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CARDIOVASCULAR RISKS ASSOCIATED WITH LONG-TERM USE OF CORTICOSTEROIDS AND IMMUNOSUPPRESSANTS: A COMPREHENSIVE REVIEW

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Abstract: **INTRODUCTION** The introduction highlights the widespread use of corticosteroids and immunosuppressants in managing various chronic conditions, noting their efficacy in controlling disease activity but also their significant long-term side effects. It focuses on the cardiovascular risks associated with these medications, including hypertension, dyslipidemia, and insulin resistance. The introduction sets the stage for a comprehensive review of the pathophysiological mechanisms and strategies for managing these risks. **OBJETIVE** To assess the increased cardiovascular risk in patients using corticosteroids and immunosuppressants for long periods. **METHODS** This is a narrative review which included studies in the MEDLINE – PubMed (National Library of Medicine, National Institutes of Health), COCHRANE, EMBASE and Google Scholar databases, using as descriptors: "Cardiovascular risk" AND "Long-term corticosteroid use" AND "Immunosuppressant therapy" AND "Hypertension and dyslipidemia" OR "Chronic inflammation and metabolic syndrome" in the last years. **RESULTS AND DISCUSSION** The results and discussion sections elaborate on the increased incidence of cardiovascular events in patients on long-term corticosteroid therapy, supported by multiple studies demonstrating a higher risk of myocardial infarction, stroke, and heart failure. It delves into the biological mechanisms, such as sodium retention, oxidative stress, and endothelial dysfunction, that contribute to these risks. The discussion also compares the cardiovascular impacts of different immunosuppressants and underscores the importance of personalized treatment plans and regular monitoring to mitigate these risks. **CONCLUSION** The conclusion reiterates the critical need for careful management of cardiovascular risk in patients using long-term corticosteroids and immunosuppressants. It emphasizes the role of personalized medicine, lifestyle modifications, and pharmacological interventions in optimizing therapeutic outcomes. The conclusion calls for ongoing research to develop targeted interventions and explore alternative therapies with lower cardiovascular toxicity to ensure the safe and effective use of these essential medications.

Keywords: Cardiovascular disease; Corticosteroids; Immunosuppressants; Hypertension; Insulin resistance.

INTRODUCTION

The utilization of corticosteroids and immunosuppressants is a cornerstone in the management of various inflammatory, autoimmune, and transplant-related conditions[1]. These medications, while efficacious in controlling disease activity and preventing organ rejection, have a broad spectrum of side effects, particularly when used long-term[1]. Corticosteroids exert their effects by mimicking the action of hormones produced by the adrenal glands, primarily through the suppression of inflammation and modulation of the immune response[1]. Immunosuppressants, on the other hand, work by inhibiting various components of the immune system, thereby reducing the risk of organ rejection and controlling autoimmune diseases[1].

Despite their therapeutic benefits, the chronic use of these agents is associated with a myriad of adverse effects[2]. Corticosteroids, for instance, are notorious for causing metabolic disturbances, osteoporosis, muscle wasting, and an increased risk of infections[2]. Immunosuppressants also carry significant risks, including nephrotoxicity, hepatotoxicity, and an increased susceptibility to malignancies[2]. The epidemiology of long-term corticosteroid and immunosuppressant use highlights a substantial patient population

exposed to these risks, particularly those with chronic conditions such as rheumatoid arthritis, systemic lupus erythematosus, and solid organ transplant recipients[2].

Cardiovascular disease (CVD) is one of the most significant long-term risks associated with chronic corticosteroid and immunosuppressant therapy[3]. Numerous studies have established a clear link between prolonged corticosteroid use and an increased incidence of hypertension, dyslipidemia, and accelerated atherosclerosis, all of which contribute to heightened cardiovascular risk[3]. The pathophysiological mechanisms underlying these associations are multifaceted[3]. Corticosteroids can induce hypertension through fluid retention and increased vascular resistance, while also promoting insulin resistance and central obesity, both of which are key components of metabolic syndrome[3]. Immunosuppressants, depending on the agent, can also contribute to cardiovascular risk through mechanisms such as endothelial dysfunction, lipid abnormalities, and direct cardiotoxic effects[3].

Comparative studies on different immunosuppressants reveal varying degrees of cardiovascular risk[4]. For example, calcineurin inhibitors like cyclosporine and tacrolimus are associated with significant hypertension and dyslipidemia, whereas agents such as mycophenolate mofetil may have a more favorable cardiovascular profile[4]. The impact of these medications on lipid metabolism is particularly concerning, with corticosteroids often causing hyperlipidemia characterized by elevated levels of low-density lipoprotein (LDL) and triglycerides[4]. This dyslipidemia, coupled with hypertension, significantly accelerates the process of atherosclerosis[4].

Blood pressure regulation is another critical area affected by long-term corticosteroid and immunosuppressant use[5]. Corticosteroids, through their mineralocorticoid activity, can cause significant sodium retention and potassium excretion, leading to hypertension[5]. Immunosuppressants such as cyclosporine exacerbate this effect through mechanisms involving the renin-angiotensin-aldosterone system[5]. The relationship between corticosteroid use and insulin resistance is well-documented, with prolonged exposure leading to decreased insulin sensitivity and an increased risk of developing type 2 diabetes[5]. This insulin resistance is a key driver of cardiovascular morbidity, further compounded by the pro-inflammatory state induced by chronic corticosteroid therapy[5].

Endothelial dysfunction is another pathophysiological consequence of long-term corticosteroid and immunosuppressant use[6]. Corticosteroids impair endothelial function through oxidative stress and reduced nitric oxide bioavailability, while certain immunosuppressants exacerbate this effect by directly damaging endothelial cells[6]. The increased risk of atherosclerosis in patients on long-term corticosteroid therapy is well-established, with studies showing accelerated plaque formation and increased arterial stiffness[6].

Patients with pre-existing cardiovascular comorbidities are particularly vulnerable to the adverse effects of long-term corticosteroid and immunosuppressant use[7]. The combination of these medications with underlying conditions such as hypertension, diabetes, and dyslipidemia significantly elevates the risk of cardiovascular events[7]. Case studies of patients using these medications highlight the severe cardiovascular outcomes, including myocardial infarction, stroke, and heart failure[7]. Protocols for cardiovascular monitoring in patients on long-term corticosteroid and immunosuppressant therapy are essential for mitigating these risks[8]. Regular monitoring of blood pressure, lipid profiles, and glucose levels, along with appropriate

lifestyle modifications and pharmacological interventions, can help manage and reduce cardiovascular risk[8]. Strategies such as the use of antihypertensive agents, statins, and antidiabetic medications are commonly employed to counteract the adverse effects of these drugs[8].

Current guidelines emphasize the importance of minimizing the dose and duration of corticosteroid and immunosuppressant therapy to reduce cardiovascular risk[9]. The need for further studies to better understand the long-term cardiovascular risks and develop more effective mitigation strategies is evident[9]. This narrative review aims to comprehensively assess the increased cardiovascular risk in patients using corticosteroids and immunosuppressants for long periods, evaluating the incidence of cardiovascular events, underlying biological mechanisms, and effective strategies for risk management[9].

OBJETIVES

To assess the increased cardiovascular risk in patients using corticosteroids and immunosuppressants for long periods.

SECUNDARY OBJETIVES

1. To compare the cardiovascular risk among different types of immunosuppressants.
2. To analyze the impact of long-term corticosteroid use on lipid profiles and glucose metabolism.
3. To discuss strategies for mitigating cardiovascular risks associated with corticosteroid and immunosuppressant use.
4. To review current guidelines and propose recommendations for monitoring and managing cardiovascular risk in these patients.
5. To evaluate the incidence of cardiovascular events, such as myocardial infarction, stroke, and heart failure, in these patients.
6. To explore the underlying biological mechanisms leading to increased cardiovascular risk with long-term corticosteroid and immunosuppressant use.

METHODS

This is a narrative review, in which the main aspects of increased cardiovascular risk in patients using corticosteroids and immunosuppressants for long periods in recent years were analyzed. The beginning of the study was carried out with theoretical training using the following databases: PubMed, sciELO and Medline, using as descriptors: "Cardiovascular risk" AND "Long-term corticosteroid use" AND "Immunosuppressant therapy" AND "Hypertension and dyslipidemia" OR "Chronic inflammation and metabolic syndrome" in the last years. As it is a narrative review, this study does not have any risks.

Databases: This review included studies in the MEDLINE – PubMed (National Library of Medicine, National Institutes of Health), COCHRANE, EMBASE and Google Scholar databases.

The inclusion criteria applied in the analytical review were human intervention studies, experimental studies, cohort studies, case-control studies, cross-sectional studies and literature reviews, editorials, case reports, and poster presentations. Also, only studies writing in English and Portuguese were included.

RESULTS AND DISCUSSION

The incidence of cardiovascular events in patients using long-term corticosteroids is significantly higher compared to the general population[10]. Studies have demonstrated that chronic corticosteroid use is associated with a two- to threefold increase in the risk

of myocardial infarction, stroke, and heart failure[10]. This elevated risk is primarily driven by the adverse metabolic effects of corticosteroids, including hypertension, dyslipidemia, and insulin resistance[10]. The dose-response relationship is evident, with higher doses and longer durations of corticosteroid therapy correlating with greater cardiovascular risk[10]. Biological mechanisms leading to increased cardiovascular risk with corticosteroids involve multiple pathways[11]. Corticosteroids promote hypertension through sodium retention and increased vascular resistance, while also inducing dyslipidemia by elevating LDL and triglyceride levels[11]. These metabolic disturbances contribute to the development of atherosclerosis, with studies showing accelerated plaque formation and increased arterial stiffness in patients on long-term corticosteroid therapy[11]. Additionally, corticosteroids impair glucose metabolism, leading to insulin resistance and an increased risk of type 2 diabetes, further exacerbating cardiovascular risk[11].

Comparative analysis of different immunosuppressants reveals varying degrees of cardiovascular risk[12]. Calcineurin inhibitors such as cyclosporine and tacrolimus are associated with significant hypertension and dyslipidemia, whereas mycophenolate mofetil and azathioprine have a more favorable cardiovascular profile[12]. The impact of these medications on endothelial function is also notable, with calcineurin inhibitors causing endothelial dysfunction and promoting atherosclerosis[12]. The choice of immunosuppressant should therefore consider the cardiovascular risk profile of the patient, with a preference for agents with lower cardiovascular toxicity[12]. The relationship between corticosteroids and hypertension is well-documented, with studies showing that long-term corticosteroid use leads to significant increases in blood pressure[13]. This hypertensive effect is mediated through mineralocorticoid activity, causing sodium retention and potassium excretion[13]. Immunosuppressants such as cyclosporine exacerbate this effect by activating the renin-angiotensin-aldosterone system, further increasing blood pressure[13]. The management of hypertension in patients on long-term corticosteroid therapy involves the use of antihypertensive agents, lifestyle modifications, and regular monitoring of blood pressure[13].

Insulin resistance is another major consequence of long-term corticosteroid use, contributing to the increased cardiovascular risk[14]. Corticosteroids decrease insulin sensitivity by interfering with insulin signaling pathways and promoting the accumulation of visceral fat[14]. This insulin resistance leads to hyperglycemia and an increased risk of type 2 diabetes, which in turn exacerbates cardiovascular morbidity[14]. The management of insulin resistance in corticosteroid users involves dietary modifications, physical activity, and the use of antidiabetic medications[14]. Endothelial dysfunction is a key factor in the development of atherosclerosis in patients on long-term corticosteroid and immunosuppressant therapy[15]. Corticosteroids impair endothelial function by increasing oxidative stress and reducing nitric oxide bioavailability[15]. Immunosuppressants such as cyclosporine further contribute to endothelial dysfunction by directly damaging endothelial cells[15]. The combination of these effects leads to accelerated plaque formation and increased arterial stiffness, significantly elevating the risk of cardiovascular events[15].

Patients with pre-existing cardiovascular comorbidities are particularly vulnerable to the adverse effects of long-term corticosteroid and immunosuppressant use[16]. The combination of these medications with conditions such as hypertension, diabetes,

and dyslipidemia significantly increases the risk of cardiovascular events[16]. Case studies of patients on long-term corticosteroid and immunosuppressant therapy highlight the severe cardiovascular outcomes, including myocardial infarction, stroke, and heart failure[16]. These case studies underscore the importance of vigilant cardiovascular monitoring and management in this patient population[16]. Protocols for cardiovascular monitoring in patients on long-term corticosteroid and immunosuppressant therapy are essential for mitigating cardiovascular risk[17]. Regular monitoring of blood pressure, lipid profiles, and glucose levels, along with appropriate lifestyle modifications and pharmacological interventions, can help manage and reduce cardiovascular risk[17]. Strategies such as the use of antihypertensive agents, statins, and antidiabetic medications are commonly employed to counteract the adverse effects of these drugs[17]. Additionally, the use of alternative therapies with a lower cardiovascular risk profile should be considered whenever possible[17].

The need for continuous cardiovascular parameter monitoring in corticosteroid users is evident from the high incidence of cardiovascular events in this population[18]. Regular monitoring allows for the early detection and management of hypertension, dyslipidemia, and insulin resistance, thereby reducing the risk of cardiovascular events[18]. The implementation of structured monitoring protocols, including regular follow-up visits and laboratory tests, is crucial for optimizing cardiovascular outcomes in patients on long-term corticosteroid therapy[18]. This approach ensures timely interventions and adjustments in therapy to manage emerging cardiovascular risk factors effectively[18]. The relationship between corticosteroids and heart failure is complex, with studies showing that chronic corticosteroid use is associated with an increased risk of heart failure[19]. This risk is mediated through multiple pathways, including hypertension, dyslipidemia, and insulin resistance[19]. The management of heart failure in corticosteroid users involves the use of standard heart failure therapies, along with careful management of corticosteroid therapy to minimize cardiovascular risk[19]. The role of genetics in increasing cardiovascular risk in corticosteroid users is an emerging area of research, with studies suggesting that genetic factors may influence the susceptibility to corticosteroid-induced cardiovascular effects[19].

The comparison of cardiovascular effects between corticosteroids and other immunosuppressive treatments is crucial for informed therapeutic decisions[20]. Studies indicate that while corticosteroids significantly elevate cardiovascular risk, other immunosuppressants like azathioprine and mycophenolate mofetil have relatively lower cardiovascular toxicity[20]. This differential risk underscores the need for personalized treatment plans that weigh the benefits of disease control against potential cardiovascular harms[20]. Lifestyle factors, such as diet and physical activity, also play a critical role in modulating cardiovascular risk in patients on long-term corticosteroid therapy[20]. Interventions aimed at promoting a heart-healthy lifestyle can significantly mitigate the adverse cardiovascular effects of these medications[20]. The challenges of clinical management of patients on long-term corticosteroids are multifaceted[21]. Clinicians must balance the therapeutic benefits of corticosteroids against their potential for causing significant harm[21]. This balancing act is complicated by the need to manage comorbid conditions that may also contribute to cardiovascular risk[21]. Regular follow-up and patient education are essential components of effective management, ensuring that

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patients adhere to monitoring protocols and lifestyle modifications designed to reduce cardiovascular risk[21].

Current guideline recommendations emphasize the importance of minimizing corticosteroid exposure and using the lowest effective dose for the shortest duration possible[22]. These guidelines advocate for the use of steroid-sparing agents and alternative therapies whenever feasible[22]. Additionally, they recommend routine cardiovascular risk assessment and the implementation of preventive strategies, such as the use of statins and antihypertensive medications, to mitigate the cardiovascular risks associated with long-term corticosteroid use[22]. The relationship between corticosteroids and metabolic syndrome is well-documented[23]. Corticosteroids promote the development of central obesity, dyslipidemia, hypertension, and insulin resistance, all of which are components of metabolic syndrome[23]. This syndrome significantly increases the risk of cardiovascular events, highlighting the need for comprehensive management strategies that address all components of metabolic syndrome in patients on long-term corticosteroid therapy[23].

The impact of corticosteroids on the renin-angiotensin-aldosterone system (RAAS) is another critical factor in their cardiovascular risk profile[24]. Corticosteroids can activate the RAAS, leading to sodium retention, potassium excretion, and increased blood pressure[24]. This activation contributes to the hypertensive effects of corticosteroids and exacerbates cardiovascular risk[24]. Understanding the interactions between corticosteroids and the RAAS is essential for developing effective strategies to manage hypertension in corticosteroid users[24]. Short- and long-term implications of corticosteroid use on cardiovascular health are profound[25]. In the short term, corticosteroids can cause acute increases in blood pressure and glucose levels, while long-term use leads to chronic hypertension, dyslipidemia, and an increased risk of cardiovascular events[25]. Managing these implications requires a comprehensive approach that includes regular monitoring, lifestyle modifications, and the use of adjunctive therapies to mitigate cardiovascular risk[25].

The interaction between corticosteroids and other medications can also influence cardiovascular risk[26]. For instance, nonsteroidal anti-inflammatory drugs (NSAIDs) and certain antihypertensive agents can interact with corticosteroids, exacerbating their adverse cardiovascular effects[26]. Understanding these interactions is crucial for optimizing pharmacotherapy and minimizing the risk of adverse cardiovascular outcomes in patients on long-term corticosteroid therapy[26]. The relationship between corticosteroids and cardiovascular mortality is a significant concern[27]. Studies have shown that long-term corticosteroid use is associated with increased all-cause and cardiovascular mortality[27]. This increased mortality risk highlights the need for careful patient selection, dose titration, and regular monitoring to minimize the potential for harm[27].

Personalized treatment approaches are essential for managing patients on long-term corticosteroid therapy[28]. Factors such as genetic predisposition, comorbid conditions, and individual patient responses to corticosteroids must be considered when developing treatment plans[28]. Personalized approaches can help optimize therapeutic outcomes while minimizing the risk of adverse cardiovascular effects[28]. The effects of corticosteroids on heart rate variability (HRV) are also noteworthy[29]. HRV is a measure of autonomic nervous system function and is an important predictor of cardiovascular health[29]. Long-term corticosteroid use has

been associated with reduced HRV, indicating impaired autonomic function and increased cardiovascular risk[29]. Monitoring HRV in corticosteroid users can provide valuable insights into their cardiovascular health and help guide management strategies[29].

Chronic systemic inflammation is another factor that contributes to the cardiovascular risk associated with long-term corticosteroid use[30]. Corticosteroids, while reducing inflammation in the short term, can promote a chronic pro-inflammatory state when used long-term[30]. This chronic inflammation contributes to the development of atherosclerosis and other cardiovascular diseases[30]. Managing chronic inflammation through lifestyle modifications, anti-inflammatory therapies, and regular monitoring is essential for reducing cardiovascular risk in corticosteroid users[30]. Obesity is a significant contributor to cardiovascular risk in patients on long-term corticosteroid therapy[31]. Corticosteroids promote the accumulation of visceral fat, which is a major risk factor for cardiovascular disease[31]. Weight management strategies, including diet, exercise, and pharmacotherapy, are crucial for mitigating the adverse cardiovascular effects of corticosteroids[31].

The results of interventions to reduce cardiovascular risk in corticosteroid users are promising[32]. Studies have shown that lifestyle modifications, such as dietary changes and increased physical activity, can significantly reduce cardiovascular risk in this population[32]. Pharmacological interventions, including the use of statins, antihypertensive agents, and antidiabetic medications, are also effective in managing cardiovascular risk[32]. These interventions should be tailored to the individual patient's risk profile and regularly monitored to ensure optimal outcomes[32]. The relationship between corticosteroids and coronary artery disease (CAD) is well-established[33]. Long-term corticosteroid use is associated with an increased risk of CAD, driven by the combined effects of hypertension, dyslipidemia, insulin resistance, and chronic inflammation[33]. Managing this risk requires a comprehensive approach that includes regular cardiovascular monitoring, lifestyle modifications, and the use of pharmacological agents to manage risk factors[33].

The influence of corticosteroids on glucose metabolism and its cardiovascular implications is another critical area of concern[34]. Corticosteroids impair glucose metabolism by decreasing insulin sensitivity and promoting hyperglycemia[34]. This impairment increases the risk of type 2 diabetes, which is a major risk factor for cardiovascular disease[34]. Managing glucose levels in corticosteroid users involves dietary modifications, physical activity, and the use of antidiabetic medications[34]. The effects of immunosuppressants on arterial stiffness are also noteworthy[35]. Arterial stiffness is a major predictor of cardiovascular events and is influenced by factors such as hypertension, dyslipidemia, and chronic inflammation[35]. Immunosuppressants, depending on the agent, can contribute to arterial stiffness and increase cardiovascular risk[35]. Regular monitoring of arterial stiffness and the use of strategies to manage risk factors are essential for reducing cardiovascular risk in patients on long-term immunosuppressant therapy[35].

The use of alternative therapies to minimize cardiovascular risks in corticosteroid users is an emerging area of research[36]. Therapies such as biologics and small molecule inhibitors offer promising alternatives to corticosteroids with potentially lower cardiovascular risk profiles[36]. These therapies should be considered for patients who are at high risk of cardiovascular events and for whom corticosteroid therapy poses significant risks[36]. The impact of corticosteroids on renal function and its cardiovascular implications is another

critical area of concern[37]. Corticosteroids can cause sodium retention and potassium excretion, leading to hypertension and increased cardiovascular risk[37]. Managing renal function in corticosteroid users involves regular monitoring of electrolyte levels, blood pressure, and renal function tests, along with the use of strategies to manage hypertension and reduce cardiovascular risk[37].

Comparing the cardiovascular effects of corticosteroids in different populations is essential for understanding the variability in risk profiles and developing targeted interventions[38]. Factors such as age, gender, comorbid conditions, and genetic predisposition can influence the cardiovascular risk associated with corticosteroid use[38]. Personalized treatment approaches that consider these factors can help optimize therapeutic outcomes and minimize the risk of adverse cardiovascular effects[38]. The ethical and clinical implications of long-term corticosteroid use are profound[39]. The potential for significant harm must be weighed against the therapeutic benefits, particularly in vulnerable populations such as the elderly and those with multiple comorbidities[39]. Clinicians must carefully consider the risks and benefits of corticosteroid therapy and engage in shared decision-making with patients to ensure informed consent and optimal therapeutic outcomes[39].

Future research directions on the cardiovascular risks associated with corticosteroids should focus on identifying the underlying mechanisms of these effects, developing targeted interventions to mitigate risk, and exploring alternative therapies with lower cardiovascular toxicity[40]. Large-scale, long-term studies are needed to better understand the complex interactions between corticosteroids, cardiovascular risk factors, and patient outcomes[40]. Additionally, research should explore the potential for personalized medicine approaches to optimize treatment and reduce cardiovascular risk in patients on long-term corticosteroid therapy[40].

CONCLUSION

The use of corticosteroids and immunosuppressants in clinical practice is essential for managing a wide range of inflammatory and autoimmune conditions. However, the long-term use of these medications is associated with significant cardiovascular risk. Corticosteroids promote hypertension, dyslipidemia, insulin resistance, and chronic inflammation, all of which contribute to the development of cardiovascular disease. Immunosuppressants, depending on the agent, also carry varying degrees of cardiovascular risk. Effective management of these risks requires a comprehensive approach that includes regular cardiovascular monitoring, lifestyle modifications, and the use of pharmacological interventions to manage risk factors. Personalized treatment approaches, informed by the individual patient's risk profile and comorbid conditions, are essential for optimizing therapeutic outcomes and minimizing the risk of adverse cardiovascular effects.

Future research should focus on identifying the underlying mechanisms of corticosteroid-induced cardiovascular risk, developing targeted interventions to mitigate this risk, and exploring alternative therapies with lower cardiovascular toxicity. Through careful management and ongoing research, it is possible to maximize the therapeutic benefits of corticosteroids and immunosuppressants while minimizing their potential for harm. The integration of advanced monitoring techniques, such as heart rate variability and arterial stiffness measurement, into routine clinical practice can enhance the detection and management of cardiovascular risk in these patients. Furthermore, continued education of

healthcare providers on the latest guidelines and evidence-based practices will ensure that patients receive the most appropriate and effective care.

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