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Research Article

Hypertension and insulin resistance in rheumatoid arthritis: unveiling insights with mets-ir index

METS-IR indeksi perspektifinden romatoid artritte hipertansiyon ve insülin direnci

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Abstract

Aim: Hypertension (HT), together with metabolic dysfunctions and insulin resistance (IR) in its pathophysiology, is a significant risk factor for cardiovascular disease in rheumatoid arthritis (RA) patients. Identifying IR early could enhance HT management, especially in RA patients, where HT prevalence is elevated. The study aimed to assess metabolic indices, particularly the METS-IR, as predictors of HT in RA patients.

Material and Methods: This retrospective, cross-sectional study investigated the association between RA, IR, and HT in 80 RA patients and 80 age- and sex-matched controls. Patients with diabetes, pre-diabetes, or other conditions affecting insulin sensitivity were excluded, as were those on glucose-metabolism-affecting medications except low-dose glucocorticoids (<7.5 mg/day prednisone or equivalent).

Results: RA patients exhibited significantly higher HT prevalence than controls (65% vs. 22.5%; p=0.044). HOMA-IR and METS-IR scores were significantly higher in RA patients (p=0.04 and p=0.01, respectively), while QUICKI scores were significantly lower (p=0.04). Glucocorticoid use didn't affect METS-IR, HOMA-IR, or QUICKI scores. Hypertensive patients had significantly higher HOMA-IR and METS-IR scores (p=0.009 and p<0.001, respectively), with both showing a significant association with HT in multivariate analyses (p=0.002 for both). Age emerged as a significant factor in the development of HT, with each passing year increasing the likelihood by 7% (p=0.042).

Conclusion: HT was more prevalent in RA patients, with higher METS-IR levels irrespective of glucocorticoid use or disease activity. Each unit increase in METS-IR score correlated with a 15% higher HT risk. METS-IR could serve as an early prediction tool for HT in RA.

Keywords: METS-IR, Rheumatoid arthritis, Hypertension, Insulin resistance, HOMA-IR, Metabolic Indices.

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Öz

Amaç: Hipertansiyon (HT), patofizyolojisindeki metabolik disfonksiyon ve insülin direnciyle birlikte, RA hastalarında önemli bir kardiyovasküler hastalık risk faktörüdür. Bu nedenle, özellikle RA gibi HT sıklığının arttığı hastalarda, insülin direncinin erken saptanması önemlidir. Çalışmamız, ön planda METS-IR olmak üzere, metabolik indekslerin, RA hastalarında HT öngörü değerini araştırmayı amaçlamıştır.

Gereç ve Yöntemler: Bu retrospektif, kesitsel çalışmaya 80 RA hastası ile yaş ve cinsiyet açısından eşleştirilmiş 80 sağlıklı kontrol dahil edilmiştir. Diyabet, prediyabet veya insülin duyarlılığını etkileyen hastalıklar ile düşük doz glukokortikoidler dışında (<7.5 mg/gün prednizon veya eşdeğeri) glukoz metabolizmasını etkileyen ilaç kullanımı olanlar dışlanmıştır.

Bulgular: RA hastalarında HT sıklığı kontrol grubuna göre anlamlı derecede yüksekti (sırasıyla %65 ve %22.5; p=0.044). HOMA-IR ve METS-IR skorları yine RA grubunda, anlamlı derecede yüksekken (sırasıyla p=0.04 ve p=0.01), QUICKI skorları anlamlı derecede düşüktü (p= 0.04). Glukokortikoid maruziyetinin METS-IR, HOMA-IR veya QUICKI skorlarına etkisi olmadığı izlendi (sırasıyla p=0.410, p=0.583 ve p=0.583). Hipertansif hastaların ortalama HOMA-IR ve METS-IR skorları, hipertansif olmayanlara kıyasla anlamlı derecede yüksekti (sırasıyla p=0.009 ve p<0.001). Çok değişkenli analizlerde, HT ile hem HOMA-IR hem de METS-IR indeksleri anlamlı bir ilişki gösterdi (p=0.002 her ikisi için). Yaşın HT gelişimi üzerinde önemli bir faktör olduğu, yıllık %7 risk artışına yol açtığı gözlenmiştir (p=0.042).

Sonuç: Çalışmamızda HT sıklığının RA hastalarında anlamlı derecede yüksek olduğu ve glukokortikoid kullanımı veya hastalık aktivite durumundan bağımsız olarak METS-IR skorlarının anlamı derecede yüksek olduğunu gösterilmiştir. METS-IR skorunda meydana gelen her bir birimlik artış, RA hastalarında HT gelişme riskinde %15'lik bir artışa neden olmaktadır. METS-IR, bu açıdan HT için pratik bir öngörü aracı olabilir.

Anahtar Kelimeler: METS-IR, Romatoid artrit, Hipertansiyon, İnsülin direnci, HOMA-IR, Metabolik indeksler.

Introduction

Rheumatoid arthritis (RA) is a systemic, inflammatory and chronic autoimmune disorder that leads to symmetrical polyarthritis involving both small and large joints, predominantly occurring between the ages of 30 and 50 years. Globally, approximately 1% of the population is diagnosed with RA, which not only diminishes quality of life but also increases the mortality risk due to various comorbidities, particularly cardiovascular (CV) diseases. Studies show that RA patients have a 1.5 times higher risk of CV comorbidities than the general population, with CV diseases leading as the primary cause of death and accounting for 39% of all mortalities in these patients. Furthermore, individuals with RA are at 48% greater risk of experiencing CV events than those without RA (1, 2).

Among CV risk factors, hypertension (HT) is notably prevalent and potent in patients with RA. This was the strongest modifiable risk factor for CV disease in this group. A review of insurance claims in the United States revealed that 76% of RA patients were diagnosed with HT, nearly double the incidence in matched controls. This higher prevalence is consistent across the Canadian and European populations, highlighting the global relevance of HT in RA. Moreover, the incidence of HT in patients with RA is notably higher than that in the general population, with a significant incidence rate difference highlighted in the UK-based medical records (3, 4).

The link between RA and increased HT risk is complex and may involve multiple factors, including systemic inflammation, obesity, sedentary lifestyle, dietary habits, and RA medication. Understanding these relationships is crucial for managing HT in patients with RA and subsequently reducing the risk of future CV disease (5).

Further complicating the landscape of risk assessment in patients with RA is the association between HT and insulin resistance (IR) and metabolic syndrome (MS), both of which contribute to arterial stiffness and elevated CV risk. HOMA-IR (homeostatic model assessment of insulin resistance) and QUICKI (quantitative insulin sensitivity check index) indices calculate insulin resistance using fasting serum insulin and glucose levels. Meanwhile, the metabolic score for insulin resistance (METS-IR) index is a novel, non-insulin-based measure that also holds potential as a valuable predictor of HT and might provide a practical, efficient and more economical screening

tool for metabolic dysfunction according to recent studies (6-8).

In this study, to improve the early prediction and management of HT in patients diagnosed with RA, we aimed to determine the predictive value of the METS-IR index for incident HT particularly in RA patients with supporting the results with HOMA-IR and QUICKI scores.

Material and Methods

Patient Selection and Ethical Considerations

This retrospective cross-sectional multicenter study was conducted in accordance with the Declaration of Helsinki and approved by the Adana City Training and Research Hospital Clinical Research Ethics Committee with decision number 3201 at February 29, 2024).

Inclusion Criteria

Patients were selected from sequential visitors from rheumatology and physical medicine and rehabilitation outpatient clinics for routine checkup and the study only included patients diagnosed with RA based on the European Alliance of Associations for Rheumatology (formerly known as European League Against Rheumatism)/American College of Rheumatology (ACR) 2010 classification criteria for rheumatoid arthritis.

Exclusion Criteria

Exclusion criteria included patients with an HbA1c level of 5.5% or above, indicating the presence of diabetes or pre-diabetes, which could confound the relationship between RA and insulin resistance. Also, patients with comorbid conditions that could independently affect insulin sensitivity, such as thyroid disorders, Cushing's syndrome, or polycystic ovary syndrome (PCOS) were also excluded. Additionally, patients with concomitant renal, hepatic, cardiac or endocrine diseases or taking medications affecting lipid metabolism and glucose metabolism (except low dose glucocorticoids) were excluded from the study. Additonally, patients exhibiting a high disease activity level, as indicated by a disease activity score of 28 joints (DAS28) greater than 5.1 were excluded regarding the fact that acute inflammation may effect metabolic parameters.

The low-dose glucocorticoids (defined as <7.5 mg/day prednisone or equivalent) use were not exception in order to not disrupt the routine maintenance treatment. Patients treated with the higher dose of 7.5 mg/day prednisone or equivalent doses were excluded.

Data Collection

Demographic data, including age, gender and body mass index and clinical data, including HbA1c, serum glucose, serum insulin, triglycerides and high density lipoprotein (HDL) measured after an overnight fasting, were collected retrospectively. Data on HT were incorporated into the dataset from the examination notes established during the clinical assessments or from the existing diagnosis of HT. HT defined as being previously diagnosed with HT and/or being under antihypertensive treatment, or newly detected and confirmed by appropriate consecutive measurements of ≥140 mmHg systolic and/or ≥90 mmHg diastolic blood pressure during examination according to the WHO 2021 HT guideline (9). HOMA-IR was calculated according to the formula: fasting insulin (microU/L) x fasting glucose (mmol/L)/22.5. METS-IR was calculated using the following formula: ln[(2 × fasting plasma glucose (mg/dL) + fasting triglyceride (mg/dL)] × body mass index (kg/m2)/(ln[high-density lipoprotein cholesterol (mg/dL)]).

Statistical Analysis

The data were analyzed with IBM SPSS Statistics software (version 22, IBM Corp., Armonk, N.Y., USA). Descriptive statistics covered demographic and clinical features. Categorical variables were described with frequency counts and percentages, analyzed with cross-tabulations and Yates' continuity correction. For numerical variables, either mean ± standard deviation (for normal distribution) or median with minimum-maximum ranges (for non-normal distribution) were presented. Normality was tested using Kolmogorov-Smirnov or Shapiro-Wilk tests. Based on distribution, independent sample t-tests and Mann-Whitney U tests were used for two independent groups, while Kruskal-Wallis H tests or One-way ANOVA were used for more than two groups. Statistical significance was set at $p < 0.05$, with interpretations reported as $p < 0.05$, $p < 0.01$, or $p < 0.001$. Univariate and multivariate logistic regression analyses assessed factors influencing HT presence in RA patients, calculating odds ratios (ORs) and 95% confidence intervals (CIs) for risk assessment.

Results

This study evaluated a cohort of 80 patients diagnosed with RA along with a control group of 80 age and sex-matched individuals. All participants were classified as nondiabetic with HbA1c levels < 5.5%. The general demographic characteristics of the RA and control groups are presented in Table 1.

Table 1. Demographic data and comparison of hypertension and metabolic indices between control and patient groups

	Control (n=80)	RA (n=80)	p
Age	50.06 ± 10.375	51.69 ± 8.857	0.062
Gender			0.661
Female	68 (85%)	71 (87.75%)	
Male	12 (15%)	9 (11.25%)	
BMI	27.109 ± 4.845	27.25 ± 4.296	0.876
HT			
No	62 (77.5%)	28 (35%)	0.044*
Yes	18 (22.5%)	52 (65%)	
Disease Duration		6 (1-15) years	
DAS 28		3.1 (2.1-5.2)	
CRP		5,5 (0.1-10.2)	
HOMA-IR	1.2 (0.2–6.1)	1.8 (0.8–4.8)	0.04*
QUICKI	0.4 (0.3–0.5)	0.3 (0.2–0.4)	0.04*
METS-IR	37.7 (22.4–122.62)	39.9 (28.3–32.6)	0.01*

* $p < 0.05$
Values within parentheses represent minimum and maximum values
RA: Rheumatoid Arthritis, BMI: Body Mass Index, HT: Hypertension, DAS28:(Disease Activity Score 28), CRP: C-Reactive Protein, HOMA-IR: Homeostatic Model Assessment of Insulin Resistance, QUICKI: Quantitative Insulin Sensitivity Check Index, METS-IR: Metabolic Score for Insulin Resistance

Patients with RA showed significantly higher HT prevalence compared to control group (65% vs. 22.5%, p= 0.044). The metabolic indices HOMA-IR (p = 0.04) and METS-IR (p = 0.01) were also significantly higher in patients with RA and as expected, QUICKI (p = 0.04) (was significantly lower in the RA group. (Table 1).

To assess the effect of glucocorticoid therapy on metabolic indices in patients with RA, a comparative analysis was performed between patients who did not use glucocorticoids (n=26) and those who received low-dose glucocorticoid therapy (n=54). The median age of patients in the low-dose glucocorticoid group was slightly higher comparing patients not using glucocorticoids (59 vs. 51.5, respectively, p=0.04). METS-IR scores were 40.8 (range 28.5-54.7) for those not on glucocorticoids compared to 39 (range 28-59.6) for those on low-dose glucocorticoids. HOMA-IR values were 1.5 (range 0.7-3.5) for those not on glucocorticoids compared to 1.5 (range 0.4-4.8) for those on low-dose glucocorticoids. QUICKI scores were 0.4 (range 0.2-0.4) for non-glucocorticoid users and 0.4 (range 0.2-0.4) for low-dose glucocorticoid users. Neither of these differences in metabolic indices reached statistical significance (p= 0.410 for METS-IR, p= 0.583 for HOMA-IR and p= 0.583 for QUICKI).

To assess the influence of disease activity on metabolic indices in patients with RA, a comparative analysis was performed between patient groups categorized by disease activity levels: remission, low-disease activity and moderate-disease activity, as defined by the Disease Activity Score in 28 joints (DAS28). The HOMA-IR values were as follows: for the remission group the value was 1.6 (range 0.7 -4.8), for the low disease activity group was 1.7 (range 0.8 -3.3) and for the moderate disease activity group was 1.4 (range 0.5 - 4.0). The QUICKI values for the remission group was 0,4, for the low disease activity group the value was 0,4 and for the moderate disease activity group the value was 0,36. The METS-IR values for the remission group was 40,2, for the low disease activity group was 39,9 and for the moderate disease activity group was 39,8. There were no statistically significant differences between the DAS28 groups (p = 0.6 for HOMA-IR, p = 0.6 for QUICKI and p = 0.8 for METS-IR).

Comparative analysis of metabolic indices between RA patients with and without HT revealed statistically significant differences. The average METS-IR and HOMA-IR scores, indicatives of insulin resistance, were higher in hypertensive patients compared to non-hypertensive counterparts. (44.9 vs. 36.7, p<0,001 for METS-IR and 1.7 vs. 1.3, p= 0.009 for HOMA-IR, respectively) (Table 2).

Table 2. Comparison of metabolic indices in RA patients with and without hypertension

	HT		
	No	Yes	p
HOMA-IR	1.3 (0.2–6.1)	1.7 (0.4–4.3)	0.009*
QUICKI	0.4 (0.2–0.4)	0.3 (0.3–0.5)	0.059
METS-IR	36.7 (22.3–53.5)	44.9 (30.0–122.6)	<0.001**

* $p < 0.05$; ** $p < 0.001$
Values within parentheses represent minimum and maximum values
HT: Hypertension, HOMA-IR: Homeostatic Model Assessment of Insulin Resistance, QUICKI: Quantitative Insulin Sensitivity Check Index, METS-IR: Metabolic Score for Insulin Resistance

Univariate analysis showed that age was a significant factor of HT, with each year increasing the odds by 7% (OR 1.07, 95% CI 1.02-1.12, p = 0.006). This relationship remained significant in the multivariate model (OR 1.059, 95% CI 1.002-1.12, p = 0.042). HOMA-IR and METS-IR were both significantly associated with HT in the univariate model, with ORs of 1.10 (p < 0.001) and 1.15 (p < 0.001), respectively. These relationships of HOMA-IR and METS-IR also remained significance in the multivariate analyses (OR 1.10 and 1.13, p=0,002 for both, respectively) (Table 3).

Table 3. Logistic regression analysis of factors associated with hypertension in RA patients

	Univariate Logistic Regression		Multivariate Logistic Regression	
	OR (95% CI)	p	OR (95% CI)	p
Age	1.07(1.02-1.12)	0.006**	1.059 (1.002-1.12)	0.042*
HOMA-IR	1.10 (0.91-1.33)	<0.001***	1.10 (0.92-1.21)	0.002**
QUICKI	0.00 (0-20.29)	0.121		
METS-IR	1.15 (1.07-1.23)	<0.001***	1.13 (1.05-1.21)	0.002**

OR: Odds Ratio; CI: Confidence Interval; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Values within parentheses represent minimum and maximum values
HOMA-IR: Homeostatic Model Assessment of Insulin Resistance, QUICKI: Quantitative Insulin Sensitivity Check Index, METS-IR: Metabolic Score for Insulin Resistance

Discussion

The use of metabolic indices to gauge insulin resistance, a known risk factor for HT, has emerged as a practical approach in clinical practice (10). These indices serve not only as tools for the early detection of metabolic dysfunctions that precede HT but also help stratify patients according to their CV risk (6). One of these indices, METS-IR, designed as a practical surrogate of insulin resistance based on BMI, fasting plasma glucose, high-density lipoprotein and triglyceride levels. While the strong association of METS-IR score with increased frequency of HT, CV events and mortality was shown by several studies (5,7,8,11,12), our study is the first to extends this understanding to patients with RA, underscoring the importance of these indices in predicting CV complications, such as HT.

As declared by several studies, insulin resistance, a well-known risk factor for CV disease, appears to be exacerbated by the systemic inflammatory state induced by RA, potentially through mechanisms involving cytokine-mediated interference in insulin signaling pathways (11,13,14).

Consistent with the literature, the prevalence of HT, HOMA-IR and METS-IR scores were significantly higher while, as expected, QUICKI score was significantly lower in our RA group comparing healthy controls. These findings suggest that insulin resistance is more prominent in patients with RA comparing general population. The increase in METS-IR and its association with HT observed in our study are particularly noteworthy. There was a clear association between HT and elevated metabolic indices in RA patients, as evidenced by higher scores of HOMA-IR and METS-IR in hypertensive patients than in their non-hypertensive counterparts. This correlation supports the hypothesis that systemic inflammation observed in RA may exacerbate insulin resistance, thereby contributing to an increased risk of HT.

Compared with existing studies, Han et al. found a strong correlation between elevated METS-IR levels and CV events in the general population, which aligns with our findings in the RA cohort (7). This suggests that metabolic dysfunction, as measured by METS-IR, may be a critical and specific indicator of HT risk not only in the general population but also in patients with RA who are already at increased CV risk. The consistent observation across various studies that RA patients exhibit worse metabolic profiles than controls could reflect an underlying link between active inflammatory pathways in RA and metabolic disturbances. This connection underscores the need for comprehensive approaches that address both inflammation and metabolic health to HT risk in patients with RA (12,16,17).

The logistic regression analyses presented in our study indicated that specific increments in metabolic indices significantly elevate the risk of developing HT in patients with RA. The ORs derived from both univariate and multivariate logistic regression models suggested a direct relationship between these metabolic scores and HT risk. For each unit increase in METS-IR score, there was an associated 15% increase in the likelihood of HT. This effect remained significant in the multivariate analysis, highlighting METS-IR as a robust predictor of HT in patients with RA.

Another important point of our study is while the presence of systemic inflammation due to rheumatoid arthritis was observed to increase the frequency of HT and insulin resistance compared to the control group, multivariate analyses revealed that the degree of inflammation determined by the DAS28 score did not have any effect on these variables. This important result suggests that RA can create systemic effects, such as increase in HT and insulin resistance, regardless of the inflammatory activity in the joints, even in a state of remission.

Investigating the interplay between RA disease activity, medication effects and metabolic indices could provide deeper insights into the pathophysiology of CV risk in RA and refine the risk stratification models for this patient population. The pronounced metabolic dysfunction in patients with RA might highlight the necessity of routine screening for HT and metabolic dysfunction in this group. The early identification and management of these risk factors could play a crucial role in reducing CV morbidity and mortality in patients with RA. Furthermore, the significant differences in metabolic scores between patients with RA and controls emphasize the need for tailored therapeutic strategies that address not only the inflammatory aspects of RA but also their metabolic effects.

These results suggest that clinicians should monitor these indices closely in patients with RA as part of their routine CV risk assessment and management strategies.

Limitations

The retrospective and cross-sectional nature of our study, which included a relatively low number of patients, makes it impossible for us to observe the long-term effects of insulin resistance and HT in RA patients and to examine the effects of medical treatments on these variables.

Conclusion

Our study demonstrated that HT is significantly more prevalent among patients with rheumatoid arthritis, highlighting the urgent need for targeted CV risk management in this population. The findings revealed that METS-IR and HOMA-IR levels were distinctly higher in patients with RA, establishing a clear and significant link between increased METS-IR and HOMA-IR scores and elevated risk of HT. Each unit increase in the METS-IR score corresponded to a 15% increase in the risk of developing HT in patients with RA. This relationship was consistently significant underlining the reliability of METS-IR as a predictive marker of HT in this patient population. The practical implications of our findings suggest that routine assessment of METS-IR in patients with RA could significantly enhance the predictive accuracy for HT, allowing for earlier and potentially more effective interventions. By integrating METS-IR into the standard RA management protocols, clinicians can offer a more nuanced and effective approach to managing the complex interaction of inflammation, metabolic dysfunction and CV risk in patients with RA.

Conflict of interest

The authors declare no conflict of interest. The contributions of this study are as follows:

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Prior publication

The authors declare that all or any part of the material in this work has not been published anywhere before, and is not currently under consideration for publication elsewhere. This includes symposiums, lectures, books, invited articles, submissions in electronic format and preliminary papers of all types, except abstracts of up to 400 words.

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