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Article

Relationship between corticotherapy and increased cardiac risk in patients with rheumatoid arthritis

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Rheumatoid arthritis is an autoimmune inflammatory joint disease with global prevalence of 0.4% to 1.0%. Extra-articular manifestations increase its morbidity and severity, and cardiovascular diseases present the greatest risk. Therapeutic approaches have been used to treat rheumatoid arthritis, often involving the use of multiple classes of drugs with different mechanisms and forms of action. Corticosteroid therapy is widely used in this therapeutic combination; however, its use has been widely questioned because of its high toxicity and some negative effects, including the possibility of increased cardiovascular risk, depending on the dosage. Some studies have provided important insights into how glucocorticoids have an impact on cardiac complications in patients with rheumatoid arthritis. Most of these studies have concluded that exposure to these drugs at high or cumulative doses is associated with increased risk of death, as well as possibly being associated with the presence of a positive rheumatoid factor.

Keywords: Cardiovascular risk. Glucocorticoids. Rheumatoid arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, inflammatory, autoimmune disease that can affect joints through deformities and serious levels of destruction (Negrei *et al*., 2016; Hunter *et al*., 2017). Table I shows the diagnostic criteria for RA according to Aletaha *et al*., 2010. The prevalence for the global population varies between 0.4% and 1.0%, with a peak incidence between 30 and 50 years of age; the disease particularly affects women (Singh *et al*., 2016; Hunter *et al*., 2017). When RA has extra-articular manifestations, the morbidity and severity of the disease increase. In this case, there may be a decrease in life expectancy of five to ten years in relation to the general population;, this is mainly related to the higher risk of cardiovascular disease (CVD), which is two to five times higher (Ortega Hernandez *et al*., 2009; Birru Talabi *et al*., 2017).

New approaches have been used to treat RA; these involve the use of multiple classes of drugs that have different mechanisms and forms of action. These types of treatment include low doses of intra-articular non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids (CGs), disease-modifying antirheumatic drugs (DMARDs), and immunobiological agents. The decision to use a particular drug is always based on a balance between effectiveness and safety (Singh *et al*., 2016). The therapies which are currently used have undergone significant changes, the most recent of which is related to the prevention of progressive structural

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injuries and the improvement of quality of life for individuals (Kirwan, Gunasekera, 2017).

TABLE I – The 2010 American College of Rheumatology/ European League Against Rheumatism classification criteria for RA

Joint involvement (0-5)	
1 large joint	0
Joint involvement (0-5)	1
1-3 small joints (large not counted)	2
4-10 small joints (large not counted)	3
> 10 joints (at least one small joint)	5
Serology (0-3)	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
Duration of symptoms (0-1)	
< 6 weeks	0
≥ 6 weeks	1
Acute-phase reactants (0-1)	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1

Adapted by Aletaha *et al.*, 2010. Classification criteria for RA (score-based algorithm: add score of categories A-D; a score of ≥6/10 is needed to classify a patient as definitely having RA). ESR- *erythrocyte sedimentation rate. CRP*- C-reactive protein.

Glucocorticoids were first used for patients with RA in 1948 (Black *et al*., 2017) and they are one of the most popular drugs used for this purpose. They have brought relief to patients who have used them as a part of therapy; however, some adverse effects have been reported after long-term use (Ferreira, Ahmed Mohamed, Emery, 2016). In addition to the treatment of RA, GCs are also commonly used as anti-inflammatories and as immunosuppressive therapy in diseases such as asthma and inflammatory bowel disease (Li Wei, 2004).

Although it is considered to be beneficial, corticosteroid therapy has proved to be controversial because of the high levels of toxicity it produces (Singh *et al*., 2016). Most of its negative effects depend on the dose that is applied, which indicates that toxicity can be avoided if the dosage is maintained under certain thresholds (Buttgereit *et al*., 2004).

Rheumatoid arthritis and cardiovascular risk

The increased risk of CVD in patients with RA is primarily due to the fact that this disease is an independent risk factor (Li Wei, 2004; Li *et al*., 2006) and may be influenced by other traditional factors and the systemic inflammatory process (Hunter *et al*., 2017). The prevalence of CVD in these individuals is double that of control groups when the same age groups are compared. The search for an explanation why this occurs earlier and more intensely in patients with RA has been the focus of several studies (Hunter *et al*., 2017; Kirwan, Gunasekera, 2017).

It is believed that the main reason why RA tends to be a risk factor in relation to cardiovascular complications is the acute and chronic inflammatory process present in its pathophysiology, which favors, among others, the formation of atheromatous plaque (Braun *et al*., 2017; Hunter *et al*., 2017). Atherosclerosis is a multifactorial, slow and progressive disease with a silent progression that takes place over decades before reaching clinical significance. This is the result of a series of highly specific cellular and molecular responses, understood as a chronic inflammatory response, which occurs systemically in the arterial walls, in which the deposit of lipids, inflammatory cells and fibrous elements into arterial walls usually cause obstructions (Arias de la Rosa *et al*., 2018). This process can originate from the interaction of several metabolic and nutritional factors, mechanical forces and abnormal proteins etc. Coronary arteries are the main target, and coronary artery disease (CAD) can lead to acute myocardial infarction (AMI), which is the main cause of death in Western civilization (El Bakry *et al*., 2017).

RA can occur concomitantly with one or more of the classic risk factors already described, such as

smoking, hypercholesterolemia, aging, type 2 diabetes mellitus (DM) and systemic arterial hypertension (SAH) (Braun *et al*., 2017; Unnikrishnan *et al*., 2017). There has been some doubt regarding the occurrence of RA as an isolated risk factor, or as being associated with other factors in relation to CVD (Chiu *et al*., 2015). In this process there is an inflammatory component related to the underlying disease, which is characterized by infiltration of the inner layer of the arteries by activated monocytes, T cells, and the increased production of proinflammatory cytokines, as well as the presence of autoantibodies (Arias de la Rosa *et al*., 2018).

The inflammatory component of atherosclerosis presents some similarities with the inflammatory process of RA such as high levels of C-reactive protein (CRP), cytokines and fibrinogen (Braun *et al*., 2017). It is possible that the association of factors present in the systemic inflammation of RA accelerates atherosclerosis. It is therefore important to evaluate the levels of some of these markers, such as hs-CRP and myeloperoxidase, in patients with RA because higher levels may represent important information in relation to increased risks of CV events (Amaya-Amaya *et al*., 2013).

It is also known that systemic inflammatory conditions such as RA can lead to endothelial dysfunction, mainly due to increased levels of circulating cytokines. Some studies have shown the indirect presence of endothelial dysfunction. This is evidenced, for example, by lower endothelium-dependent vasodilatation in patients with RA compared to healthy individuals. The endothelium plays an important role in controlling vascular tone, platelet activity and thrombogenesis. Consequently, endothelial function is very important in relation to the formation of atherosclerotic plaque. Endothelial dysfunction is one of the first steps in the development of atherosclerotic plaque (Haque, Mirjafari, Bruce, 2008).

Inflammatory and immunological damage to the vascular wall may induce endothelial dysfunction and increased arterial stiffness, which may subsequently increase body pressure (Bartoloni, Alunno, Gerli, 2018). Chronic inflammatory disorders, in particular RA and systemic autoimmune diseases, have been associated with increased arterial stiffness, which is widely recognized as a reliable marker of CVR in the general population and in patients with chronic inflammatory and autoimmune diseases. In addition, the clinical relevance of arterial stiffness is its ability to predict cardiovascular events and morbidity, together with other cardiovascular risk factors, including SAH (Amaya-Amaya *et al*., 2013; Bartoloni *et al*., 2018).

Glucocorticoids in the treatment of rheumatoid arthritis

Glucocorticoid (GC) action starts by its diffusion from blood plasma through the lipid cell membrane (Arias de la Rosa *et al*., 2018). The symptomatic action of glucocorticoids is usually associated with drugs used for disease remission; quick (Negrei *et al*., 2016) the symptomatic action of glucocorticoids is rapid and is related to decreasing the activation, proliferation, differentiation and survival of many inflammatory cells, such as T-helper 1 lymphocytes (Th1) (Li Wei, 2004). This reduces proinflammatory cytokine levels, such as interleukin (IL) 1-b, IL-2, IL-3, IL-6, tumor necrosis factor - alpha (TNF- alpha), interferon gama (IF-gama) and IL-17, and promotes anti-inflammatory effects (Verhoeven *et al*., 2016).

GCs interact with intracellular receptors that control the gene transcription of genes encoding cox-2, NF-kB, AP-1, IL-2, and inducible NO synthase. They also inhibit osteocalcin in osteoblasts and promote transcription modification of genes for the synthesis of collagenase and the increased synthesis of lipocortin, which has a negative feedback effect on the hypothalamus and anterior pituitary. As a consequence of this action there is a decrease in the loss of bone mass and less joint deformation (Buttgereit *et al*., 2004).

Despite the fact that high doses of glucocorticoids are related to a greater effect of the drug, low doses for rheumatoid arthritis patients are effective (Ferreira, Ahmed Mohamed, Emery, 2016; El Bakry *et al*., 2017). Therefore, daily doses of prednisone (or other equivalent drugs) that are lower than or equal to 7.5 mg are recommended during the first six months of treatment (Negrei *et al*., 2016).

Therapy using glucocorticoids for RA patients must be carefully prescribed. Its administration is only indicated for short periods (Kirwan JR, Boers, Shea, 2009; Kirwan, Gunasekera, 2017). Some retrospective studies have found decreasing rates for the progression of erosion linked to rheumatoid arthritis by adding glucocorticoids to the gold standard therapy (Kirwan Jr, Boers, Shea, 2009; Udachkina *et al*., 2017). Buttgereit *et al*. (2004) suggested that adding 7.5 mg of prednisone to DMARDs may result in the faster resolution of symptoms compared to the isolated use of DMARDs, as

well as leading to the stagnation of radiographic erosion (Kirwan Jr, Boers, Shea, 2009).

Glucocorticoid therapy and cardiovascular risk in patients with rheumatoid arthritis.

The increased secretion of cortisol, even at physiological levels, implies higher cardiovascular risk, and several studies have proposed that subclinical Cushing's syndrome could be a significant risk factor (Radhakutty *et al*., 2016). The effects of glucocorticoids on cardiovascular risk are controversial. Although glucocorticoids can enhance cardiovascular risk they can also reduce the very same associated risk factors by decreasing vascular or systemic inflammation (Negrei *et al*., 2016). In specific situations, such as giant cell arteritis, endothelial function is impaired in patients with active disease; nevertheless, glucocorticoids improved endothelial function after the suppression of an inflammatory condition (Davis *et al*., 2007).

The side effects of glucocorticoids in terms of blood pressure, insulin resistance, lipid profile, fat distribution and coagulation proteins increases the risk of cardiovascular risk in patients with RA (Hunter *et al*., 2017). Although literature reports have associated these effects with high doses of glucocorticoids there is no current evidence linking these effects with low doses of glucocorticoids (Davis *et al*., 2007; Hunter *et al*., 2017).

Some mechanisms in relation to the connection between the use of GCs and some of the risk factors for cardiovascular disease have already been identified. Hypertension caused by the use of exogenous glucocorticoids occurs in approximately 20% of patients.

GCs are able to enhance transepithelial sodium transport in the presence of enzymatic inhibition in the kidneys (Aviña-Zubieta *et al*., 2013). Proximal tubular reabsorption of sodium may be indirectly increased following chronic exposure to GCs. In vascular tissue, exogenous glucocorticoids magnify the response to vasoconstricting agents. In this tissue the indirect effects are an upregulationof the expression of the receptors to many of the vasoconstrictors, and a downregulation of the effects of the potential vasodilator agents. Thus, glucocorticoids have the capacity to alter both circulating volume and vascular resistance. More recently, the damaging effects of GCs on the endothelium have been demonstrated, increasing reactive oxygen species such as superoxide (Aviña-Zubieta *et al*., 2013; del Rincón *et al*., 2014).

Prolonged therapy with high doses of corticosteroids leads to peripheral resistance to insulin and hyperinsulinemia. GCs interfere in the metabolism of carbohydrates, promoting higher levels of glycemia by stimulating gluconeogenesis, and increasing the intestinal absorption of glucose (Hunter *et al*., 2017).

The modification of the lipid profile by the use of GCs is due to an increase in the synthesis of VLDL and a reduction in the release of the adrenocorticotropic hormone (ACTH), which causes an increase in total cholesterol and LDL-cholesterol, and a decrease in HDL-cholesterol. ACTH may act by increasing the activity of the LDL cholesterol receptor (Davis *et al*., 2007).

Redistribution of body fat occurs, as in Cushing's syndrome, with an increase in adipose tissue in the dorsum-cervical region, the face and the supraclavicular area, together with a loss of adipose tissue at the extremities (Black *et al*., 2017). One hypothesis for this phenomenon is that the peripheral adipocytes of the trunk differ in their sensitivities relative to insulin and the lipolytic effects facilitated by GCs. Adipocytes from the trunk region would respond predominantly to higher insulin levels due to GC-induced hyperglycemia, whereas peripheral adipocytes would be less sensitive to insulin and respond more to the effects of other lipolytic hormones facilitated by corticosteroids. In addition, there is increased appetite and fluid retention, which causes edema and weight gain (Mazzantini *et al*., 2010).

Several mechanisms linking RA and the use of GCs to factors predisposing the increase of CVR have been identified. The inflammatory process involving RA, as well as corticotherapy, may trigger the development of diabetes, hypertension, endothelial dysphonia and atherogenic dyslipidemia (Davis *et al*., 2007; Mazzantini *et al*., 2010). The manner in which each of these factors is triggered and how they act in relation to CVR, as well as points of action common to both, are illustrated in Figure 1.

An article published in 2004 described a study performed in Tayside (UK) which approached 400,000 patients exposed to glucocorticoid therapy. This study included patients who received one or more doses of the medication from 1993 to 1996. Daily medication doses were categorized as a high (over 7.5 mg), intermediary (less than 7.5 mg) and low (inhaled or topic corresponding to physiological dose). This study concluded that the relative cardiovascular risk for the high dosage group was 2.56, suggesting that the proposed dose, time of treatment and cumulative exposure could be important factors regarding this effect (Li Wei, 2004).

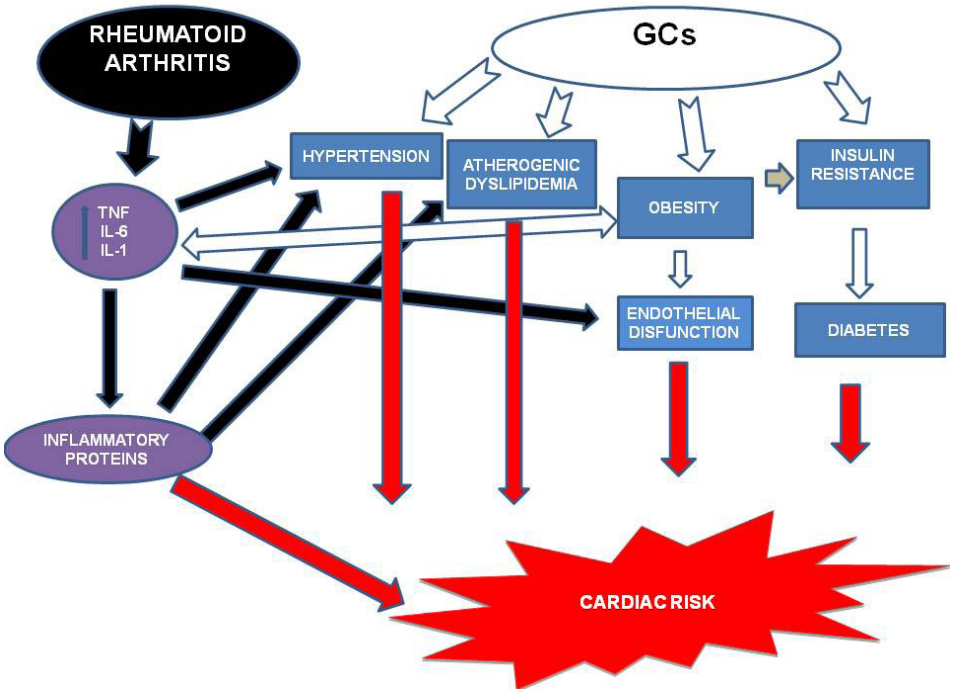

FIGURE 1 – Graphical abstract of RA and GCs mechanisms for predisposing the increase of CVR.
Note: RA is a factor that induces cytokines and proinflammatory proteins; the effects of GCs on blood pressure, insulin resistance, lipid profile, body weight and fat distribution can significantly increase the risk of CVD in patients with RA. Figure 1 illustrates the different ways in which RA and the use of GCs can act on the predisposing factors to CVR (red arrows). The initial point of the RA process is the activation of the production of TNF, IL6 and IL1. The relationship between CGs and the factors predisposing to RCV are directly or indirectly indicated. In some situations there is an interaction between factors which are triggered by the disease and the treatment.

In another study performed in Rochester (Minnesota, USA), 603 adult patients with rheumatoid arthritis were monitored from 1955 to 1995 by their medical records. Exposure to glucocorticoids was determined in three different ways: cumulative exposure; recent exposure (less than three months) versus past exposure (over three months); and average daily dose (less than 7.5 mg per day or over 7.5 mg per day). The authors defined cardiovascular events (such as acute myocardial infarction, cardiac insufficiency and death by cardiovascular causes) according to some validated criteria. Patients exposed to glucocorticoids, but who were negative for rheumatoid factor, presented no greater risk of cardiovascular events regardless of dosage or time of use compared to the reference negative rheumatoid factor group. On the other hand, patients who tested positive for rheumatoid factor presented an enhanced risk of cardiovascular events, mainly those with greater cumulative exposure, higher average daily dose and recent usage of glucocorticoids. Positive rheumatoid factor (RF) patients with high cumulative exposure to glucocorticoids had a 300% greater risk of cardiovascular events. The authors concluded that patients with positive RF presented a higher risk of cardiovascular events after using glucocorticoids. This suggests that exposure to glucocorticoids for patients with positive RF modulates cardiovascular events in AR patients. The underlying mechanisms for this are still unknown (Davis *et al.*, 2007).

A 2010 retrospective review of medical records of 365 patients with RA showed that 81.3% were using glucocorticoids. Of the glucocorticoid users, 13.1% had a history of acute myocardial infarction, meanwhile only 1.5% of those patients who had not used glucocorticoids had a history of acute myocardial infarction. The authors verified that RA patients treated with low doses of glucocorticoids exhibited a higher prevalence of myocardial infarction than those who were never treated. The high prevalence of cardiovascular events among RA patients suggests the need to adopt measures to identify and closely monitor risk factors, as well as preventive actions, for those

undergoing long-term treatment with glucocorticoids (Mazzantini *et al*., 2010).

In 2013, a cohort study of 8,384 incident cases of RA and primary exposure to glucocorticoids between 1997 and 2006 was published. The use of glucocorticoids was based on the following: four time-dependent variables (current use, current dose, cumulative dose and cumulative duration); demographic adjustments comorbidities; cardiovascular drugs use; tendency to develop the disease; and RA characteristics. This study identified 298 incidents of myocardial infarction. Moreover, the multivariate models demonstrated the association between glucocorticoid usage and a 68% higher risk of myocardial infarction. Likewise, distinct multivariate models identified that daily dose, cumulated time of use, and cumulative dose were also associated with a higher risk of myocardial infarction. In the same multivariate model, current use and cumulative use were independently associated with increased risk of myocardial infarction. The aforementioned study concluded that glucocorticoid useis linked with a higher risk of myocardial infarction in patients with RA. This suggests a dual risk effect of cardiovascular disease; an immediate effect mediated by the current dose, and the effect of long-term usage (Aviña-Zubieta *et al*., 2013).

Del Rincón *et al.* (2014) assessed 779 patients with RA out of a total of 7,203 people with the disease who were evaluated over a period of one year. A total of 237 of the patients died during that period (mortality rate of 3.2%). A total of 393 patients (50%) were receiving glucocorticoids early in the study. The authors suggested that daily doses of 7.5 mg or lower of prednisone in RA patients can be regarded as safe in terms of the mortality risk linked to cardiovascular diseases; nonetheless, higher doses are related to progressively increased mortality rates. In the same way, cumulative doses of 40 mg of prednisone were associated with a similar mortality risk compared to unexposed patients; however, higher doses were found to increase the mortality rate. In contrast to patients not using corticoids, the minimum threshold daily dose of prednisone related to mortality increased by cardiovascular diseases was 8 to 15 mg (del Rincón *et al*., 2014).

DISCUSSION

RA is an independent risk factor in relation to cardiovascular diseases as a result of the thickness of the intima and media layers of the common and femoral carotid arteries. Such risk was correlated with the severity and chronicity of this rheumatologic disease (El Bakry *et al.,* 2017). In addition, dyslipoproteinemia and endothelial inflammation, (factors associated with atherosclerosis) are more common in patients with RA (Verma, Syngle, Krishan, 2017). Further studies are required in order to elucidate the contribution of the RA autoimmune process to atherosclerosis and possible exogenous factors like the treatment used in the atherosclerosis process.

Glucocorticoids may have a direct impact on endothelial cells through glucocorticoid α receptors (Verhoeven *et al*., 2016). Animal studies have suggested the harmful effect of glucocorticoids and endothelial dysfunction in non-inflammatory states, as well as a protective effect on endothelial cells during inflammation (Lauper, Gabay, 2017). The higher the dosage used in treatment, the greater the effect (Ferreira, Ahmed Mohamed, Emery, 2016). Furthermore, the long-term use of glucocorticoids results in secondary harmful effects such as hyperglycemia, hepatosteatosis and insulin resistance (Radhakutty *et al*., 2016; Patel *et al*., 2017).

The use of glucocorticoids as a factor that potentially increases cardiovascular diseases in RA was analyzed by Ruyssen-Witrand *et al*., 2011, who identified 37 studies assessing cardiovascular risk factors in patients with RA who were also treated with low doses of glucocorticoids (less than 10 mg per day of prednisone). The analysis revealed heterogeneous relative results. The authors observed some evidence of a protective effect in relation to lipid profiles, but also a rise in insulin resistance and serum glucose. Four of the six studies highlighted a link between major cardiovascular events in patients with RA and positive risk factors. On balance, the use of glucocorticoids seems to increase cardiovascular risk, although the evidence is variable and incomplete (Gullick, Scott, 2011; Black *et al*., 2017).

Long-term use of prednisone for patients with RA can be associated with many factors that increase cardiovascular disease risk such as high blood pressure (HBP) (Black *et al*., 2017). Basal blood pressure and age are more important factors in relation to developing significant HBP than low doses of glucocorticoids (Naranjo *et al*., 2008). There is an important connection between the speed of the atherosclerotic process in patients using glucocorticoids. Several studies have suggested that patients with RA who do not use medication have an increased risk of developing advanced atherosclerosis compared with people without

RA. This indicates that atherosclerosis may be related to disease and medicines (Naranjo *et al,* 2008; Ferreira, Ahmed Mohamed, Emery, 2016). Lipid profile is also affected by the use of glucocorticoids, resulting in increases in the levels of total plasmatic cholesterol, LDL- cholesterol (low-density lipoprotein), HDL-cholesterol (high-density lipoprotein) and triglyceride, in a dose-dependent effect (García-Gómez *et al*., 2008). In low doses, the anti-inflammatory effect of glucocorticoids results in a subsequently favorable lipid profile. According to some analyses, the cardiovascular risk factor in patients with RA is related to the dose of glucocorticoids, disease activity, comorbidities and co-treatments (Park *et al*., 2002; Sokka *et al*., 2009).

To assess the effects of glucocorticoids on CVD in patients with RA, Dessein *et al*., (2004) tested the role of glucocorticoids in CVR factors. The use of intramuscular, intra-articular and intravenous doses was associated with insulin resistance (IR). The use of glucocorticoids was not associated with obesity, dyslipidemia or hypertension. In 2006, the same scientific group found that there was an association between the sonographic factors of metabolic syndrome and the presence of subclinical atherosclerosis through the sonographic determination of the thickness of the intima-media of the common carotidartery. Hypertension, IR and hypertriglyceridemia were found to be independent risk factors for subclinical atherosclerosis (Dessein, Tobias, Veller, 2006).

Patients with RA undergoing chronic therapy with low doses of glucocorticoids demonstrated a higher prevalence of comorbidities, such as cardiovascular diseases, compared with those who never used glucocorticoids (Park *et al*., 2002; Naranjo *et al*., 2008). This may be the consequence of high disease activity, as well as the use of glucocorticoids. The data available do not make it possible to confirm or exclude the role of glucocorticoids. Nevertheless, some data indicate a negative effect of the long-term use of glucocorticoids in patients with RA (García-Gómez, *et al*., 2008).

The use of glucocorticoids can provide advantages for patients with RA; however, their use may result in significant toxicity, counterbalancing the positive effects derived from usage (Del Rincón *et al*., 2014).

CONCLUSION

Several studies have provided important insights into the impact of glucocorticoids on cardiac complications in patients with RA. The majority of these studies conclude that the use of glucocorticoids in high or cumulative doses is associated with a higher risk of death in those with RA and may also be associated with positive risk factors. This knowledge is important so that physicians can avoid exceeding certain dosages in order to avoid exposing their patients to a higher risk of death. Further studies should be conducted to determine beneficial thresholds for doses of glucocorticoids for patients.

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