794	**p = .012***	p = .980	r = −0.254	r = −0.119

FBS: Fasting Blood Sugar, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, TG: triglyceride, Chol: Cholesterol, TNF-α: Tumor Necrosis Factor. * P < 0.05

Table 4. The correlation between FBS, lipid profile, Raptor and TNF-α with DAS-28.

RA Patients	FBS	HDL	LDL	LDL/HDL	TG	chol	Raptor	TNF-α
DAS-28	p = .298	p = .006	p = .690	P = .086	p = .339	p = .792	p = .731	p = .606
	r = 0.181	r = −.0461	r = −.009	R = −0.319	r = 0.147	r = −0.046	r = −0.062	R = −0.090

FBS: Fasting Blood Sugar, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, TG: triglyceride, Chol: Cholesterol, TNF-α: Tumor Necrosis Factor, DAS-28: Disease Activity Score 28

recruitment of mTOR subunits, and cellular localization of mTORC1 complex (Hara et al. 2002). So far, no study has evaluated the correlation between raptor gene expression in peripheral blood leukocytes and lipid profile in RA patients. In our survey, the gene expression of Raptor was reduced remarkably in peripheral blood leukocyte of RA patients ($P < .001$). Given the regulatory role of Raptor in the mTORC1 complex, the reduced gene expression of this subunit may disrupt the activation of the mTORC1 complex and compromise its physiologic effect in the immune and metabolic process of peripheral blood leukocytes in RA patients. In our investigation, the concentration of plasma HDL was significantly higher in RA patients compared to healthy subjects($p = .001$), the HDL usually inhibits atherosclerosis onset through various mechanisms(Ansell et al. 2005). Given the high prevalence of CVD in RA patients, the increased levels of HDL in our patients may not have its classical protective effects against cardiovascular disorders. It has become apparent that in the inflammatory conditions similar to RA, HDL is not functionally protective furthermore, it has been shown that HDL may gain proinflammatory properties via peroxidation reaction in the context of systemic autoimmune disease and it may be considered as a risk factor for atherosclerosis and CVD in these special circumstances(Ansell et al. 2003; Hahn et al. 2007; Van Lenten et al. 2006). In this study our patients were under treatment with both combination DMARD and methylprednisolone, Interestingly it has previously been shown that both anti-inflammatory drugs, like prednisolone and DMARD regimen, especially hydroxychloroquine (HCQ) remarkably increase the function and the plasma levels of HDL (Charles-Schoeman et al. 2017; Desai et al. 2014; O'Neill et al. 2017). Parallel to previous finding the plasma levels of LDL were significantly reduced in our patient's group ($p = .001$) Myasoedova and his colleague showed that low-density lipoprotein (LDL) cholesterol decline precipitously prior to RA clinical manifestations and paradoxically lower LDL levels are associated with increased cardiovascular risk in these patients. (Myasoedova et al. 2010, 2011, 2009). The suppressive impact of acute or chronic high-grade inflammatory condition on LDL cholesterol levels is well appreciated (Firestein et al. 2016; Hahn et al. 2007). Given the inflammatory mechanisms underpinning the pathophysiology of RA, our results support the suppressive effect of inflammation on serum levels of cholesterol LDL which may lead to unfavorable atherogenic index (LDL: HDL cholesterol ratio) which has been documented previously(Hahn et al. 2007). TEAR (The Treatment of Early Aggressive Rheumatoid Arthritis) study showed that RA patients under monotherapy with (MTX) or triple therapy with (MTX plus sulfasalazine plus hydroxychloroquine) have shown an increase in both HDL and LDL plasma levels (Navarro-Millán et al. 2013). This finding was not in line with our investigation, which showed reduced serum levels of LDL in RA patients. The data controversy regarding lipid profile in RA may be attributable to the variable factors, including the therapeutic regimen, which we used in our study (MTX, PSL, HCQ), different lifestyles, and various genetic backgrounds of our patients (Balder et al. 2018). In the following to determine whether the dampened gene expression of Raptor has an impact on the lipid and glucose metabolism, as well as TNF-α, a classical inflammatory cytokine, we assessed the correlation between the gene expression of Raptor, the plasma levels of glucose, lipids, lipoproteins, and TNF-α. Except for triglyceride which had a significant negative correlation with Raptor gene expression ($P = .012$, $r = -0{,}0431$) we could not detect any noticeable association between

Raptor and other study variables, including, lipids and glucose as well as plasma TNF-α.It is considerable to note that mTORC1 activation by stimuli like TNF-α has been implicated in the metabolism of fatty acids and triglycerides(Ma et al. 2013). TNF-α with its inflammatory characteristic plays a crucial role in pathological events underpinning the development and progression of RA, and it is one of the critical target of biological DMARDs collectively referred to as TNF-α inhibitors (Ma and Xu 2013). In our study, we could not find any significant association between Raptor gene expression and serum levels of TNF-α in our RA patients. Besides that, there was a not significant difference between the serum levels of TNF-a in RA patients and healthy subjects, which may be the result of the therapeutic regimen, we used for the control of RA in our patients(Giacomelli et al. 2002). In the following, we could not find any significant correlation between Raptor gene expression and DAS-28, a well-established criterion for the evolution of RA disease activity. Our result indicated that reduced raptor gene expression observed in our patients does not have any substantial effect on RA severity, which is affected by different variables. As mentioned previously, Raptor contributes to several aspects of metabolisms, especially lipids molecules with that regards we surveyed the possible correlation between Raptor gene expression and BMI in our patients similar to disease activity we could not find any significant association between BMI and the gene expression of Raptor in peripheral blood leukocytes (p = .160, r = −0.254). Besides that, in contrast to the previous studies, there was not a significant difference between patients and the control group in BMI which may be due to the effects of different factors including nutritional status, drug regimen, lifestyle, as well as genetic background (Armstrong et al. 2006; Feng et al. 2016).

Study limitations

In this study, we did not determine the effect of the DMARD regimen on our variables, including the Raptor gene expression, plasma lipids, and sugar. The other limitation of our study is our small sample size.

Conclusion

Reduced gene expression of Raptor may contribute to deregulated metabolic and immunological process in RA patients, and abnormal HDL and LDL plasma levels may be considered as one of the critical CVD risk factors in these patients.

Acknowledgments

We thankfully acknowledge the deputy of research and technology of the Kermanshah University of Medical Sciences for financial support of this work.

Funding

This work was supported by the Kermanshah University of Medical Sciences grant number [96604].

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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