

COMORBIDITY OF CARDIOVASCULAR DISEASES AND RHEUMATOID ARTHRITIS

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic disease related to swelling of joints which lead to restriction in movement due to pain and deformity mainly in feet, ankle, wrist, and fingers. It is an autoimmune disease, and the manifestations caused due to its occurrence are not clearly understood. In today's time, it has been observed that comorbid conditions account for most of the deaths as they influence the outcome of RA and limit therapeutic options. The most common comorbid conditions which are diagnosed in RA patients are generally cardiovascular (CV) abnormalities, several infections, certain mental disorders, and malignancies. Among which CV comorbid diseases are the most common kind relating to disorders of heart and blood vessel that eventually leads to severe conditions such as angina, myocardial infarction, stroke, rheumatic heart disease, and many more. RA affects the quality of life of patients directly or indirectly, but it mainly shows a significant increase in the prevalence of CV diseases. Hence, it is essential to diagnose and understand about the related manifestations when one is suffering from RA. These studies will aid to make better treatment and management strategies. Hence, an attempt has been made in this review article regarding the epidemiology, impact of both diseases and related risk factors. It also gives information in brief about the pathological causes of the comorbidity and summarizes measures that may be used in the prevention and treatment of these conditions.

Keywords: Cardiovascular diseases, Comorbidity, Rheumatoid arthritis, Inflammation.© 2017 The Authors. Published by Innovare Academic Sciences Pvt Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>) DOI: <http://dx.doi.org/10.22159/ajpcr.2017.v10i5.16078>**INTRODUCTION**

Rheumatoid arthritis (RA) is a chronic, incurable disease characterized primarily by painful joint inflammation [66]. Comorbidity is a medical condition that co-exists along with the disease of interest for instance. RA comorbidity can be further defined in terms of a current or past condition. It represents either an active, past or transient illness. It may be linked to the rheumatic disease process itself and/or its treatment, or it may be completely independent. Due to these links, comorbidities have grown in importance to physicians and researchers because they greatly influence the patient's quality of life, the effectiveness of treatment, and the prognosis of the primary disease. A given RA patient can approximately have 1.6 comorbidities and its frequency increases with increase in age. The more comorbidities a patient is identified with, it leads to more utilization of health facilities which has an impact not only on personal costs but also escalates societal costs. Ultimately, poor quality of life leads to greater chances of hospitalization and mortality. Such complications affect patient care, making diagnosis and treatment decisions more challenging. If presence of co-morbidity is more than one is prone towards more interference in on-going drug treatment and also face problems like increased medical costs and raised risk of mortality. Hence, it is essential to recognize such illnesses and to ensure the care of every individual patient [1].

Patients with RA suffer significantly with increased cardiovascular (CV) morbidity and mortality when compared with the general population [2]. CV diseases (CVD) are the ones relating to disorders of heart and blood vessel which lead to severe conditions such as angina, myocardial infarction (MI), stroke, rheumatic heart disease, carditis, and many more [3,4].

17.5 million people die each year from CVDs, an estimated 31% of all deaths worldwide. It can be established from recent literary work that the mortality of most people suffering from RA is largely due to the presence of a cardiac suffering in the same individual. Ischemic heart

disease is among the most common CVDs significantly in individuals with RA [3,4]. Improper adherence to medications is also major patients' problem remains one of the main issues in the treatment of CVD problem like hypertension [65].

As per described previously the other comorbid disorders with RA are as follows:

Infections

Tuberculosis (TB) is the most common infection which is prone to occur in RA patients. Mortality rate associated due to this infection is about 25% in RA patients. Cause of this disease arousal is still not known whether it is due to immune dysfunction of RA patient or due to drugs used in treating individual infection or both diseases [57,60].

Mental disorders

Anxiety and depression are the most common mental diseases as such reason behind is generally increased disease condition in RA patients [61,64].

Malignancies

Leukemia and several myelomas have greater chances to arise in RA patient, but the reason behind this malignancy is still unknown [60].

STUDY EVIDENCE

The latest population-based study carried out compares RA and non-RA subjects and suggests that those with RA show a 3.17-fold higher risk for having hospital MI and an almost 6-fold increased risk of having a silent MI. Thus, the data expresses a progressive incidence of silent MI and of sudden death after its occurrence [5].

EPIDEMIOLOGY OF COMORBIDITY OF CVDS AND RA

As per the survey report of community-based cohort study which was carried out from the period of 1985-1989, among 183 patients with

age of 52 years, concentrating more on female population (63%), were diagnosed with the early RA. The study included continuous recording of additional comorbidities along with RA. The results of the same stated that along with RA diagnosis, at least one comorbidity was present in 43% of the patients. The comorbid conditions like CVDs, including hypertension (16% of patients), stroke, and malignancy, were found to be most common, among which majority of patients (82%) developed additional comorbidities during their follow-up treatment. It was predicted from the cohort study that aging of the population and the presence of comorbidity along with RA was the cause for the development of comorbidities [5].

Again in 2000 and 2007, a similar cohort study was conducted which stated 1383 (19.2%) of patients in total were diagnosed with hypertension as a comorbid condition along with RA. The study reported the result in terms of prevalence which was found to be 20% in men were as 18.8% in women out of 465 cases and 918 cases, respectively. The prevalence of chronic hypertension among the RA population did not exist in the rheumatoid factor (RF)-positive subgroup. However, there was increased risk of development of chronic hypertension in the RF-negative subgroup [5].

Another study conducted for the study of prevalence of the comorbid conditions, i.e., the comorbidities in RA (COMORA) study which had two major objectives were conducted for the same. The first objective was evaluation of the variability in the prevalence of comorbidities and their risk factors. The second objective was assessment of distinctive national treatment recommendations between the already existing ones and its implementation in routine clinical practice for the detection and prevention of these developing comorbidities [7].

The majority of periodically associated diseases either past or current were found to be: 6.6% of CV events which included MI, stroke, and elevated blood pressure in a patient population of 11.2% with RA. There was high intercountry variability observed for the prevalence of comorbidities and the proportions of the candidates subjected to the study, complying with the treatment recommendations for prevention and management of these comorbidities [6].

A systemic evaluation of comorbidities in COMORA study observed abnormalities like elevated blood pressure in 11.2% which identified conditions of hyperglycemia in 3.3% and hyperlipidemia in 8.3% cases under the study [6].

Thus, the study concluded that the higher death rate appeared as the consequences due to an increased prevalence of CV risks, an increased incidence of infections, and the development of certain malignancies in patients with RA [7,8].

IMPACT OF RA ON CVD

Awareness is already there regarding arthritis affecting body joints but unfair or unaware news is such that arthritis is also responsible for causing several CV disorders such as heart attack, atrial fibrillation, atherosclerosis, and high blood pressure. As per the nature reviews rheumatology more than about 50% death is observed in a patient of RA due to heart diseases. Inflammation regardless is a troublemaking disorder causing heart disease. In this, the inflamed cells get into the blood vessels where they cause increase in the release of cytokines and serum proteins which in turn promote more inflammation. This inflammation also leads in rupturing of deposited plaques on blood vessels which proves to be a triggering factor responsible for causing heart attack as per arthritis and rheumatism review inflammation does not act alone but it is found to be acting in increased amount in patients who are having heart disease risk factors in addition to it, like high blood pressure or diabetes or atherosclerosis.

Risk factors

- According to Figs. 1 and 2, smoking may increase level of nicotine which in turn leads to increase in chances of heart failure
- High cholesterol level in blood serum increases chances of atherosclerotic attack
- High blood pressure occurs as one of the major comorbid disorder in RA patients
- Overweight is also that solely responsible for CVD and condition may even get worse if proper exercise is not being done long with a regular diet plan.

As per a disease control committee, there have been some ratios indicating the amount of CV disorder, patient is having because of arthritis [6]

- 53% of RA patients have high blood pressure
- 66% of RA patients are overweight
- 20% of RA patients do smoking [13-15].

Hence on the basis of a survey made about one-fourth adult with any arthritis form has heart disease. Thus, concluded as per one of the review author along with a reduction in CV risk, inflammation is required to be reduced too with habitual risk factors such as blood pressure, diabetes, high lipids, and smoking.

IMPACT OF CVDs ON RA

CVDs are found to be highly prevailing in RA patients and they contribute significantly in raising morbidity and mortality rates [51]. In the case of RA patients they are considered to be as a kind of clinical manifestation. As a part of recent findings silent MI in RA patients as comorbidity leads to death of the patient because of certain known risk factors such as damaged peripheral blood vessels gets revascularized and also certain genetic abnormalities [21]. The CV impact on RA at certain extent is still considered to be unknown and it is under core observation. Several heart patients along with this disorder are having rheumatism which proves to be an elevator in causing an increase in comorbid activity. Awareness, in this case, is must before its expansion.

Risk factors

- Decreased exercise may be one of the reasons for manifesting CVD in rheumatic patients due to reduction in mobility
- Fluid retention may be responsible for its spread in different areas of the body and also affects vital organs too.

Because of resting in heart patients it may also result in occurrence of edema and swelling particularly in legs, feet and the ankles due to prolonged sitting pitting edema occurrence is also due pressing of puffy areas that are being inflamed. It mainly affects liver and kidney not synonymous to heart failure [9]. This swelling due to heart disease may also reach to hips, scrotum, abdominal wall, and eventually abdominal cavity. Hence, daily weight checkup is required to be done by the heart patients because the amounts of fluid retention in turn either result into joint pain or increase in shortness of breath. Thus, strict diet program and exercise program to be followed up. In short clinical manifestations of both RA and CVDs are linked with each other [9].

CLINICAL PRESENTATION

There lies a close correlation between the morphology of progressive carotid atherosclerosis and inflammation, which insinuates elevations in inflammatory biomarkers which indicate occurrence of atherosclerosis [20]. Specific systemic inflammatory biomarkers show a remarkable increase in the risk of CV death in patients with RA [21,22]. A substantial increase in the levels of proinflammatory mediators such as tumor necrosis factor-alpha (TNF- α), interleukin (IL-6), and IL-17

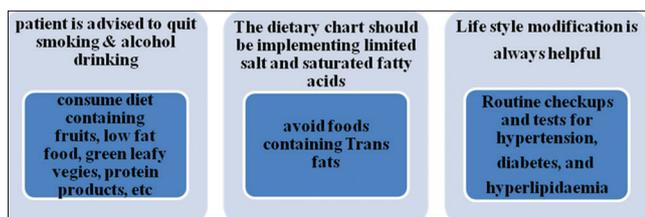


Fig. 1: Basic steps to reduce the risk of comorbidity

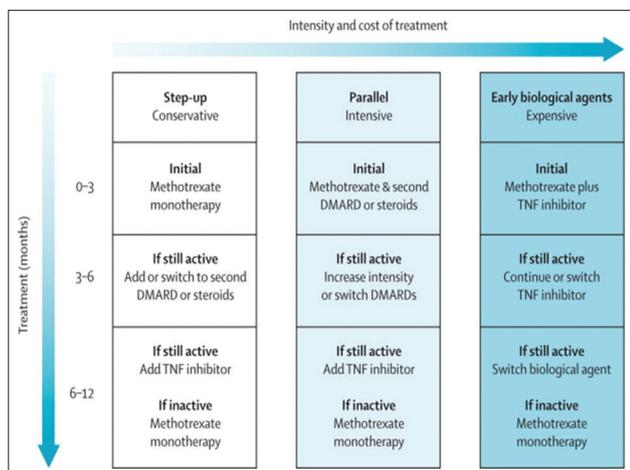


Fig. 2: Treatment algorithm for comorbidity

damage the endothelium as well as the myocardium which predisposes insulin resistance [23-25,38,39]. C-reactive protein (CRP) at minimal level acts as an essential indicator of subsequent death from CVD in patients with recent onset of arthritis [26]. High concentration of CRP indicates increased carotid media thickness [27].

Some clinical features such as higher erythrocyte sedimentation rate, rheumatoid nodules, vasculitis, large joint swelling, and rheumatoid lung are independently correlated with increased risk of death due to CVD [21].

A modern study compares individuals with RA and controls which showcased association of TNF- α and IL-6 with the complexity of coronary artery calcification occurring in RA. Increased stiffness of arteries occurring in RA can be well correlated with CRP and IL-6 levels [26]. In patients with new onset of congestive heart failure, high sedimentation rate was found in 6 months preceding the detection of cardiac dysfunction which indicated that an enhanced inflammatory pathogenesis may lead to cardiac dysfunction due to inflammatory arthritis [31-34]. The extent and chronicity of inflammatory processes were measured with the circulating levels of inflammatory biomarkers and was linked to carotid atherosclerosis development in RA [27]. The overall amount of adhesion molecules such as soluble vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1, and endothelial-leukocyte adhesion molecule related to vascular damage were higher in RA. VCAM-1 levels have been correlated with carotid atherosclerosis in individuals with RA [28].

The exact role of IL-17 in premature vascular damage in RA is believed to be unraveled; a recent research indicated that cytokines play a major role in atherosclerosis development in murine models of vascular diseases [32,33]. This study also reported elevated circulating level of IL-17 in cases with acute coronary syndrome [34]. IL-17 is produced along with interferon- γ INF- γ by coronary artery infiltrating T-cells. These cytokines act synergistically to cause

proinflammatory responses in vascular smooth muscles [35]. IL-17 also showed an increase in myocardial fibrosis in animal models having heart injury [36]. Thus, many evidences are collected that support the fact that IL-17 plays a regulatory role in the development of atherosclerosis [37].

Inflammatory biomarkers

RA and CVD have a common inflammatory mechanism. Specific systemic inflammatory biomarkers such as IL-6, IL-17, and TNF which are elevated in RA are well correlated with increased risk of CV death in patients [24,38].

Revelation of proatherogenic lipid profile

A recent study between 87 women with RA and with 50 healthy ones revealed a proatherogenic profile in women with RA. Lipoprotein A was considerably increased, and high-density lipoprotein cholesterol was found to be decreased in them [24,39].

Metabolic abnormalities

One study involving 154 cases of RA showed a high prevalence of metabolic syndrome. Insulin resistance was observed due to an alleged increase in oxidative stress as well as over expression of pro-inflammatory cytokines [40].

Genetic association

Many genetic links have been established for the comorbidity of CVD and RA such as histocompatibility complex [41], human leukocyte antigen DRB1 genotype [42], the IL-6-174C allele [43] and the TNF- α -1031 T/C polymorphism [44].

Cellular alterations

Cellular level changes can induce CVD in patients already suffering with RA. Exceeding population of CD4+CD28- T-cells in such individuals generally predisposes atherosclerotic plaques and unstable angina [45].

EXTRA-ARTICULAR SYMPTOMS OF RA

An epidemiological research linked few extra-articular manifestations of RA such as rheumatoid nodules, vasculitis, and rheumatoid lung with increased risk of CV death in patients [46].

As per a survey data internationally the prevalence of RA is believed to range from 0.4 to 1.3% [52,53] also on the basis of Rochester Epidemiology Project it was found that there was increase in RA among female individuals annually and comparatively reduction of about 0.5% was found in male individuals [54]. Life time risks as per that epidemiology report were estimated about 4% in female and 3% in male [55]. Multiple studies reported that in the past half century with diagnosed RA has increased mortality rates compared to the general population [56]. It was also reveal regarding the comorbid disorders among which ischemic heart diseases were diagnosed too in patient with RA [56]. People with RA have greater evidence of atherosclerosis [57] and risk of silent MI [58] too. A 2015 study found that risk of CVD rose [59]. It is unknown whether the increase in CVD mortality is due to the disease, the risk factors found in people with RA (e.g., presence of hypertension, more likely to be smokers), or the effects of the drugs used to improve the health condition [58,60].

WORSENING DUE TO COMORBIDITY

Patients are more prone for the development of chronic comorbid disorder on the basis of age as well as gender. Of the main diseases group CVDs were developed as a new comorbid disorder. These diseases might develop after a longer period than our median follow-up duration of nearly 3 years. The patient may also experience reduced life expectancy and increased mortality even though there has been reduction in disease. There is about 70% increase in death rate as a risk factor of CVD in arthritis. Out of which is 5-10% in men

and 2-4% in women aged 50-67 years [12]. It has also been found that patient with RA along with diabetes are less prone for developing angina but they are more susceptible in getting MI attacks and even sudden cardiac deaths. Possibilities of getting recurrent ischemic attacks are also more in rheumatic patients. Patient with RA if is having comorbidity of CVD along with it also has a higher rate of getting suffered from depression. Studies have also found that pre-clinical atherosclerotic attacks are also found in RA patient. Confusion still exists regarding preventive measures to be taken in CV risks. Even uncertainty is at its peak regarding how RA to be treated along with avoidance of future CV risks as some medications used in RA might have dual effect on the risk of CV morbidity. As an example steroids might decrease CV risks along with its reduction in inflammation but in turn it also causes elevation in proatherosclerotic lipid profile levels. Hence, these accelerated elevating CV complications along with RA are considered to be complex. Overall, studies have finally discovered that this increasing CV complications and mortality in RA must be provided with proper treatment in which traditional and non-traditional risks factors are of topmost importance in patient population [13].

TREATMENT OF COMORBIDITY

The recommended treatment for the comorbid condition following arthritis medications which offers heart protective benefits.

Treatment with tumor necrosis factor-alpha inhibitors

A recent study in 2011, which was published in the Annals of Rheumatic Diseases, observed that patients under these biologics, such as etanercept, infliximab or adalimumab had a reduced risk of developing heart disease. Another study of Johns Hopkins in the same year observed that the patients with RA, when administered with TNF- α inhibitors, had a lower rate of thickening in their carotid arteries approximately 37% than those not consuming it. A survey study published in the American Heart Journal observed that, in the elderly patients with RA, TNF- α inhibitors elevated the risk of heart failure as it was very clearly distinguished between the effect of these biologics on the heart muscles and on the arteries [10].

Treatment with methotrexate

Methotrexate is a disease-modifying antirheumatic drug (DMARD) which is considered as the first line agent and often given to patients with RA. Evidence-based British review in 2010 comprising 18 studies was published in Rheumatology, observed that patients with RA taking methotrexate had reduced chances of developing a heart. "A large amount of research shows that methotrexate can reduce the risk of heart disease," through the reduction in the plaque accumulation in the arteries [10].

Treatment with hydroxychloroquine

An evidence British review which was conducted in 2011 and published in Current Opinions in Lipidology observed that hydroxychloroquine worked on improving the risk factors associated with heart diseases such as blood sugar and cholesterol levels. The study also concluded that the effect of this biologic on the reducing risk factors associated with heart diseases was still under the study [10].

CURRENT RECOMMENDATIONS FOR TREATMENT OF COMORBIDITY

RA is a chronic inflammatory disease. RA sufferers along with chronic inflammatory condition they too suffer from CVD as comorbid disorder and prevalence of mortality rate is also higher due to this in RA patients [14] hence the current recommended medication for this is TNF- α blocker (TNF- α antagonist).

TNF- α mechanism

Initial stimulus for joint inflammation activates macrophages which in a diseased joint secrete TNF- α , which activates some endothelial cells,

other monocytes, and synovial fibroblasts. Activated endothelial cells upregulate adhesion molecule expression, resulting in recruitment of inflammatory cells to the joint. Monocyte activation has a positive feedback effect on T-cell and synovial fibroblast activation. Activated synovial fibroblasts secrete interleukins, which recruit additional inflammatory cells. With time, the synovium hypertrophies lead to destruction of bone and cartilage in the joint, causing the characteristic deformity and pain of RA [48].

This anti-TNF is given which generally causes decrease in the activity by reducing systemic and local inflammation [15]. This TNF- α antagonist eventually decreases unfit coagulation and CV risk associated with RA. Anti-TNF role in thrombotic mechanism as per the evidence so far available indicates it can modify CV risks which are associated along with RA [14].

NATURAL TNF BLOCKERS

Mechanism of curcumin (a compound present in turmeric): Turmeric supplements containing curcuminoids lessen joint inflammation and its destruction by blocking several inflammatory pathways and simultaneously reduce production of certain proteins which in turn triggers pain. It has been found that it has its influence on more than 700 genes, and it can inhibit both excessive activity and the synthesis of cyclooxygenase-2 (COX-2) and 5-lipoxygenase, as well as other enzymes that have been implicated in inflammation [15,49].

Mechanism of catechins (a compound present in green tea): Catechins from green tea are effective in rheumatism. Two types of catechins such as epicatechin gallate and epicatechin are having activity of anti-inflammatory along with protecting the cartilage destruction. This is found to be a unique activity of catechins. Hence as per the study, it has been proved that green tea contains catechins which prevent and protects the cartilage from getting destroyed [15,50].

Even activation of cannabinoid receptors, i.e., CB₁ or CB₂ by usage of cannabis or *Echinacea purpurea* shows their activity of anti-inflammatory by TNF- α inhibition [15].

Adverse effects

These natural anti-inflammatory agents are found to have maximum advantages and the highest improving features of reducing joint inflammation along with protecting cartilage destruction. Safest prescribed medications with zero adverse effects [49].

SYNTHETIC TNF BLOCKERS

Mechanism

They are determined to be a type of biologic DMARDs. These agents are a group of novel therapeutics based on recent advances. Main activity is these TNF- α antagonist bind with TNF- α in circulation of synovia region and neutralizes it that is reducing its inflammatory activity. They also control activity of osteoclasts and also osteoclast genesis thereby inhibiting joint destruction.

Adalimumab

It is a fully human anti-tumor necrosis factor-alpha monoclonal antibody which is produced by phage display technology [16,51].

Infliximab

This drug is 25% mouse derived and 75% human. The binding epitope for TNF is of mouse origin while the immunoglobulin G fragment is human based [16,51].

Golimumab

Approved for moderate to severe arthritis [16,51].

Tocilizumab is the commonly used synthetic TNF blockers [16].

Adverse effects

Injection site reaction, several allergic reactions, increased risk of infections such as TB and fungal, neurological disorders, increase in lymphoma and skin cancer, possible worsening of heart disease [51].

OTHER THERAPIES IN COMORBIDITY

Other therapies include anti-RA drugs, nonsteroidal anti-inflammatory drugs (COX-2 inhibitors), steroidal anti-inflammatory drugs (glucocorticoids), and disease modifying anti-rheumatoid drugs (methotrexate) [18,19].

Along with these medications, lifestyle modifications also add on reduction in risks associated with the comorbid disorders. Smoking cessation, blood pressure and cholesterol control, blood sugar kept within the safe range, weight control, diet, exercise helps to achieve all these goals for proper and maintained health conditions. In the case of inflammation due to RA and in contribution CV risk also persists it can be lowered using proper RA medications which can dramatically decrease CV abnormalities. Through one study it has been found that use of DMARDs in RA patients can reduce CV risks too about 60-70%.

CONCLUSION

CVD as per above discussion is being one of the reasons of death in RA patients and mortality rate is nearly about 40%. Patients with RA from 10 years or more are at a 2-fold increased risk for MI and stroke. Congestive cardiac failure leads to excess mortality cases than myocardial ischemia. Dyslipidemia, insulin resistance, prothrombotic state, hyperhomocysteinemia, and immune mechanisms as T-cell activation subsequently lead to endothelial dysfunction which causes arterial stiffness, as an analog of causing accelerated atherosclerosis in RA patients. Eventually, it's concluded RA is having a major and greater effect on CV in terms of disease rate and also on the basis of its mortality rate which is found to be increasing along with upcoming days. As per a researcher diagnosis of patients with RA should be done with time to address potential heart risks in the future [19]. Concluding as such comorbid diseases are having a great impact on life as well as on treatment itself, so in that case defensive care should be our main treatment spot.

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