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GROWTH DIFFERENTIATION FACTOR 15 AS A POTENTIAL DIAGNOSTIC BIOMARKER FOR RHEUMATOID ARTHRITIS A SYSTEMATIC REVIEW

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Abstract

Background

This systematic review aimed to evaluate the significance of growth differentiation factor 15 (GDF-15) in diagnosis of rheumatoid arthritis (RA).

Objective

To determine the role of growth differentiation factor 15 (GDF-15) as a potential biomarker in diagnosis of rheumatoid arthritis (RA).

Methodology

A comprehensive literature search was conducted using search strings including "rheumatoid arthritis" and "growth differentiation factor 15" across multiple electronic databases including PubMed, Embase, Web of Science and Cochrane library. The protocols of the systematic review were registered in the International Prospective Register of Systematic Reviews (PROSPERO). Moreover, this systematic review is aligned by the Preferred Reporting Project for Systematic Review and Meta-Analysis (PRISMA) website

Result

A total of 469 documents were retrieved, and five clinical studies were ultimately included. In the included studies, GDF-15 serum levels were found to be notably greater in RA patients than in healthy individuals, and these levels exhibited a positive correlation with disease severity. Furthermore, increased GDF-15 serum levels were associated with specific gene variations in RA patients, but varied according to ethnicity. In two included studies, GDF-15 showed high diagnostic sensitivity and specificity for highly active RA, demonstrating its utility as a diagnostic biomarker of RA.

Conclusion

GDF-15 expression is increased in RA patients and is associated with disease activity; thus, GDF-15 is potentially an effective diagnostic biomarker for RA. However, additional high-quality studies, especially randomized controlled trials and cohort studies with follow-up data, are needed to assess the role of GDF-15 in RA.

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INTRODUCTION

Rheumatoid arthritis (RA) is an extensive systematic autoimmune disease known to cause persistent synovial membrane inflammation(1).Its advancement can also cause bone deformities and chronic pain thereby effecting quality of life ad life expectancy(2,3).The continual increase in RA prevalence differs among countries and ethnic groups ranging from 0.5% to 1%(4,5).At present ,there is no therapy that interrupt the RA course and all treatment options aim to reduce chances of remission or reduce disease activity in patients (6,7). Moreover, RA management poses a significant financial burden on patients ,their families and society. A systematic review showed the direct cost of biological therapies ranging from USD $10,000 to $27,000 (9).

Early diagnosis have significant effect on RA management, its progression and disability limitation.(11-14).Laboratory tests are crucial in diagnosis with biomarkers such as the CRP level, ESR and the presence of RA specific autoantibodies such as Rheumatoid factor (RF) and anti-citrulline peptide antibodies (ACPAs) contributing to the diagnostic process (6,11). Although CPR and ESR both are associated with radiological progression but these markers are non-specific indicators of inflammation process (15). There is a limitation to predictive capability of RF for erosion of bone and it is primarily impactful in the early disease stage with declining accuracy as the disease progresses (16). ACPA is the most reliable biomarkers for assessment of joint damage due to its enhanced specificity and sensitivity (17). However, negative results have also been documented in some specific subgroups (18). As a result, researchers are focusing on identifying new biological markers that could enhance early intervention strategies and improve patient outcomes (19).

The Growth differentiation factor 15 (GDF 15), also called as macrophage inhibitory cytokine 1 (MIC-1) was first identified in 1997 and it belongs to the TGF-β superfamily of cytokines associated with cellular stress (20,21). Various conditions like most types of cancer, cardiovascular and renal conditions and sever infections increases the level of GDF 15 levels in the bloodstream (22-25). Previous studies have also shown the elevated levels of GDF 15 in patients of other diseases like systemic lupus erythematous (SLE and inflammatory bowel disease (IBD) (26). Elevated serum GDF-15 has also been associated with RA disease activity (27). Some studies have also been focused on the genetic variations of GDF-15 in RA patients and explain the contribution of gene polymorphism (28,29). A systematic review is needed for establishing definitive relationship between GDF-15 and RA as literature showed a potential relationship between GDF-15 and RA. Therefore, the aim of this systematic review is to investigate the relationship between RA and GDF-15 and whether it is associated with disease activity, while identifying its potential as a diagnostic biomarker for RA.

Methods

Data sources and search strategy

A comprehensive literature search was conducted using search strings including “rheumatoid arthritis” and “growth differentiation factor 15” across multiple electronic databases including PubMed, Embase, Web of Science and Cochrane library. The protocols of the systematic review were registered in the International Prospective Register of Systematic Reviews (PROSPERO). Moreover, this systematic review is aligned by the Preferred Reporting Project for Systematic Review and Meta-Analysis(PRISMA) website (30).

Inclusion and exclusion criteria

The inclusion criteria for this systematic review include the study population compromising individuals diagnosed with RA, with no restrictions on comparator group; serum GDF-15 levels and primary parameter of evaluation with or without the gene variation analysis and diagnostic value; with full text literature must be available in English. The excluded studies include Reviews, meta-analyses, editorials, letters, and genetic or animal research.

Study selection and data extraction

literature screening was conducted Independently by Two authors (XL, WL), firstly filtering duplicate studies and then narrowing down the selection via inclusion and exclusion criteria. Difference in opinions among controversial articles were resolved via discussion, and in case of disagreement, a third experienced author (YL) was consulted. Inclusions were made by comprehensively evaluating previously

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mentioned criteria. The extracted data for included studies include data pertaining to authorship, publication year, study design, characteristics of the study population (including number, race/ethnicity, age, and sex), disease duration and activity levels, complications encountered during the study period, and key findings.

Quality assessment

As included studies were mostly cross sectional, with only one case series study (31), the included literature was assessed using Agency for Healthcare Research and Quality (AHRQ) assessment scale (32). THE AHRQ scale is used for quality assessment of cross-sectional studies (33). Moreover, when incorporating various study designs, the AHRQ bias risk tool was used to evaluate common risk of bias in the included studies, thereby eliminating the need for using different bias risk tools separately, thus simplifying the evaluation process.(34).This scale compromises of 11 components each answered with "yes "or "no" or "Unclear"(Table I). "1" score is assigned for "yes" while "0" is for "no". The cumulative score ranges from 0 to 3 for low quality, 4 to 7 for medium quality, and 8 to 11 for high quality.

Table 1. Methodological Quality Assessment of included studies (n=9)

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12
Brown et al (2007)[31]	Y	Y	U	Y	Y	Y	U	Y	Y	N	Y	Y
Tanrıkulu et al (2017)[35]	Y	Y	Y	Y	Y	Y	Y	Y	U	N	Y	Y
Mendoza-Vázquez et al (2019)[36]	Y	U	N	U	Y	U	N	U	N	Y	N	Y
Esalatmanesh et al (2020)[19]	Y	Y	U	U	Y	Y	Y	U	N	Y	N	Y
He and He (2022)[27]	Y	Y	U	Y	Y	Y	Y	Y	N	Y	N	Y

Q1 = Define the source of information (survey, record review); Q2 = List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications; Q3 = Indicate time period used for identifying patients; Q4 = Indicate whether or not subjects were consecutive if not population-based; Q5 = Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants; Q6 = Describe any assessments undertaken for quality assurance purposes (e.g. test/retest of primary outcome measurements); Q7 = Explain any patient exclusions from analysis; Q8 = Describe how confounding was assessed and/or controlled; Q9 = If applicable, explain how missing data were handled in the analysis; Q10 = Summarize patient response rates and

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completeness of data collection; Q11 = Clarify what follow-up, if any, was expected and the percentage of patients for whom incomplete data or follow-up were obtained.
N, no; U, unclear; Y, yes.

Results

In initial search, total 469 articles were obtained from the electronic databases (Web of Science =403, Cochrane library = 7, Embase = 46, PubMed =13).427 remained after excluding 42 duplicate articles. Irrelevant and review, meta-analysis and animal studies were kept excluded. After such a process. Only 10 relevant articles remained whose full text were fully examined. After examination, only five studies were included in this systematic review (Figure1).

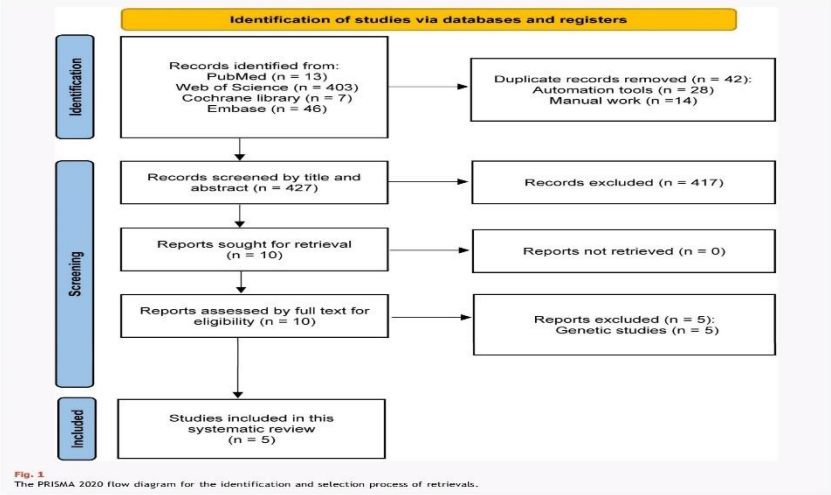

Fig. 1
The PRISMA 2020 flow diagram for the identification and selection process of retrievals.

Three cross sectional studies contain high quality results (AHRQ score of 8 to 9), one medium quality (AHRQ score = 6) and another of low quality (AHRQ score = 3). The study published by Mendoza- Vázquez et al (36) showed important results irrespective of lacking extensive methodological details.
Table II provides the main summary of key findings. The genetic impact of GDF-15 and RA was exposed by Brown et al (31) and He and He,[27] via allelic gene analysis. Out of five studies ,four resulted in association between GDF-15 and RA, indicating a positive correlation between serum levels of GDF-15 and disease activity in RA patients while Mendoza-Vázquez et al,(36)showed contradictory findings. Three findings also revealed that GDF-15 may hold diagnostic value in relation to RA.(19,27,35)

Table II. Summary of the population characteristics and main analysis of the included studies(n = 5).

	Brown et al[31]	Tanrıkulu et al[35]	Mendoza-Vázquez et al[36]	Esalatmanesh et al[19]	
Variable	(2007)	(2017)	(2019)	(2020)	He and He[27] (2022)
Country	USA	Turkey	Mexico	Iran	China
RA/CG, n	83/271	46/36	162/0	100/55	455/455
Age, yrs (either mean (SD) or	RA: 64 (SD 13)	RA: 44.21 (SD 8.40)		RA: 35.7 (SD 9.4)	RA: 56.00 (IQR 49.00 to 64.00) CG: 55.00 (IQR 48.00 to

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median (IQR))	CG: 43 (SD 13)	CG: 44.14 (SD 10.79)	RA: 57.2 (SD 11.5)	CG: 36.4 (SD 10.6)	65.00)
Sex (RA), n	37 F/24 M	12 F/34 M	N/A	100 F/0 M	343 F/112 M
Disease duration, yrs (either mean (SD) or median (IQR))	10.8 (SD 8.3)	7.36 (SD 7.68)	13.60 (SD 9.50)	3 (IQR 1 to 7)	0.50 (IQR 0.00 to 6.50)
Activity analysis	Y	Y	Y	Y	Y
Gene analysis	Y	N	N	N	Y
ROC analysis	N	N	N	Y	Y

***CG, control group; F, female; M, male; N, no; N/A, not applicable; RA, rheumatoid arthritis; ROC, receiver operating characteristic; Y, yes.**

Higher expression of GDF-15 in RA patients

An increase in GDF-15 levels in RA was found in most of the studies. (19,27,31,35). A statistically significant increase in GDF-15 levels in the serum of RA patients as compared to those in the healthy control group (Table III) was showed up by all the four studies. Although He and He's (27) study did not specify the GDF -15 Value for RA and control groups, the graph of original data showed an increment in GDF-15 and serum levels in RA patients. Moreover, Brown et al (31) found out higher GDF-15 expression compared to samples from individuals with reactive arthritis and meniscal pathology. It could be linked to pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin (IL)-1β, or IL-6 stimulating GDF-15 expression in synovial tissue. (37).

Indication of GDF-15 of RA activity

Increased levels of serum were subjected to be seen in higher disease activity RA patients (Table III) (19,27,31,35). At first Brown et al (31) distinguished disease activity among enrolled patients by the use of haemopoietic stem cell transplantation(HSCT) for those with more severe disease and outpatients with less severe disease. Succeeding studies by Tannkulu et al (35), Mendoza –Vazquez et al (36) and Esalatmanesh et al (19) used the disease activity score -28 (DAS28) (38) to categorize RA patients into active and non-active groups. Three studies revealed that higher GDF -15 serum levels corresponds to RA patients with higher disease activity. But Mendoza-Vazquez et al (36) demonstrated no association between GDF-15 and RA disease activity.

Table III. Serum growth differentiation factor (GDF-15) levels in different populations of included studies (n = 5). Values are expressed as mean (SD), in pg /ml.

Variable	Brown et al[31] (2007)	Tanrıkulu et al[35] (2017)	Mendoza-Vázquez et al[36] (2019)	Esalatmanesh et al[19] (2020)	He and He[27] (2022)
RA	1,084 (687)	1,465.92 (902.05)	435.54 (310.64)	548.2 (314.02)	Unavailable
CG	487 (197)	993.23 (955.01)	N/A	270.7 (167.9)	Unavailable
Active RA	HSCT: 1,334 (906)	1,749.79 (847.43)	455.09 (333.47)	989.0 (161.9)	Unavailable
Non-active RA	Outpatients : 1,002 (584)	1,069.88 (853.59)	406.36 (272.94)	349.0 (144.0)	Unavailable

CG, control group; HSCT, haemopoietic stem cell transplantation; N/A, not applicable; RA, rheumatoid arthritis.

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Particularly, CRP and ESR levels (the serological indicators related to disease activity) also have a connection with serum GDF -15 levels (Table IV). All of the included studies examined the relationship between GDF-15 and CRP and three of them reporting that RA patients with higher serum CRP levels has higher GDF-15 levels (19,27,31). But the findings of Tanrıkulu et al (35) contradicted the association between CRP and GDF-15 levels. Pearson correlation between serum GDF-15 and levels and CRP performed by Mendoza-Vázquez et al (36) also showed non-significant correlation. Three out of five studies provided supportive evidence for a potential correlation between these two variables (19,27,35).

Table IV. The association of serum levels of GDF-15 with CRP and ESR.

Variable	Brown et al[31] (2007)	Tanrıkulu et al[35] (2017)	Mendoza-Vázquez et al[36] (2019)	Esalatmanesh et al[19] (2020)	He and He[27] (2022)
GDF-15 & CRP	(+)	(-)	(-)	(+)	(+)
GDF-15 & ESR	N/A	(+)	N/A	(+)	(+)
Selection methods	HSCT/outpatients	DAS28-ESR	DAS28-CRP	DAS28-ESR	DAS28-ESR

(+), related; (-), not related; DAS28, Disease Activity Score-28; GDF-15, growth differentiation factor 15; HSCT, haemopoietic stem cell transplantation; N/A, not applicable

GDF-15 gene polymorphisms in RA

Out of five studies, two studies analyzed genetic variations in RA patients and recognized differences in genes on comparison with healthy individuals (27,31). Brown et (31) were the pioneers in the investigation of genetic variations in the GDF-15 among RA patients. Their remarkably discovery was that those with the D allele experiences earlier onset of RA and are more susceptible to develop erosive disease as compared to H allele. The connection between RA risk and GDF-15 gene variations (specifically, rs1055150, rs1058587, rs3787023, and rs4808793) was explored by He and He's (27). They reported that the frequencies of GG, GC, GG + GC genotypes, and the G allele in rs1055150 were notably higher in RA patients. Similar to that the frequencies of the CC genotype and C allele in rs3787023 were more prevalent in RA patients than in the control group. But no significant differences were reported in the serum GDF-15 levels among RA patients with different genotypes (27).

GDF-15 for RA diagnosis

GDF-15 was confirmed to have a potential use as a biomarker for prediction of RA. Esalatmanesh et al (19) assessed the predictive capability of GDF-15 for RA and its disease activity by implication of receiver operating characteristic (ROC) analysis. The findings of their study reported the GDF-15's excellent predictor attribute of high RA activity when GDF-15 levels surpass 705 pg./ml, this indicates high RA activity, with a sensitivity of 96% and specificity of 92%. (19). He and He's study (27) also assessed the predictive ability of GDF-15 for RA. The ROC analysis revealed an AUC of 0.692 when comparing serum GDF-15 levels in the RA group with those in the control group. But, GDF-15 was reported to have limited sensitivity and specificity in distinguishing between low and moderate activity, as well as between patients with low activity and those in disease remission (19).

Despite a comprehensive literature search, only five clinical studies met the inclusion criteria due to lack of relevant studies. Generalizability of the results may be limited due to limited number of studies with their small sample sizes.in addition to that, the reliability of the results may b affected by the potential

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heterogeneity among the included studies. Firstly, the population of the studies originated from East Asian, Central Asian, and Western countries, with the observed genetic variations among the populations. Secondly, the studies spanned a lengthy period from 2007 to 2022, during which different methodologies were used in measuring serum GDF -15 levels. But, this study has preliminarily elucidated the relationship between GDF-15 and RA, and further research are required to confirm these findings in future.

Discussion

An overview of clinical researchers on GDF-15 and its association with RA has been provided by this systematic review. It demonstrated that GDF-15 has the potential to serve as a diagnostic biomarker for RA and to assess disease activity. Variations in GDF-15 alleles among RA patients and variations between different ethnic groups has been identified and observed in this review.

Total 469 items from the literature were extracted from multiple databases and five studies were selected for analysis in this systematic review. Among five included studies, four studies reported a positive relationship between GDF-15 and RA, while one study suggested n relationship (36). Higher frequencies of specific alleles in RA patients was observed via gene polymorphisms analysis while the results from various ethnic studies were contradictory. Moreover, GDF-15 displayed high specificity and sensitivity in prediction of RA with severe clinical manifestations and remarkably increased inflammatory markers (e.g., CRP, ESP), generally classified as high disease activity deployed on standardized assessment tools such as DAS28-ESR/CRP, showing that it is a valuable diagnostic tool for RA.

Several types off cell including cancer cells, macrophages, endothelial cells, smooth muscle cells, and adipocytes, are capable of secreting GDF-15(39).Accordingly ,numerous determinants can contribute to increased plasma GDF-15levels, by which physiological stimuli such as muscle contraction and exercise are noteworthy (40,41).A contemporary study suggests that circulating GDF-15 levels increases with age and are ordinarily uninfluenced by sex variations(42).In pregnant women,GDF-15 levels rise incrementally with gestational age ,reaching at its peak around the 3rd month of pregnancy(43).Moreover, findings of the research reported that GDF-15 levels are increased in multiple disease states (40,44).For example ,Wang et al (45) outlined elevated serum GDF-15 levels in cardiovascular patients, presenting its possible utility in detection of myocardial infarction and mortality prediction. In the same fashion, Tuegel et al (46)reported a positive correlation between GDF-15 levels and chronic kidney disease (CKD),implying that higher levels are indicative of increased mortality risk. In addition to that, although glucose homeostasis remains ambiguous (22), increased serum GDF-15 has been associated with impaired glucose tolerance, insulin resistance, diabetes, and related complications. Afflictions such as oxidative stress, inflammation, and cancer can also result in profoundly increased GDF-15 levels, with titers reaching up to one hundred times above optimal functional values (47).

Current research is intended to annotate the association between GDF-15 and RA to support the progress of more accurate diagnostic approaches and quality therapeutic strategies. The function of GDF-15 in the pathogenesis of RA remains ambiguous. There has been an indication that GDF-15 may possess a two directional impact on RA progression, with both pro-inflammatory and immunosuppressive properties(48,49).Research also suggested that GDF-15 can be induced by inflammatory stimulation of immune and parenchymal cells and coordinate tolerance to inflammatory damage(24).Moreover ,the properties autocrine regulator of macrophage activation and inhibition of lipopolysaccharide induced TNF- α production (resulting in inhibition of macrophage activation)of GDF-15 has also been reported by contemporary researches(21,30,50).In addition to that ,mediation of anti-inflammatory effects by reduction of leucocyte migration to inflammatory sites is also a function of GDF-15(51).GDF also acts as a as binding to glial cell line-derived neurotrophic factor receptor α (GFRα)-like (GFRAL) and its co-receptor Ret consequently inducing anorexia and declining food consumption(22,52-54).But ,more researches are needed to elucidate the underlying mechanism of GDF-15 in other diseases, such as RA discussed here in.

Increased GDF-15 serum levels assist in estimation of high disease activity in RA. Disease activity

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monitoring is essential for RA treatment, as accurately assessing its activity level enables the implementation of attuned therapeutic approaches. When patient's joints are inflamed because of an active disease, they may get advantage from inflammatory suppression therapy. But in case of joint damage due to prior active disease, suppression of inflammation is of no use (55). The evidence of higher levels of serum GDF-15 in the group with active disease and its positive correlation with morning stiffness and tender joint count was also supported by Tanrıkulu et al (35). Furthermore, all included studies examined the correlation between GDF-15 and two inflammatory markers (CRP and ESR) in RA patients, and most findings indicated a positive association (19,27,31,35,36). The elevated levels of that CRP and ESR in RA patients was also supported by evidence (56).But, Tanrıkulu et a(35) suggested no correlation between CRP and GDF-15,indicationg that p53 pathway activation may inhibit IL-6 production in rheumatoid joints resulting in reduction of serum CRP levels. As a matter of fact ,the results suggested the classification methods of RA activity were different among different studies (Table IV). DAS28-CRP was used by Mendoza- Vázquez et al (36) for classification of the activity of RA patients and reported no association of GDF-15 with CRP and DAS28-CRP. But, previous studies indicated that there are differences between DAS28-ESR and DAS28-CRP, and they are not interchangeable (57,58). In comparison with DAS28- CRP, DAS28-ESR is generally higher, especially in moderate or high disease activity populations. The recommendations of American College of Rheumatology (ACR) do not differentiate them yet, which means that DAS28-ESR ≤ 3.2 and DAS28- CRP ≤ 2.6 were defined as low disease activity and disease remission, respectively, in both scoring systems (59). Previous studies have assessed the variations between DAS28-ESR and DAS28-CRP, indicating that the cut-off values of disease remission to DAS28-CRP should be < 2.4(60). Such considerations was not taken into account by Mendoza-Vázquez et al (36) which may have altered their conclusions. It is recommended that future studies investigating the role of GDF-15 in assessing disease activity among RA patients should employ a standardized index when utilizing the DAS28 score, or appropriately adjust diverse scores to overcome potential bias.

The association between GDF-15 gene polymorphism and susceptibility to RA has raised greater concerns (26,27,28,31,61). Notably, researches encompassing possessing diverse ethnic group have shown contradictory findings. The analysis into the gene polymorphism of GDF-15 started rapidly after the conduction of correlational analysis in RA patients by Brown et al (31). Their results suggested that D allele was associated with earlier onset and joint erosion. The allelic variation at position 6 of the mature GDF-15 protein results in a substitution from histidine (H allele) to aspartate (D allele), also known as rs1058587(62).AS a consequence ,the Brown et al's (31) findings were also validated via a Swedish study involving 723 RA patients by showing demonstrating significant differences in the frequencies of GG and GC genotypes at rs1058587 between RA patients and controls(61).But, He and He(27) examined the Chinese Han population and reported an association between RA and both the G allele at rs1055150 and C allele at rs3787023 still no significant association was observed for rs1058587.In a similar manner, the correlation between the rs1058587 polymorphism and the risk of RA in 310 Colombian RA patients using the TaqMan allelic discrimination assay(28) was also conducted in a study in Latin America which resulted in contradictory the findings reported by Brown et al(31).Interestingly ,Ye et al (26)assessed the relationship between rheumatic disease and GDF-15 by using existing genetic data in a Mendelian randomization study published in 2021 found the no significant association exists between GDF-15 and RA. He and He (27) concluded that this result is due to laboratory-based investigations offering greater reliability in comparison with Mendelian randomization designs.

However, this review has some limitations because it is the pioneer systematic review on RA and GDF-15.

Initially, a limited number of relevant studies were included. But, comprehensive analysis based on existing English literature was done. Secondarily, a high level evidence (i.e., randomized controlled trials -RCTs) was inadequate because of the absence of published studies in this area. This is due to the availability of only cross sectional studies without any follow-up period to track changes in GDF-15 levels over time (i.e., lack of longitudinal studies). Moreover, lack of studies

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demonstrating the mechanism by which GDF-15 affects RA was also a contributing factor. In future studies, it is essential to conduct additional prospective and cohort studies, supplemented with higher-level evidence such as RCTs, to document the dynamic changes of GDF-15 during the disease or post-treatment. In addition to that, running basic experiments will provide deeper insights into the diagnostic and therapeutic function of GDF-15 in RA.

In essence, elevated levels of the protein GDF-15 in the blood are associated with rheumatoid arthritis (RA), and this increase is linked to the disease's activity. In other words, higher GDF-15 levels are observed in RA patients, and these levels tend to rise as the RA becomes more active. Moreover, the polymorphism of GDF-15 gene was also associated with RA patients, but varied among different ethnic groups. In addition to that, there exist a need of more prospective and high-level evidence studies (RCTs) to understand the role of GDF-15 in RA. To sum up, GDF-15 may be a potential biomarker for the diagnosis of RA and impose profound impact to the cure of RA.

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