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ORIGINAL ARTICLE

# Insulin resistance and adverse lipid profile in untreated very early rheumatoid arthritis patients: A single-center, cross-sectional study in China

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***ABSTRACT***

**Objectives:** This study aims to evaluate the presence and factors related to insulin resistance (IR) in untreated very early rheumatoid arthritis (RA) patients.

**Patients and methods:** Between June 2020 and July 2021, a total of 90 RA patients (29 males, 61 females; mean age: 49.3±10.2 years; range 24 to 68 years) and 90 age-, sex- and body mass index (BMI)-matched controls (35 males, 55 females; mean age: 48.3±5.1 years; range 38 to 62 years) were included. Homeostatic model assessment was applied to evaluate IR (HOMA-IR) and β-cell function (HOMA-β). Disease activity score 28 (DAS28) was used to estimate disease activity. Lipid profile, hemoglobin A1c (HbA1c), glucose, insulin, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were measured. Logistic regression analysis was performed to investigate the relationship between the IR and clinical features of RA patients.

**Results:** The RA patients had higher HOMA-IR values ($p<0.001$) and adverse lipid profile. The IR was positively correlated with age ($r=0.35$, $p<0.01$), CRP ($r=0.42$, $p<0.001$), ESR ($r=0.33$, $p<0.01$), disease duration ($r=0.28$, $p<0.01$), and DAS28 ($r=0.50$, $p<0.001$). The DAS28, CRP and age, but not sex and menopausal status, were independently associated with IR.

**Conclusion:** Insulin resistance was present in untreated very early RA patients. The DAS28, CRP, and age were independent predictors for the presence of IR. Based on these findings, RA patients should be evaluated early for the presence of IR to reduce the risk of metabolic diseases.

***Keywords:*** Abnormal lipid level, disease activity, insulin resistance, very early rheumatoid arthritis.

Rheumatoid arthritis (RA) is a chronic autoimmune disease with the presence of multiple autoantibodies and systemic inflammation that may lead to progressive synovitis, bone erosion and destruction of the joints, which is associated with an increased risk of morbidity and mortality. The prevalence of metabolic syndrome characterized by obesity, increased blood pressure, dyslipidemia and hyperglycemia has been enormously increasing worldwide, in part, linked to the epidemic of RA.[1-3] Insulin resistance (IR) status is a core feature of metabolic syndrome, and if left uncontrolled, may lead to type 2 diabetes and cardiovascular disease. Chronic low-grade inflammation involved in the pathogenesis of IR has been delineated.[4-6] Inflammatory cytokines including tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-6, various adipokines and acute-phase reactants are involved in the development of IR, which indicates inflammatory disease such as RA may be a potential cause for metabolic diseases. This

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is further supported by a recent study showing a rapid beneficial effect on IR and insulin sensitivity in non-diabetic RA patients via IL-6 receptor blockade.[7]

Several studies have reported the presence of IR and impaired β-cell function in RA patients. However, most of these studies involved subjects with long-term treated RA.[8-10] The potential effects of RA medication on IR may be overlooked in these studies. Indeed, although the effect of non-steroidal anti-inflammatory drugs (NSAIDs) on IR is quite limited,[8] the use of glucocorticoids obviously alters glucose metabolism. Dessein and Joffe[9] reported that short-term treatment with low daily dose glucocorticoids resulted in enhanced β-cell function due to its anti-inflammatory effects, while another study indicated that chronic glucocorticoid use might lead to decreased insulin sensitivity, impaired glucose tolerance (IGT), and β-cell function in RA patients.[11] Moreover, disease-modifying anti-rheumatic drugs (DMARDs) and anti-TNF-α therapy significantly reduced homeostasis model assessment of IR (HOMA-IR)[12] and the incidence of metabolic syndrome.[13]

Little is known about whether IR occurs at the onset of the disease or due to chronic longstanding systemic inflammation or drug exposure such as glucocorticoids.[9,10,14] Moreover, data on sex-specific variations and menopausal status and their impact on IR in early RA patients are rare. Sex-related variations and menopausal status have not been described in treatment-naive very early RA patients. To address this, in the present study, we aimed to investigate the presence and factors associated with IR in untreated very early RA subjects.

## PATIENTS AND METHODS

This single-center, cross-sectional study was conducted at School of Medicine, the Second Affiliated Hospital of Zhejiang University and health checkup center, Department of Rheumatology between June 2020 and July 2021. A total of 90 RA patients (29 males, 61 females; mean age: 49.3±10.2 years; range 24 to 68 years) and 90 age-, sex- and body mass index (BMI)-matched controls (35 males, 55 females; mean age: 48.3±5.1 years; range 38 to 62 years) were recruited. The patients were evaluated when very early RA diagnosis was made. Inclusion criteria were as follows: RA disease duration was required to be <12 weeks, age ≥18 years, and a diagnosis of RA according to the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria.[15] Those with chronic disease such as IGT status, diabetes, myocardial infarction, stroke, renal failure, cancer and other inflammatory disease were not included. Patients and controls were excluded, if they were pregnant or breastfeeding or had a presence of infection. To minimize the potential effects of drug exposure on IR, those receiving anti-TNF-α therapy, prednisone or DMARDs, or anti-diabetic drugs were also excluded. However, as NSAIDs are often used in the management from the initial phase of RA, patients undergoing NSAIDs were not excluded.

### Diagnostic criteria

The HOMA-IR cut-off values varied in different population due to genetic, physiological and environmental factors. In the present study, a HOMA-IR score of >2.41 was defined as IR based on the 75$^{th}$ percentile of healthy individuals in a large Chinese cohort.[16]

Impaired glucose tolerance and diabetes were diagnosed according to the recommendations of the American Diabetes Association (ADA).[17] All patients and controls underwent an oral glucose tolerance test (OGTT). Those with IGT status and diabetes were excluded. Normal BMI category ranged from 18.5 to 24.9 kg/m$^2$. Obesity was defined as a BMI of ≥30 kg/m$^2$.[18] Menopausal status was determined by self-report.

### Assessment

The HOMA-IR developed by Matthews et al.[19] was applied as a parameter to estimate IR (HOMA-IR) and β-cell function (HOMA-β).[20] The calculation formula was as follows: HOMA-IR=fasting insulin (μU/ml)×FG (mmol/L) /22.5. As C-peptide is widely considered as a better marker than insulin for β-cell function,[21] in this study, we used C-peptide to evaluate β-cell function by using the HOMA calculator. Disease activity score 28 (DAS28) using erythrocyte sedimentation rate (ESR) was used to estimate disease activity.

### General characteristics and biochemical measurements

All examinations were performed according to standard protocols. Height and weight were measured in the morning with the subjects wearing light clothing and no shoes. The BMI was calculated by dividing the individual's weight in kilograms by the square of height in meters.

Blood samples were collected after a 12-h overnight fast. The serum levels of total cholesterol (TC), triglyceride (TG) and glucose were detected by enzymatic methods with an automatic biochemical analyzer (AU-5831, Beckman Coulter, Brea, USA). Direct assay methods were used for measuring high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol by an automatic biochemical analyzer (AU-5831, Beckman Coulter, Brea, USA). Apolipoprotein A1 (APOA1) and apolipoprotein B (APOB) were also determined by an automatic biochemical analyzer (AU-5831, Beckman Coulter, Brea, USA). Hemoglobin A1C (HbA1c) was determined by an automatic glycohemoglobin analyzer (HLC-723G8, Tosoh Corp. Kyoto, Japan). Insulin and C-peptide were detected by an ADVIA Centaur XP automatic chemiluminescence system (Siemens Healthineers AG, Erlangen, Bayern, Germany). C-reactive protein (CRP) was detected by immunoturbidimetric assay with an automatic biochemical analyzer (AU-5831, Beckman Coulter, Brea, USA). The ESR was determined with an automatic method (Alifax Test 1, Alifax, Padova, Italy). Rheumatoid factor (RF) was detected by an automatic specific protein analyzer (Siemens Healthcare, Erlangen, Bayern, Germany). Anti-cyclic citrullinated peptide (anti-CCP) was measured by an automatic enzyme immunoassay analyzer (Quanta lyser-240, Inova Diagnostics, San Diego, CA, USA).

Disease duration was defined from RA-associated symptom onset to diagnosis. Swollen joint count (28 joints) and tender joint count (28 joints) were examined by an experienced rheumatologist. Self-assessment of disease activity by patients was measured by a Visual Analog Scale (VAS) ranging from 0 to 100 mm. Then, the DAS28 was calculated by using the DAS28 calculator.[22]

### Statistical analysis

Statistical analysis was performed using the SPSS version 16.0 software (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed in mean ± standard error (SE) for continuous variables and in number and frequency for categorical variables. Values of HOMA-IR were logarithm transformed before analysis, as they were non-normally distributed. The chi-square test or one-way analysis of variance (ANOVA) was used to compare characteristics of the patient groups. For comparisons between two groups, the two-tailed Student t-test was used for normally distributed variables, and logarithm transformed before analysis or Wilcoxon rank-sum test for non-normally distributed variables. Correlation analysis was assessed by the Pearson correlation analysis. Univariate and multivariate logistic regression were performed to ascertain potential independent factors associated with the presence of IR. A *p* value of $<0.05$ was considered statistically significant with 95% confidence interval (CI).

## RESULTS

### Clinical characteristics of the patients and healthy subjects

A total of 90 RA patients and 90 controls were enrolled in this study. The clinical characteristics of the subjects are shown in Table 1. Compared to the controls, RA patients had increased levels of HOMA-IR, CRP, ESR, TG, LDL cholesterol, TG/HDL cholesterol ratio and fasting insulin ($p<0.001$, $p<0.001$, $p<0.001$, $p<0.01$, $p<0.05$, $p<0.001$, and $p<0.001$, respectively), and decreased level of HDL and APOA1 ($p<0.001$ for both). There were no significant differences in the HOMA-β value, TC, APOB, glucose and C-peptide levels between the RA group and controls.

### HOMA-IR value was increased in RA patients

In our study, 36% of RA subjects and 19% of the controls showed abnormal HOMA-IR

**Table 1.** General characteristics and biochemical measurements of study subjects

| | RA patients (n=90) | | | | Controls (n=90) | | | |
|---|---|---|---|---|---|---|---|---|
| Characteristics | n | % | Mean±SD | Range | n | % | Mean±SD | Range |
| Age (year) | | | 49.3±10.2 | 24-68 | | | 48.3±5.1 | 38-62 |
| Sex | | | | | | | | |
| Female | 61 | 68 | | | 55 | 61 | | |
| Male | 29 | 32 | | | 35 | 39 | | |
| BMI (kg/m$^2$) | | | 22.0±2.5 | | | | 22.4±1.9 | |
| Lipid profile | | | | | | | | |
| TG (mmol/L) | | | 1.8±0.9** | | | | 1.4±0.6 | |
| TC (mmol/L) | | | 4.4±1.1 | | | | 4.4±1.1 | |
| HDL (mmol/L) | | | 1.1±0.3*** | | | | 1.4±0.3 | |
| LDL (mmol/L) | | | 2.8±0.8* | | | | 2.6±0.6 | |
| Apo A1 (g/L) | | | 1.0±0.2*** | | | | 1.2±0.2 | |
| Apo B (g/L) | | | 1.0±0.2 | | | | 1.0±0.2 | |
| TG/HDL ratio | | | 1.9±1.5*** | | | | 1.2±0.8 | |
| Fasting serum glucose (mmol/L) | | | 5.0±0.5 | | | | 4.9±0.7 | |
| Fasting serum insulin (mLU/mL) | | | 10.6±4.8*** | | | | 7.2±3.8 | |
| C-Peptide (nmol/L) | | | 0.4±0.1 | | | | 0.5±0.1 | |
| HOMA-IR | | | 2.3±1.1*** | | | | 1.6±1.0 | |
| HOMA-IR >2.41 | 32 | 36 | | | 17 | 19 | | |
| HOMA-beta cell (%) | | | 92.8±28.3 | | | | 103.3±36.3 | |
| HbA1c (%) | | | 5.5±0.4 | | | | 5.5±0.4 | |
| CRP (mg/L) | | | 40.2±32.0*** | | | | 2.3±2.5 | |
| ESR (mm/h) | | | 52.2±31.4*** | | | | 8.8±5.6 | |

RA: Rheumatoid arthritis; SD: Standard deviation; BMI: Body mass index; TG: Triglyceride; TC: Total cholesterol; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; APO A1: Apolipoprotein A1; APO B: Apolipoprotein B; HOMA: Homeostasis model assessment; IR: Insulin resistance; HbA1c: Hemoglobin A1c; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; Comparisons between RA patients with controls are assessed by one-way ANOVA or Chi-square test. Only statistically significant differences are marked with symbols. A *p* value <0.05 is considered as statistically significant. * p<0.05, ** p<0.01,*** p<0.001.

values. Compared to the control group, the mean HOMA-IR value was significantly higher in RA patients (2.3±1.1) than controls (1.6±1.0, p<0.001).

### Comparisons of characteristics between RA groups

The RA patients were further divided into three subgroups according to sex and menopausal status. The clinical characteristics of the subjects are shown in Table 2 and Table 3.

Compared to the premenopausal patients, male RA patients had higher TG (2.0±0.9 *vs.* 1.5±0.8 mmol/L, p<0.05), LDL cholesterol (3.1±0.6 *vs.* 2.4±0.7 mmol/L, p<0.001), APOB (1.1±0.1 *vs.* 0.9±0.2 g/L, p<0.001), fasting glucose (5.0±0.5 *vs.* 4.8±0.4 mmol/L, p<0.05) and HOMA-IR value (2.4±1.1 *vs.* 2.2±1.1, p>0.05), and with longer disease duration, but lower HOMA-β value (86.8±24.8% *vs.* 104.1±28.8%, p<0.05) and HDL cholesterol (1.0±0.2 *vs.* 1.1±0.3 mmol/L, p<0.05). Compared to the premenopausal patients, postmenopausal patients had higher APOB (1.0±0.2 *vs.* 0.9±0.2 g/L, p<0.05), LDL cholesterol (2.9±0.8 *vs.* 2.4±0.7 mmol/L, p<0.05) and fasting glucose (5.0±0.5 *vs.* 4.8±0.4 mmol/L,

**Table 2.** General characteristics and biochemical measurements of RA patients

| | Male | | | | Female | | | | Female | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | (n=29) | | | | RA patients (n=90) | | | | Controls (n=90) | | | |
| Characteristics | n | % | Mean±SD | Range | n | % | Mean±SD | Range | n | % | Mean±SD | Range |
| Age (year) | | | 50.0±10.1 | 24-68*** | | | 38.3±5.7 | 27-46### | | | 55.5±6.3 | 47-67▲ |
| BMI (kg/m²) | | | 21.7±2.4 | | | | 21.5±2.4 | | | | 22.5±2.6 | |
| Lipid profile | | | | | | | | | | | | |
| TG (mmol/L) | | | 2.0±0.9* | | | | 1.5±0.8 | | | | 1.8±1.0 | |
| TC (mmol/L) | | | 4.6±0.9 | | | | 4.0±1.2 | | | | 4.6±1.2 | |
| HDL (mmol/L) | | | 1.0±0.2* | | | | 1.1±0.3 | | | | 1.1±0.3 | |
| LDL (mmol/L) | | | 3.1±0.6*** | | | | 2.4±0.7# | | | | 2.9±0.8 | |
| Apo A1 (g/L) | | | 1.0±0.2 | | | | 1.1±0.3 | | | | 1.1±0.2 | |
| Apo B (g/L) | | | 1.1±0.1*** | | | | 0.9±0.2# | | | | 1.0±0.2 | |
| TG/HDL ratio | | | 2.2±1.3 | | | | 1.5±1.2 | | | | 2.0±1.7 | |
| Fasting serum glucose (mmol/L) | | | 5.0±0.5* | | | | 4.8±0.4# | | | | 5.0±0.5 | |
| Fasting serum insulin (mIU/mL) | | | 11.2±4.9 | | | | 10.3±4.7 | | | | 10.4±4.9 | |
| C-Peptide (nmol/L) | | | 0.4±0.1 | | | | 0.4±0.1 | | | | 0.4±0.2 | |
| HOMA-IR | | | 2.4±1.1 | | | | 2.2±1.1 | | | | 2.3±1.2 | |
| HOMA-IR >2.41 | 11 | 37.93 | | | 7 | 30.43 | | | 14 | 36.84 | | |
| HOMA-beta cell (%) | | | 86.8±24.8* | | | | 104.2±28.8 | | | | 90.4±28.5 | |
| HbA1c | | | 5.5±0.4 | | | | 5.3±0.5 | | | | 5.5±0.4 | |
| CRP (mg/L) | | | 46.4±34.1 | | | | 44.6±37.3 | | | | 32.1±24.1 | |
| ESR (mm/h) | | | 49.0±32.3 | | | | 54.3±32.2 | | | | 53.4±30.9 | |

RA: Rheumatoid arthritis; SD: Standard deviation; BMI: Body mass index; TG: Triglyceride; TC: Total cholesterol; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; Apo A1: Apolipoprotein A1; Apo B: Apolipoprotein B; HOMA: Homeostasis model assessment; IR: Insulin resistance; HbA1c: Hemoglobin A1c; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; Data are expressed as mean±SE; Comparisons among RA patients are assessed by one-way ANOVA. Only statistically significant differences are marked with symbols. A p value < 0.05 is considered as statistically significant. * $p<0.05$; ** $p<0.01$; *** $p<0.001$ represents statistically significant differences between male group and premenopausal group. ▲ $p<0.05$; ▲▲ $p<0.01$; ▲▲▲ $p<0.001$ represents statistically significant differences between male group and postmenopausal group; # $p<0.05$; ## $p<0.01$; ### $p<0.001$ represents statistically significant differences between premenopausal and postmenopausal group.

**Table 3.** Disease-specific parameters of RA subjects

| | Male | | | Female | | | Female | | |
|---|---|---|---|---|---|---|---|---|---|
| | (n=29) | | | Premenopausal group (n=23) | | | Postmenopausal group (n=38) | | |
| Characteristics | n | % | Mean±SD | n | % | Mean±SD | n | % | Mean±SD |
| RF (IU/mL) | | | 411.1±631.8 | | | 360.7±649.7 | | | 159.2±198.8▲ |
| Anti-CCP (RU/mL) | | | 416.4±423.9 | | | 368.2±308.3 | | | 437.3±467.3 |
| Disease duration (weeks) | | | 6.9±2.7 | | | 5.5±2.0* | | | 6.7±2.5 |
| DAS28 score | | | 4.3±0.9 | | | 4.1±0.8 | | | 4.2±0.7 |
| DAS28 ≤3.2 | 2 | 6.90 | | 2 | 8.70 | | 3 | 7.89 | |
| 3.2 <DAS28 ≤5.1 | 21 | 72.41 | | 19 | 82.61 | | 30 | 78.95 | |
| DAS28 >5.1 | 6 | 20.69 | | 2 | 8.70 | | 5 | 13.16 | |
| Using NSAIDs | 23 | 79.31 | | 16 | 69.57 | | 29 | 76.32 | |

RA: Rheumatoid arthritis; SD: Standard deviation; RF: Rheumatoid factor; Anti-CCP: Anti-cyclic citrullinated peptide; DAS28: 28-joint disease activity score; NSAIDs: Non-steroidal anti-inflammatory drugs; Comparisons among groups are assessed by one-way ANOVA. Only statistically significant differences are marked with symbols. A *p* value <0.05 is considered as statistically significant; * p<0.05; ** p<0.01; *** p<0.001 represents statistically significant differences between male group and premenopausal group. ▲p<0.05; ▲▲ p<0.01; ▲▲▲p<0.001 represents statistically significant differences between male group and postmenopausal group.

p<0.05). Compared to the postmenopausal female patients, younger male patients had higher RF levels (411.1±631.8 *vs.* 159.2±198.8 IU/mL, p<0.05). No significant differences in HOMA-IR score, lipid profile, HbA1c, glucose, insulin, CRP, ESR, and disease activity (DAS28) (p>0.05 for all) were observed among three groups.

### DAS28 was associated with the presence of IR in RA

Pearson correlation analysis demonstrated that IR was positively correlated with age (r=0.35, p<0.01), CRP (r=0.42, p<0.001), ESR (r=0.33, p<0.01), disease duration (r=0.28, p<0.01) and DAS28 (r=0.50, p<0.001), indicating a moderate to good correlation between IR and DAS28. It showed no significant correlation between HOMA-IR score and BMI, RF, or anti-CCP antibody. The associations of clinical characteristics with IR in RA patients are shown in Figures 1 and 2.

Univariate and multivariate logistic regression analyses were performed to ascertain potential independent factors associated with the presence of IR (Table 4). In the univariate model, DAS28 (6.003, CI: 1.638-22.005),

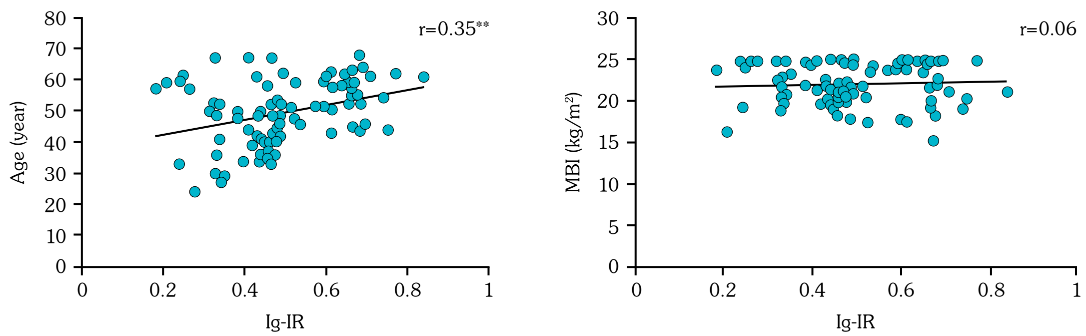


**Figure 1.** Association of age and BMI with insulin resistance in RA patients was analyzed by Pearson correlation analysis. Only statistically significant differences are marked with symbols.

BMI: Body mass index; lg: Logarithm; IR: Insulin resistance; r: Correlation coefficient; RA: Rheumatoid arthritis.

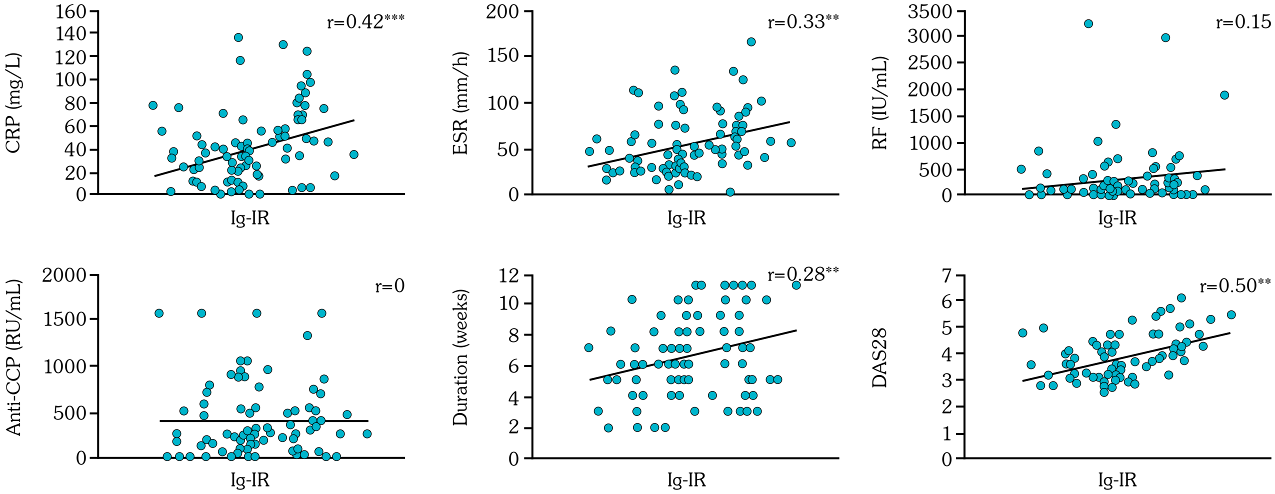


**Figure 2.** Association of RA features with insulin resistance in RA patients was analyzed by Pearson correlation analysis. Only statistically significant differences are marked with symbols.

CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; RF: Rheumatoid factor; lg: Logarithm; IR: Insulin resistance; Anti-CCP: Anti-cyclic citrullinated peptide; DAS28: 28-joint disease activity score; r: Correlation coefficient.

**Table 4.** Univariate and multivariate logistic regression analyses for factors associated with the presence of IR in RA patients

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *p* | OR | 95% CI | *p* |
| Age (year) | 1.1 | 1.013-1.193 | 0.023 | 1.096 | 1.011-1.187 | 0.026 |
| Sex | 0.577 | 0.137-2.431 | 0.453 | 1.617 | 0.389-6.73 | 0.509 |
| Menopausal status | 0.552 | 0.013-23.739 | 0.757 | | | |
| Body mass index | 1.286 | 0.98-1.688 | 0.07 | 1.258 | 0.969-1.633 | 0.085 |
| Disease duration (weeks) | 1.07 | 0.765-1.497 | 0.693 | | | |
| DAS28 score | 6.003 | 1.638-22.005 | 0.007 | 5.75 | 1.754-18.844 | 0.004 |
| RF (IU/mL) | 1.001 | 0.999-1.002 | 0.505 | | | |
| Anti-CCP (RU/mL) | 0.999 | 0.998-1.001 | 0.396 | 0.999 | 0.998-1.001 | 0.475 |
| C-reactive protein | 1.047 | 1.018-1.076 | 0.001 | 1.047 | 1.018-1.076 | 0.001 |
| Erythrocyte sedimentation rate | 0.983 | 0.954-1.013 | 0.265 | 0.981 | 0.953-1.011 | 0.213 |
| Using NSAIDs | 1.911 | 0.219-16.651 | 0.558 | | | |

IR: Insulin resistance; RA: Rheumatoid arthritis; CI: Confidence interval; DAS28: 28-joint disease activity score; RF: Rheumatoid factor; Anti-CCP: Anti-cyclic citrullinated peptide; NSAIDs, nonsteroidal anti-inflammatory drugs; Menopausal status is for female group. A *p* value <0.05 is considered as statistically significant.

age (1.1, CI: 1.013-1.193) and CRP (1.047, CI: 1.018-1.076) were associated with IR. In the multivariate model, DAS28 (5.75, CI: 1.754-18.844), age (1.096, CI: 1.011-1.187), and CRP (1.047, CI: 1.018-1.076) remained independently associated with IR.

## DISCUSSION

In the present study, we observed increased HOMA-IR value and adverse lipid profile in very early RA patients. The DAS28, CRP and age, but not sex and menopausal status, were shown to be independently associated with IR in RA patients.

The presence of IR is demonstrated in established RA, but in the early stage of RA, the results are inconclusive. Interestingly, a study indicated that a severe insulin resistant state was present in early untreated RA patients; however, BMI was significantly higher in RA group compared to the controls in this study.[23] Mirjafari et al.[24] also observed a higher HOMA-IR score in early rheumatoid arthritis (ERA) patients; however, this study included patients treated with DMARDs and glucocorticoids. Another study included 46 untreated early RA patients. This study showed no significant difference in HOMA-IR and HOMA-β scores between early RA patients and controls. However, both RA patients and controls were overweight.[25] These studies provide new insights into understanding of the link between IR and RA. However, as overweight, obesity, cardiovascular diseases, and type 2 diabetes are well-recognized to be related with IR,[26,27] these findings have limitations that IR state might have been overestimated and may be not consistent with each other and the present study.

In the current study, we applied the HOMA method to access IR and β-cell function. Hyperinsulinemic euglycemic clamp and hyperglycemic clamp are considered as the gold-standard method for quantifying insulin action and insulin secretion of β-cell, respectively. However, glucose clamp technique requires glucose readings every 5 min for a few hours, making it difficult to recruit patients in clinical and epidemiological studies. The HOMA method developed by Matthews et al.[19] is a validated, simple and reliable tool to access IR and β-cell function, and is widely used in clinical study. Moreover, the close correlation between the results from HOMA and glucose clamp method is demonstrated,[20] making HOMA model a suitable tool for clinical study. In our study, although the mean score of HOMA-IR in RA cases was normal (mean HOMA-IR=2.33), it was statically significantly higher than controls. More intriguingly, 36% of the RA patients showed IR with a HOMA-IR score of >2.41 compared to 19% in controls in our study. A possible explanation for elevated HOMA-IR value in early RA is that various proinflammatory cytokines are demonstrated to be increased during a prolonged period of asymptomatic stage. Indeed, Karlson et al.[28] reported that IL-6 level was significantly higher in preclinical RA, and TNF receptor 2, a crucial inflammatory biomarker was increased 12 years prior to RA symptoms. Both IL-6 and TNF-α, core proinflammatory cytokines in clinical phase of RA, are well-known to induce IR state. Therefore, IR state may start in early RA, or even in the preclinical phase.

In addition, disruption of lipid profiles characterized by high TG and LDL cholesterol, as well as low HDL cholesterol and APOA1 were observed in RA cases in current study. The TG/HDL ratio, which is an independent risk for cardiovascular disease, was demonstrated to be elevated in the present study. These data are similar to the previous studies in early untreated RA subjects. Importantly, high TG and LDL cholesterol, along with low HDL cholesterol and APOA1, have been demonstrated as risk factors for cardiovascular disease.[29,30] Recently, a study emphasized the importance of diabetes mellitus and cardiovascular risk management in patients with RA, and moreover, the authors pointed out that experience could be learnt from cardiovascular disease prevention programs to benefit RA patients.[31]

Similar to the findings in previous reports, DAS28 and CRP were found to be positively correlated with IR,[32] and demonstrated to be independent predictors in logistic regression analysis in the present study. A positive association between ESR and IR was observed, but it was not an independent risk factor for IR, maybe due to relatively small sample size. However, as DAS28 is more accurate than CRP and ESR as a disease activity measure in RA, the present study confirmed disease activity as an independent predictor for the risk of IR. These findings emphasize the importance of evaluation of metabolic disorders in RA patients and early treatment of RA to reduce disease activity and prevent the development of IR and dyslipidemia.

Additionally, we also found that age was an independent risk factor for IR in RA. As the IR prevalence increases in the general population with age, it is not surprising that older male patients and postmenopausal women had higher HOMA-IR value, LDL cholesterol, APOB, and fasting glucose than premenopausal women in our study. Menopausal state is known to cause weight gain, IR, and dyslipidemia in women.[33]

However, in the present study, it was not an independent risk factor for IR in RA. The possible reason may be that age of menopause is affected by patient's general health status, as reduced ovarian function has been observed in patients with chronic disease including type 2 diabetes and RA.[34,35] Therefore, RA per se or disease activity may be a major cause for IR in these patients.

Moreover, the increased fasting insulin was observed in RA group, with no significant difference in HOMA-β value compared with controls. This result is not consistent with previous reports in established RA.[10,11] One possible explanation for this finding is pancreatic β-cell compensation. Indeed, the changes in β-cell function in the progression of diabetes can be viewed as five stages: compensation, stable adaption, early unstable decompensation, stable decompensation and severe decompensation.[36] The authors indicated that, during the compensation stage, insulin secretion increased to maintain normoglycemia secondary to IR.

Nonetheless, certain limitations of the current study should be recognized. The sample size of our study is small and from a single center. Additionally, we did not have enough cases of RA patients with different genetic background and environmental factors.

In conclusion, IR was present in untreated very early RA patients in the current study. The DAS28, CRP, and age were significant independent predictors for the presence of IR. Therefore, the IR status should be evaluated early in RA patients to reduce the risk of metabolic diseases.

**Ethics Committee Approval:** The study protocol was approved by the School of Medicine, The Second Affiliated Hospital of Zhejiang University (IR2020001179). The study was conducted in accordance with the principles of the Declaration of Helsinki.

**Patient Consent for Publication:** A written informed consent was obtained from each patient.

**Data Sharing Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Author Contributions:** Statistical analysis and manuscript writing: Y.L.; study design, interpretation of data: X.W.H.; statistical analysis and interpretation of data; W.H.X.; data collection and statistical analysis: Z.X., C.Y.H.; data collection, statistical analysis and interpretation of data: Z.H.B., W.Q.H.; All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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