Systematic Review of the Association Between IgG Glycosylation and Rheumatoid Arthritis

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Abstract

Background: Rheumatoid arthritis is a systemic autoimmune disease characterized primarily by polyarticular, symmetric, erosive arthritis. IgG glycosylation has been demonstrated to participate in numerous immune processes and is associated with the occurrence and development of RA. Objective: To conduct a systematic review of studies on the association between IgG glycosylation and rheumatoid arthritis, providing a decision-making reference for the formulation of rheumatoid arthritis prevention strategies. Methods: Systematically searched PubMed, Web of Science, CNKI, Wanfang Medical Database, and VIP Database for association studies between IgG glycosylation and rheumatoid arthritis, with the search period up to May 1, 2024; used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to evaluate the quality of evidence for the included literature. Results: A total of 469 relevant studies were retrieved, and 45 studies were finally included in the systematic review. The exposure factor in all studies was IgG glycosylation levels, and the outcomes included pre-clinical RA, early RA, active RA, remission RA, and pregnancy RA; GRADE showed that most of the evidence provided by the included literature was of moderate to low quality (88.9%). Conclusion: This systematic review found that direct IgG glycosylation indicators and their derived structures are associated with RA, and also demonstrate good predictive capability in identifying RA and evaluating RA treatment efficacy; however, to obtain more accurate conclusions, future high-quality, large-sample randomized controlled trials are needed for validation.

Full Text

Preamble

IgG Glycosylation and Rheumatoid Arthritis: A Systematic Review

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Abstract

Background: Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by multiple symmetrical erosive arthritis. IgG glycosylation has been shown to play a role in various immune processes and has been associated with the onset and progression of RA. **Objective:** To systematically review the relationship between IgG glycosylation and RA, and offer insights for the development of RA preventive strategies. **Methods:** We conducted a systematic review of studies on the association between IgG glycosylation and RA in PubMed, Web of Science, CNKI, Wanfang Database, and Weipu Database as of May 1, 2024. The quality of evidence was assessed using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) framework. **Results:** A total of 469 relevant studies were identified, and 45 studies were included in this systematic review. The exposure factors in these studies were IgG glycosylation levels, and the outcomes included preclinical RA, early RA, active RA, RA in remission, and RA during pregnancy. GRADE assessment indicated that most of the evidence provided was of low to moderate quality (88.9%). **Conclusion:** This systematic review revealed that IgG glycosylation and its derived structures were associated with RA and demonstrated predictive capabilities in identifying RA and evaluating therapeutic outcomes. However, for more precise conclusions, future research should prioritize high-quality, large-scale randomized controlled trials.

Keywords: IgG glycosylation; Rheumatoid arthritis; Systematic review; GRADE

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease with unclear etiology and pathogenesis, primarily manifested as multiple symmetrical erosive arthritis or synovitis [1]. The global incidence of RA is approximately 0.5%-1%, with a prevalence of about 0.42% in China. The disease disproportionately affects women, whose incidence is 2-3 times higher than that of men [1,2]. Although considered a rare disease, RA' s incidence and prevalence have been

increasing annually in recent years [3]. Furthermore, RA leads to cardiovascular disease, pulmonary disease, and malignant tumors, becoming a major cause of premature mortality and imposing a substantial economic burden on society [4].

Glycosylation is an enzymatic post-translational modification where oligosaccharides are transferred to specific sites on biological macromolecules (such as proteins and lipids) to form glycoconjugates (i.e., glycoproteins and glycolipids) [5]. Immunoglobulin G (IgG) is a major component of humoral immunity, accounting for over 75% of serum immunoglobulins and representing the most abundant immunoglobulin in human plasma [6,7]. Alterations in IgG glycosylation, including galactosylation, sialylation, fucosylation, and bisecting N-acetylglucosamination, have been confirmed to participate in numerous immune processes and may play important roles in regulating rheumatoid diseases [8].

Methods

1.1 Inclusion and Exclusion Criteria

1.1.1 Inclusion Criteria

(1) **Study Population:** RA patients without restrictions on age, clinical stage, ethnicity, or outpatient/inpatient status; no restrictions on healthy control group conditions. (2) **Outcome Measures:** RA (including preclinical, onset, early, activity level, and remission stages). (3) **Study Design:** Analytical and experimental studies including cross-sectional studies, case-control studies, cohort studies, and randomized controlled trials.

1.1.2 Exclusion Criteria Studies meeting any of the following conditions were excluded: duplicate publications; animal experiments or other non-human studies; studies unrelated to the topic; commentaries or reviews; Mendelian randomization studies; studies not using IgG glycosylation as an exposure factor; studies not using RA as an outcome or not providing outcome-related indicators.

1.2 Search Strategy and Process

Following PRISMA guidelines, we conducted comprehensive searches in PubMed, Web of Science (WOS), CNKI, Wanfang Medical Database, and Weipu Database for studies on the association between IgG glycosylation and RA, with search dates from database inception to May 1, 2024. We employed a combination of subject headings and free-text terms, with search strategies adapted for each database. English subject headings included: 1) Immunoglobulin G OR IgG; 2) glycosylation OR glycan OR glycosylated OR N glycosylation OR N-glycan; 3) rheumatoid arthritis OR rheumatoid OR arthritis. The PubMed search strategy was: ((Immunoglobulin G[Title/Abstract]) OR (IgG[Title/Abstract]))

AND ((N-glycosylation[Title/Abstract]) OR (glycan[Title/Abstract]) OR (glycosylation[Title/Abstract]) OR (glycan[Title/Abstract]) OR (glycosylated[Title/Abstract])) AND ((rheumatoid arthritis[Title/Abstract]) OR (rheumatoid[Title/Abstract]) OR (arthritis[Title/Abstract])). The WOS search strategy was: ((AB=(Immunoglobulin G) OR AB=(IgG)) AND (AB=(N-glycosylation) OR AB=(N-glycan) OR AB=(glycosylation) OR AB=(glycan) OR AB=(glycosylated)) AND (AB=(rheumatoid arthritis) OR AB=(rheumatoid) OR AB=(arthritis))). Chinese subject headings included: 1) immunoglobulin; 2) glycan or glycosylation; 3) rheumatoid arthritis. The search process involved: 1) computer searches using all subject headings and keywords; 2) screening literature by title and abstract against inclusion criteria and retrieving full texts; and 3) manually searching references of included studies to identify potentially missed literature. Literature screening was performed independently by two reviewers in a double-blind manner.

1.3 Literature Screening and Data Extraction

Two investigators independently conducted literature screening and data extraction, with cross-checking. Disagreements were resolved through discussion with a third researcher. First, duplicates were removed, then titles and abstracts were screened to exclude ineligible studies, and finally full texts were reviewed to determine inclusion. A pre-designed data extraction form was used to collect information including: basic study information (first author, country, publication year); study design characteristics (participant age, sample size, study type); exposure factors and outcome measures; and study results and main conclusions.

1.4 Quality Assessment of Included Studies

Using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system [10], two researchers evaluated the quality of evidence from included studies, with disagreements resolved through discussion with a third researcher. GRADE determines evidence quality by defining clinical questions (population, intervention, comparison, and outcomes; PICO) and collecting relevant evidence, with final quality rated as high (0 points, no downgrade), moderate (-1 point, downgrade one level), low (-2 points, downgrade two levels), or very low (-3 points, downgrade three levels) [11].

Results

2.1 Literature Selection

The search identified 469 relevant studies. After removing duplicates, 273 studies remained. Through hierarchical screening, 45 studies were ultimately included. The literature screening flowchart is shown in Figure 1 [Figure 1: see original paper].

2.2 Characteristics of Included Studies

The 45 included studies were published between 1985 and 2024, with 12 studies before 2000 and 33 after 2000. One study was in Chinese and 44 in English. The total sample size across all included studies was 8,639, with one study having a sample size greater than 1,000 [12]. Among the included studies, there were 7 cross-sectional studies, 18 case-control studies, 11 case-cohort studies, and 10 cohort and prospective studies. All studies used IgG glycosylation levels as the exposure factor, with outcome measures including preclinical RA (3 studies), post-diagnosis RA (22 studies), early RA (3 studies), RA activity levels (21 studies), RA in remission (2 studies), and RA during pregnancy (6 studies). Most studies found that direct IgG glycosylation indicators and their derived indicators (galactosylation, sialylation levels, etc.) participated in RA onset and progression. Seven studies identified the potential of IgG glycosylation as biological candidate markers for RA. Detailed characteristics of included studies are shown in Table 1 .

2.3 Quality Assessment Results

GRADE assessment revealed that most studies (88.9%) provided evidence of moderate or low quality, primarily because: no large-sample, multicenter, randomized controlled clinical trials were reported; there was heterogeneity among various assessment indicators; and RA being a rare disease resulted in small sample sizes, limiting the generalizability of findings. For these reasons, studies included in this systematic review were frequently downgraded in the evidence quality evaluation system, resulting in relatively low overall evidence levels. This indicates that caution is needed when applying these results to clinical recommendations or decision-making, requiring comprehensive judgment incorporating other relevant information and clinical experience.

Discussion

3.1 Association Between IgG Glycosylation Levels and RA

In Chinese Han populations, RA patients exhibited high levels of GP1-2 and GP24 but low levels of GP22 compared to healthy individuals [13]. Finnish RA patients showed high levels of GP3-4 and GP6 but low levels of GP8-9, GP12-14, and GP23 [14]. Notably, GP1-4 and GP6 lack terminal galactosylation and sialylation structures, while GP8-9 and GP12-14 contain terminal galactosylation structures, suggesting that decreased galactosylation increases RA risk. Multiple case-control studies, cohort studies, and other observational studies have found that increased agalactosylation of IgG glycans is associated with RA onset, activity, and progression [15-18]. Abnormal IgG galactose levels have been confirmed as a component of dysregulated humoral immune response in RA [19,20], and decreased levels are significantly associated with increased RA activity and duration [14,21-28]. Furthermore, multiple studies have found that differences in IgG galactosylation levels between RA patients and healthy individuals occur

during the preclinical stage [14,18,19,29], with significant differences observed 3 months [29], 2 years [18], and 3.5 years [19] before RA onset. Similar to IgG galactose, decreased sialylation is significantly associated with increased RA disease activity [21,23,26,28,30]. Evidence indicates that reduced galactosylation and sialylation upregulate complement-dependent cytotoxicity (CDC), promoting inflammatory responses and participating in RA pathogenesis [31,32]. Case-control and cohort studies have found significantly higher IgG fucose levels in RA patients compared to controls [28,30,33]. A multicenter case-control study found that bisecting N-acetylglucosamine levels (FA2BG2, FABG2S1) were significantly higher in seropositive RA patients than in seronegative patients, attributable to specific immunoglobulin molecules present in seropositive disease [34]. However, evidence also shows no significant differences in IgG core fucose and bisecting N-acetylglucosamine levels between RA patients and healthy individuals [26,29]. Therefore, the association between IgG core fucose, bisecting N-acetylglucosamine levels and RA onset and progression remains inconclusive.

3.2 Association Between IgG Glycosylation and RA During Pregnancy

To achieve fetal tolerance while maintaining pathogen defense, maternal immune system changes during pregnancy naturally ameliorate autoimmune diseases such as RA, while postpartum disappearance of pregnancy-related immune regulatory mechanisms typically leads to RA exacerbation [35,36]. Evidence indicates that elevated estrogen levels during pregnancy can regulate IgG galactosylation [37]. Cohort studies show that IgG1 and IgG2 galactosylation and sialylation levels increase during pregnancy, peak in the third trimester, and decline postpartum. The increase in galactosylation levels is significantly greater in RA patients with pregnancy-induced improvement than in those without improvement. During pregnancy and postpartum, RA patients exhibit significantly lower galactosylation and sialylation levels than healthy individuals, while bisecting N-acetylglucosamine levels show no significant changes, suggesting that galactosylation changes are associated with pregnancy-induced RA improvement and that glycosylation changes play an important role in this amelioration [16,38-40]. The 2013 Pregnancy-induced Amelioration of Rheumatoid Arthritis (PARA) study found that in ACPA-positive RA patients, pregnancy-induced changes in ACPA-IgG galactosylation (independent of total IgG) were significantly associated with RA activity levels, suggesting that the pathogenic relevance of pregnancy-induced ACPA-IgG galactosylation is greater than total IgG levels in ACPA-positive patients [38].

3.3 IgG Glycosylation as a Potential Biomarker for RA

Elevated rheumatoid factor (RF) and inflammatory cytokine levels are associated with RA and can serve as diagnostic markers [41,42]. Studies have found that IgG-RF galactosylation and sialylation levels are significantly reduced in RA patients [21], and positive correlations exist between IgG glyco-

sylation and RF levels [28]. Anti-citrullinated protein antibodies (ACPA) are autoantibodies targeting citrullinated proteins, confirmed as early diagnostic markers for RA [43]. ACPA-positive RA is more progressive and destructive than ACPA-negative RA, and ACPA-positive patients have lower chances of achieving drug-induced remission [44]. Research shows significant differences in agalactosylation and sialylation levels of ACPA-IgG1 between RA patients and controls [45,46]. Glycomic analysis reveals that ACPA-IgG is heavily glycosylated in its antigen-binding fragment, expressing complex variable domain glycosylation (VDG) [47]. ACPA-IgG VDG significantly increases during RA onset and decreases during drug-free remission, indicating its important role in RA occurrence and remission [12,48]. Thus, IgG glycosylation combined with RA markers such as RF and ACPA is significant in RA onset and progression.

Currently, RA diagnosis primarily relies on serological detection of ACPA and RF, but these biomarkers are only positive in 70% of RA patients [17]. Studies have confirmed that combining IgG-N glycans with RF or ACPA yields high predictive values for RA diagnosis or progression (IgG-ACPA: 80%; IgG-RF: 94%) [17,49], and IgG glycosylation biomarkers demonstrate good diagnostic efficacy in distinguishing RF-positive from RF-negative RA patients and ACPA-positive from ACPA-negative RA patients [48,50]. Additionally, combining agalactosylation levels with RF improved discrimination for RA to 91% (sensitivity: 90%; specificity: 95%; positive predictive value: 94%) [18]. Our previous research in Chinese populations found that GP1 (AUC=0.88), IgG galactosylation (AUC>0.90), and bisecting N-acetylglucosamine (AUC=0.81) all showed good predictive ability for identifying RA [13,51]. Therefore, IgG glycosylation has considerable potential as a biomarker for RA identification.

3.4 IgG Glycosylation as a Potential Biomarker for Treatment Efficacy

As early as 1996, studies found that decreased agalactosylated IgG levels were significantly associated with RA improvement after fasting (7-10 days), suggesting that IgG agalactosylation may play a role in clinical symptom improvement during fasting [52]. A clinical trial demonstrated that infliximab treatment reduced agalactosylated IgG levels in active RA patients, thereby improving clinical symptoms [53]. Conversely, increased IgG galactosylation levels were observed in RA patients after tocilizumab treatment [54]. Similarly, increased IgG galactosylation was observed in active RA patients receiving methotrexate (MTX) treatment for 12 months [55]. Furthermore, the ratio between major agalactosylated (FA2), major monogalactosylated (FA2G1), and digalactosylated Fc glycans (FA2G2) (FA2/[FA2G1+FA2G2]) was significantly associated between MTX responders and non-responders in RA patients, suggesting its potential as a biomarker for MTX clinical response (sensitivity: 73%; specificity: 79%) [56]. Increased sialic acid to N-acetylglucosamine ratio (SNA/GalNAc-L) levels were also observed in RA patients after glucocorticoid treatment [57]. However, detailed reports on prognosis and IgG glycosylation changes in RA patients achieving remission after treatment are lacking. Evidence suggests that

therapies modifying glycosylation can affect FcγRIIIa or CDC activity, thereby intervening in inflammatory processes and influencing RA onset and progression [31]. Thus, IgG glycosylation levels have potential for evaluating specific drug treatment effects in RA, providing scientific basis for their use as treatment response biomarkers.

3.5 Summary

In summary, this review outlines current research on the association between IgG glycosylation modifications and RA, revealing that IgG glycosylation indicators and their derived structures are associated with RA and play important roles in its onset and progression. Additionally, IgG glycosylation demonstrates good predictive capability in identifying RA and evaluating treatment efficacy. These findings provide scientific basis for further research on IgG glycosylation modifications in RA. However, most included literature provided moderate to low-quality evidence, and no randomized controlled trials on IgG glycosylation modifications and RA have been conducted. More high-quality, large-sample randomized controlled trials are needed in the future to obtain more accurate conclusions.

Author Contributions and Conflicts of Interest

Author Contributions: Youxin Wang proposed the research direction and was responsible for conceptualization and design. Cancan Li, Xiaoni Meng, and Haotian Wang conducted literature screening, data extraction, and quality assessment. Cancan Li drafted the initial manuscript. Xiaoni Meng provided writing guidance and language polishing. Youxin Wang was responsible for manuscript review and revision. All authors critically reviewed and modified the manuscript.

Conflict of Interest: The authors declare no conflicts of interest.

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Note: Figure translations are in progress. See original paper for figures.