REVIEW ARTICLE

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Physical Exercise as a Modulator of the Levels of Leptin/Adiponectin Relation and Inflammation in Chronic Kidney Disease

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Abstract: Chronic kidney disease (CKD) is an important factor of loss of quality of life and high rates of morbidity and mortality, where cardiovascular diseases are the main responsible for this poorer prognosis. It is verified that CKD is associated with high inflammatory levels in the body, or that it seems to contribute to these cardiovascular events. Thus, CKD is characterized by a high inflammatory profile, as well as possibly a large imbalance in adipokines due to changes in body composition. Thus, adiponectin and leptin emerge as possible inflammatory modulators, although their popular effects are not completely elucidated. On the other hand, it is proven that physical exercise can be a great tool in the treatment of CKD and in the modulation of biomarkers, stimulating in an anti-inflammatory way and promoting an adjustment in the main causes of morbidity and mortality in this population. Thus, this review seeks to elucidate the role of exercise as a modulator of inflammation and the leptin/adiponectin relationship in order to contribute to the better quality of life of this population, in addition to demonstrating the important role that exercise can exert in modulation of these biomarkers, aiming to minimize the cardiovascular effects that these biomarkers exert on this population.

Keywords: Leptin, Adiponectin, Chronic Kidney Disease, Physical Exercise

1. Introduction

Regional fat distribution has been recognized as a link between obesity and cardiovascular disease; however, abdominal obesity is seen as a better predictor of cardiovascular disease than generalized obesity, and this finding is supported by body mass index. On the other hand, the relationship between chronic kidney disease (CKD) and obesity is being discussed in the literature, and some studies demonstrate multiple mechanisms underlying the development and progression of CKD in this context. An increase in CKD plasma flow and glomerular hyperfiltration is observed, which leads to an increase in interglomerular pressure (Alizadeh *et al.,* 2018). CKD is a specific clinical condition due to progressive damage to kidney function, leading to several systemic complications, including chronic inflammation and increased cardiovascular risk. Hypertension and hormonal imbalances, such as altered levels of leptin and adiponectin, are important factors that exacerbate the complications associated with CKD. Adiponectin (ADP), which is a pro-inflammatory adipokine, has been demonstrated in patients with different levels of obesity, and this has been associated with increased urinary protein excretion, in addition to cardiovascular events (Sharma *et al.,* 2008).

Leptin (LEP) plays an important role in energy expenditure and is related to food intake. Furthermore, it may contribute to the progression of kidney disease secondary to endothelial cell proliferation and

mesangial cell hypertrophy (Wolf *et al.,* 1999). It is highlighted that ADP is an anti-inflammatory and antioxidant cytokine that may contribute to cardioprotective activity. It is known that in cases where there is kidney damage and consequent proteinuria, ADP levels rise, this relationship, however, is a response to proteinuria, but not the cause of it. Proteinuria is a CKD marker and plays an important role in triage, diagnosis and monitoring of kidney failure. Epidemiological studies demonstrate that proteinuria is an independent risk factor for cardiovascular events and CKD. In some studies, LEP concentrations have been observed to increase in patients with CKD and may be associated with the progression of renal deterioration, which may be partly attributed to impaired renal clearance (Alix *et al.,* 2014). In the study by Golembiewska *et al.,* 2013, it was argued that LEP and the LEP/ADP ratio are inversely associated with peritoneal creatinine clearance in patients who have started peritoneal dialysis.

This area, or physical exercise, emerged as an ideal practice to act in the best way and not control the clinical picture of patients with CKD. Regular and moderate physical exercise can positively affect the control of associated chronic comorbidities such as hypertension and diabetes, and also strongly reduce the risk of cardiovascular complications, as well as the modulation of the immune system, helping to reduce systemic and local chronic inflammation. Physical exercise also serves to improve the physical capacity of two patients and reduce cachexia, as well as improving the quality of life of two patients (Wilkinson *et al.,* 2016). Therefore, this review aims to elucidate the role of physical exercise as a modulator of inflammation and the relation of the levels of LEP/ADP, hence contributing with a better quality of life of the hemodialytic CKD population. Besides, we aim to show the importance of this modulation in the reduction of cardiovascular morbimortality, which are the main cause of death in this population.

2. Abdominal obesity and adipokine imbalance in chronic kidney disease (CKD)

Adipokines are hormones secreted by adipose tissue, and we can mention ADP and LEP. ADP, a 30 kDa protein hormone produced mainly by adipocytes, composed of 244 amino acids, and is composed of an N-terminal collagen-like sequence (collagen domain) and a C-terminal globular region (globular domain). Three isoforms have been identified: trimer (low molecular weight), hexamer (medium molecular weight), and multimer (high molecular weight, HMW). ADP does not bleed, circulating in globular forms as trimer, hexamer, and multimer isoforms. The latter, in other words, HMW ADP, appears to be more biologically active (Parida *et al.,* 2019).

ADP plays a fundamental role in the balance of the energy metabolism of the organism, mainly in the production of glycose and lipids, because it increases the sensitization of insulin, which, by means of the inhibition of the enzyme glycose-6-phosphatase and activation of the receptors activated by proliferators of peroxisome alpha (PPAR-α), reduces non-body glyconeogene, increases beta-oxidation of fatty acids in non-body and skeletal muscle and cellular internalization of glycose (Magherini *et al.,* 2019; Li & Shen, 2019; Krause *et al.,* 2019). Currently there is no consensus regarding the pro or anti-inflammatory role of each isoform, it is hardly known that, due to the high levels of ADP and inflammatory markers in patients with CKD, there is a predominance of some pro-inflammatory isoform not affected kidney tissue (Choi *et al.,* 2020).

ADP exerts its functions through three receptors: ADP receptor (AdipoR1) (predominant in skeletal muscles), AdipoR2 (predominant in the liver) and T-cadherin. Globular and trimeric ADP interact predominantly with AdipoR1 and AdipoR2. It is observed that hexamers and multimers interact mainly with T-cadherin receptors. ADP has different metabolic functions, such as: suppression of hepatic glycose production, increase of cellular glycose uptake, insulin sensitivity. The involvement of lipid metabolism is also observed, as it increases the oxidation of skeletal muscle fat and suppresses the accumulation of non-reactive lipids. The interaction of ADP with AdipoR1 regulates glycose metabolism, insulin sensitivity and fatty acid oxidation through the activation of the protein kinase pathway activated by 50-AMP (AMPK); The interaction with AdipoR2 induces the activation of the PPAR-α, inducing fatty acid catabolism (Parida *et al.,* 2019).

ADP is responsible for an anti-inflammatory response, as it inhibits the secretion of Tumor Necrosis Factor Alpha (TNF-α) and adhesion molecules that favor diapedesis, in addition to stimulating the secretion of interleukins (IL) as well as IL. -1 and IL-10 e, also induce macrophage transformation not anti-inflammatory type M2 (Li & Shen, 2019). However, there is a positive correlation between blood levels of

ADP, dialysis and death in CKD. The most suggested causes for the increase in these serum accumulation values are due to deficient renal filtration and an anti-inflammatory defense mechanism in response to renal injury (Przybyciński *et al.,* 2020). In patients with CKD on hemodialysis (HD) and/or peritoneal dialysis, the plasma concentration of ADP is approximately three times higher, even in people with the absence of kidney damage, and ADP is little excreted in the kidneys (Song *et al.,* 2020) (Figure 1).

It was observed that plasma ADP was correlated with visceral fat mass based on 1,442 patients with CKD divided into three groups, it was observed that Serum ADP was significantly higher in patients with macroalbuminuria than in patients without macroalbuminuria. This study verified that in an univariate linear regression analysis, serum ADP concentrations were correlated with age, albumin/creatinine ratio, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol, while they were negatively correlated with body mass index, estimated glomerular filtration rates and serum albumin and triglyceride levels (Kim *et al.,* 2016) Patients in HD have comparatively higher ADP concentrations, but some studies demonstrate that the association of ADP-mortality in this population does not consider body composition or show a consistent relationship (Choi *et al.,* 2020). From this, Rhee *et al.,* 2015, conducted a prospective cohort study to examine the baseline serum concentrations of ADP in 501 HD patients in 13 dialysis centers and observed that among 501 HD patients, 50 deaths were observed. The authors therefore conclude that a higher level of ADP is associated with a three times higher risk of death in HD patients, independently of body composition and two lipid levels (Kaynar *et al.,* 2014).

LEP is responsible for the activation of the phosphoinositol-3 kinase (PI3K) and mitogen-activated protein kinase (MAPK) extracellular signal-regulated kinase (ERK) signaling pathways, which appears to contribute to the suppression of appetite, inducing weight loss and increasing thermogenic effects. The JAK/STAT3, MAPK/ERK and PI3K pathways seem to cooperate in the regulation of energy balance (Harlan & Rahmouni, 2013).

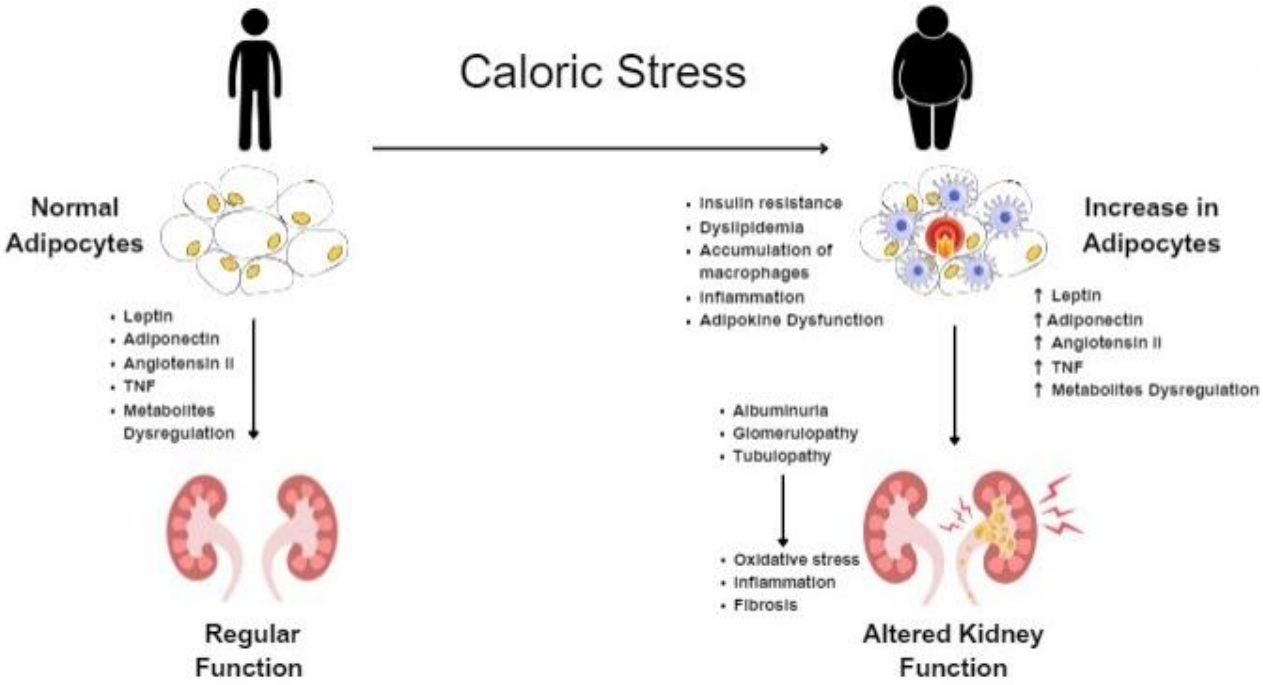

Figure 1. Correlated mechanisms between adipocytes and kidney function. The adipose tissue applies effects on kidney metabolism through a chain of secretory factors, such as leptin, adiponectin, angiotensin II, TNF and other metabolites. These factors are essential to the maintenance of renal function, when presented in physiological levels. Although, in response to excessive caloric stress, plenty of phenomenon occur, such as insulin resistance, dyslipidemia, inflammation, accumulation of macrophages and adipokine dysfunction. These factors contribute in the progression of renal dysfunction in the context of CKD, increasing oxidative stress, chronic inflammation and fibrosis, eventually causing kidney damage. Furthermore, CKD promotes an alteration of adipose tissue, which favors energy loss and, therefore, may contribute to kidney damage.

LEP circulates in free and protein-bound forms, having functions mediated by LEP receptors (LepR). LepR a, b, c, d and f are transmembrane receptors that bind to LEP and activate JAK2; LepRe lacks a transmembrane domain and is a solvent isoform. Circulating LEP binds to solute LepRe, resulting in the inhibition of central LEP transport, the most important receptor for the physiological effects of LEP, for energy homeostasis and for various other neuroendocrine functions (Myers *et al.,* 2008).

As ADP modulates the biochemical fraction of metabolism, LEP informs the brain about these reactions, indicating how much energy is being consumed, the main way to address these values is to suppress appetite and modulate energy consumption (Stępień *et al.,* 2012; Katsiki *et al.,* 2018). Furthermore, its secretion stimulates the sympathetic nervous system, culminating, among other factors, in an increase in average arterial pressure, commonly associated with obesity and kidney damage. Therefore, LEP concentration is directly proportional to the lipid volume of each individual (Stępień *et al.,* 2012; Katsiki *et al.,* 2018).

An increase in adipocytes is associated with elevated secretion of LEP, which in turn enhances the expression of the gene for transforming growth factor β 1 (TGF-β1) and other fibrotic factors, such as collagen IV and fibronectin. These factors stimulate the proliferation of mesangial cells in the kidneys. Overproduction of these cells can result in glomerulosclerosis, caused by mesangial hypertrophy within the glomeruli, thickening of the glomerular basement membrane, and an increase in the extracellular matrix (Czaja-Stolc *et al.,* 2022).

In according to Korczynska *et al.,* 2021), LEP can activate NADPH oxidase and generate reactive oxygen species (ROS), activating transcription factors and pro-inflammatory genes exacerbating existing inflammation. As ROS disrupts the excretory function of the nephron, causes the accumulation of metabolic products and impairs renal regulatory mechanisms. Recent studies imply that LEP is associated with endothelial dysfunction. In a study investigating the relationship between LEP and markers of endothelial dysfunction in patients with CKD and how LEP contributes to endothelial damage in 140 patients with CKD and 140 healthy individuals, it was observed that serum LEP levels were significantly higher in CKD than controls showed a significantly positive association with an increase in two levels of intercellular adhesion molecule-1 (sICAM-1) and vascular cellular adhesion molecule-1 (sVCAM-1), potentially contributing to endothelial dysfunction and the disintegration of the f-actin cytoskeleton. through a mechanism involving the AKT/GSK3β and β-catenin pathway (Ding et al., 2016). Among 160 patients with CKD and 160 healthy individuals, the patients with CKD presented significantly higher serum LEP levels than the control group, which were positively correlated with elevated levels of interleukin 6 (IL-6), endothelin 1 (ET-1), the human monocyte chemoattractant protein 1 (MCP-1), resulting in recombination of F-actin and aggregation of vinculin, as well as migration of endothelial cells, which leads to endothelial dysfunction through the MTA1-WNT/β-catenin pathway (Wang *et al.,* 2020).

Obesity contributes to the onset of various diseases due to chronic inflammation, oxidative stress, and disruptions in adipokine secretion. The altered secretion of adipokines linked to obesity plays a role in the development and progression of chronic kidney disease (CKD). Evidence suggests a growing connection between adipokine deregulation in obesity and CKD development. Research indicates that adipokines can impact glomerular function, and emerging studies are now identifying a connection to tubular dysfunction. More in-depth and substantiated in vivo studies are needed to explore the role of adipokines in obesity-related CKD. Additionally, understanding the molecular signaling pathways in altered renal cells is crucial for developing effective treatments for obesity-related nephropathy (Alizadeh *et al.,* 2018).

3. The role of leptin in metabolic syndrome and CKD

Metabolic Syndrome (MS) is a complex disorder represented by a set of cardiovascular risk factors, related to central fat deposition and insulin resistance. Some studies point to the relationship between CKD and MS (Greffin *et al.,* 2017). Regarding the relationship between MS and CKD, described in the literature report that the progressive increase in MS leads to a decrease in renal function and consequently creates a favorable scenario for the development of CKD. Furthermore, it is important to highlight that the risk for the onset renal function increases progressively, according to the increase in the number of MS components, and this association is independent of factors such as age, sex, race or ethnicity. (Chen *et al.,* 2004).

Among the factors that may be involved in the pathophysiology of MS, LEP plays a prominent role. This molecule is a protein composed of amino acids, predominantly produced in white adipose tissue (Martins *et al.,* 2012). It is worth highlighting that LEP performs numerous functions in the human body at an immunological level (participates in the activation and regulation of T lymphocytes, pro-inflammatory cytokines and natural killer cells), metabolic, energetic and hepatic, in addition to being an important marker of body fat (dos Santos Pinho *et al.,* 2022).

The expression and synthesis of LEP are influenced by different factors, including fasting, physical activity, sympathetic function and energy balance. Furthermore, it is noteworthy that in cases of CKD there is an increase in plasma LEP levels (Gunta & Mak, 2013), a fact that is like that found in MS, considering that in this case hyperleptinemia contributes to the development of the disease (Correia & Rahmouni, 2006).

Studies show the effectiveness of physical exercise in regulating LEP levels and resistance to this peptide can also be positively influenced by the practice of physical activities. In addition, with the practice of these activities there is a reduction in inflammatory conditions, which is typical of patients with MS, obesity and CKD (França *et al.,* 2017). Furthermore, higher intensity physical exercises generate a prolonged negative energy balance, generating a reduction in LEP and greater sensitivity to the hypothalamic region (Tan *et al.,* 2021). From this perspective, it was noted that carrying out medium or low intensity physical activities contributes to improved health in patients with CKD (Villanego *et al.,* 2020).

As mentioned, the practice of physical exercise interferes with the LEP pathway, in this sense, there are descriptions in the literature that patients with CKD have an increase in adipocytes and LEP, especially patients with obesity, thus, these compounds act on human organism by activating brain structures that increase blood pressure and inhibit the action of nitric oxide, it is also highlighted that the increase in visceral and abdominal fat generates renal compression, which impacts on intrarenal pressure and increased interstitial hydrostatic pressure in the kidneys (Silva *et al.,* 2017). In this sense, physical exercise can be a potential reducer of the action of LEP, therefore studies show that regular and prolonged physical activity can help reduce LEP, in addition to increasing the sensitivity of this hormone at the hypothalamic level, which has repercussions on reducing the risk of developing MS in addition to generating homeostasis between satiety and energy expenditure (Pilon et al, 2018), (Figure 2).

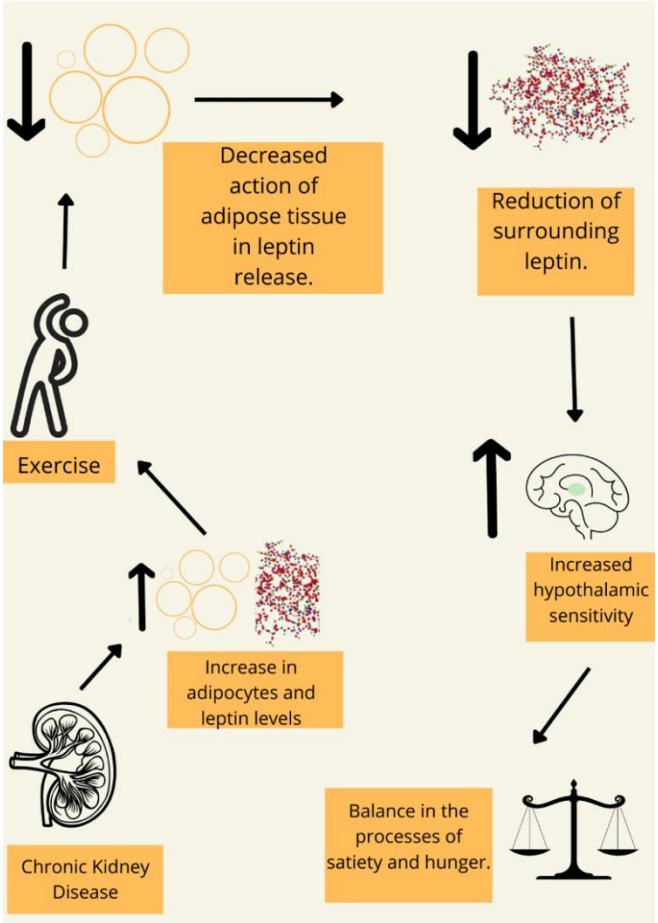

Figure 2. Mechanisms of modulation of physical exercise in the LEP pathway in patients with CKD: In summary, LEP in patients with CKD tends to be elevated. In this sense, regular and prolonged physical activity reduces the release of LEP by adipocytes, which results in increased hypothalamic sensitivity and homeostasis in the processes of satiety and hunger.

4. The role of adiponectin in metabolicsyndrome

Currently, adipose tissue is considered an endocrine organ, responsible for the synthesis of various substances (Romero & Zanesco, 2006; Prado *et al.,* 2009; Silva *et al.,* 2020). Among the adipokines secreted by adipose tissue is ADP, which plays a role in adipose tissue itself and in numerous other tissues of the body, playing a significant role in metabolic disorders, such as obesity, type 2 diabetes, coronary artery disease and metabolic syndrome (Prado *et al.,* 2009; Carballo *et al.,* 2020; Cocate *et al.,* 2011).

Among its main functions, it acts as a metabolic regulator, increasing glucose uptake and as

an insulin sensitizer in the liver and muscles, increases the oxidation of fatty acids by musculoskeletal tissue and reduces hepatic gluconeogenesis, most of these effects are mediated by the activation of adenosine activated monophosphate kinase (AMPK). It also acts as an anti-inflammatory and vasculoprotective cytokine, increasing the production of nitric oxide and reducing substances related to pro-inflammatory effects such as C-reactive protein, interleukin-6 and tumor necrosis factor (TNF), exerting an important cardioprotective factor mainly due to these properties. anti-inflammatory and anti-atherogenic (Prado *et al.,* 2009; Carballo *et al.,* 2020; Cocate *et al.,* 2011).

In patients with CKD, the loss of renal function results in increased concentrations of ADP, this concetration gradually accumulate as the glomerular filtration rate decreases. However, despite the cardioprotective property attributed to ADP, cardiovascular complications remain the main cause of mortality in these individuals, being responsible for more than 50% of deaths, which is controversial, and for this reason, some authors do not agree with this theory. of ADP cardioprotection (Kamimura *et al.,* 2012).

The excess adipose tissue associated with obesity and/or metabolic syndrome (MS) leads to higher levels of pro-inflammatory adipokines and a subsequent reduction in anti-inflammatory adipokines, causing dysregulation in gene expression, metabolic and immune functions, insulin sensitivity, angiogenesis, blood pressure, lipid metabolism, and overall body homeostasis. These disruptions are linked to cardiovascular diseases (Prado *et al.,* 2009). Some studies indicate that visceral fat secretes two to three times more pro-inflammatory cytokines compared to subcutaneous fat. Moreover, the expression of pro-inflammatory cytokines and the infiltration of immune cells are more pronounced in both subcutaneous and visceral adipose tissue in patients with chronic kidney disease (CKD) compared to healthy individuals (Kamimura *et al.,* 2012).

Therefore, some studies suggest that the mechanism involving inflammation is responsible for the increase in visceral fat, being the main determinant of circulating ADP levels. Corroborating these findings, the authors describe that hemodialysis patients had a larger area of visceral fat measured by computed tomography when compared to healthy individuals, associating this excess visceral fat with changes in the lipid profile, insulin resistance, inflammation and CVD (Kamimura *et al.,* 2012).

It is also known that a positive energy balance and a sedentary lifestyle lead to the accumulation of visceral fat, infiltration of macrophages and pro-inflammatory T cells. The pro-inflammatory phenotype of the M1 macrophage predominates and inflames adipose tissue, which in turn releases pro-inflammatory adipokines, such as tumor necrosis factor (TNF), causing mild but significant systemic inflammation (Silva *et al.,* 2020). Thus, low blood concentrations of ADP have been inversely associated with obesity (Oliveira, 2018), insulin resistance and type 2 diabetes in humans and animals (Prado *et al.,* 2009). High blood levels of ADP have been positively related to improved insulin sensitivity (Cocate *et al.,* 2011).

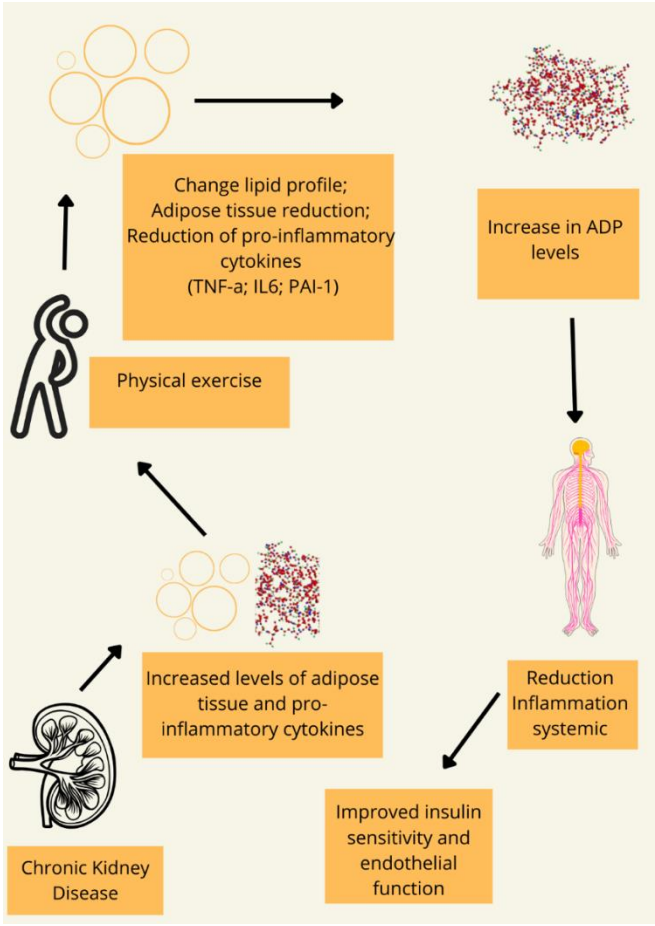

Figure 3. Mechanisms of modulation of physical exercise in the ADP pathway in patients with CKD: In summary, ADP and pro-inflammatory cytokines tends to be elevated in patients with CKD. Thus, regular and prolonged physical activity, especially with moderate intensity, has the capacity to change the lipid profile, reducing the adipose tissue and the inflammatory cytokines such as TNF-a, IL-6 and PAI-1. Also, the ADP levels tend to raise, generally reducing the systemic inflammation and generating improvements in insulin sensivity and endothelial function.

One of the non-pharmacological measures used to seek metabolic balance is physical exercise, whether acute or chronic, it has effects on insulin sensitivity and blood concentrations of ADP (Cocate *et al.,* 2011). High-intensity interval training (HIIT) has been identified as a potential strategy for preventing metabolic syndrome. Research indicates that HIIT promotes the secretion of lipolytic hormones, likely due to the role of IGF-1 in activating protein kinase B and testosterone signaling at the androgen receptor, while also enhancing oxidative capacity, which is directly linked to mitigating metabolic disorders (Silva et al., 2020). Additionally, studies highlight that physical exercise plays a role in regulating endothelial function through insulin and adipokines like ADP. Exercise contributes to a reduction in adipose tissue mass by lowering body weight, which in turn elevates ADP levels, and is associated with improvements in both insulin sensitivity and endothelial function (Carvalho *et al.,* 2006), (Figure 3).

5. Physical exercise, inflammation and the leptin/adiponectin relationship in CKD

Physical exercise can trigger a range of cellular and immunological responses in the human body, as it is responsible for causing significant neurophysiological modulation (Terra *et al.,* 2012). It is important to emphasize that the type of physical exercise, along with its duration, intensity, and frequency, significantly affects the immune system (Simpson *et al.,* 2015). Zelle et al. (2011) demonstrated that exercise interventions led to notable improvements in cardiovascular function and quality of life in patients with CKD. Additionally, exercise programs have been linked to reductions in inflammatory markers and improvements in the regulation of leptin and adiponectin levels. These two adipokines, hormones produced by adipose tissue, play crucial roles in energy metabolism and the regulation of inflammation. Leptin regulates appetite and energy expenditure, while adiponectin has anti-inflammatory and insulin-sensitizing properties. In patients with CKD, there is often an increase in leptin levels and a decrease in adiponectin levels, imbalances that are associated with increased cardiovascular risk and worsening systemic inflammation.

Studies indicate that regular exercise reduces leptin levels, possibly due to decreased body mass and increased insulin sensitivity. On the other hand, exercise tends to increase adiponectin levels, contributing to a better anti-inflammatory response and insulin sensitivity. In patients with CKD, these hormonal changes are particularly beneficial as they help mitigate systemic inflammation and cardiovascular risk. The inflammation present in this population can generate aggravating health conditions, and exercise is a way to minimize these problems (Navaneethan *et al.,* 2021).

Exercises of short duration (between 45 and 60 minutes) and of moderate intensity, performed at least three times per week, for a minimum total of 150 minutes per week, are responsible for positively modifying the immune system, once it occurs or increases chemotaxis of neutrophils and macrophages, including an increase in leukocyte function, phagocytosis, degranulation, cytotoxic and oxidative activity of both neutrophils and macrophages (Senna *et al.,* 2016). A significant decrease in pro-inflammatory cytokines and interleukins is also observed, namely: IL-6, IL-1β and TNF-α (Bigley *et al.,* 2015). Practicing moderate intensity physical exercise also favors an increase in TCD4 lymphocytes, as well as an increase in anti-inflammatory cytokines in T cells, including IL-4 and IL-10. High levels of circulating IL-10 are responsible for neutralizing the effects of pro-inflammatory cytokines, so as to prevent the influx of adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1). This form, physical exercise is considered a controller of the immune system capable of improving the defense conditions of the organism, reducing the chances of chronic diseases (Sellami *et al.,* 2018; Scheffer & Latini, 2020).

Furthermore, the exercise is responsible for altering both innate and adaptive immunity. Among the cells of innate immunity modulated by exercise, we can mention: neutrophils, dendritic cells and natural killer (NK) cells. Specifically, dendritic cells, or physical exercise increases the generation of cells derived from monocytes, in order to conduct a reduced inflammatory response in an attempt to improve immunological surveillance. As blood flow increases, as NK cells end up being requested and as a tendency to regular exercise, these cells return to the pre-excitatory or lower state, and thus generate less inflammatory process. In adaptive immunity, studies demonstrate modulation of T cells, especially Th2 cells, because these cells help in regulating the inflammatory activity of the cytokines IL-4, IL-5, IL-6 and IL-13 and the anti-inflammatory activity of the cytokine. IL-10 (Nieman & Wentz, 2019; Wang *et al.,* 2020) (Figure 4).

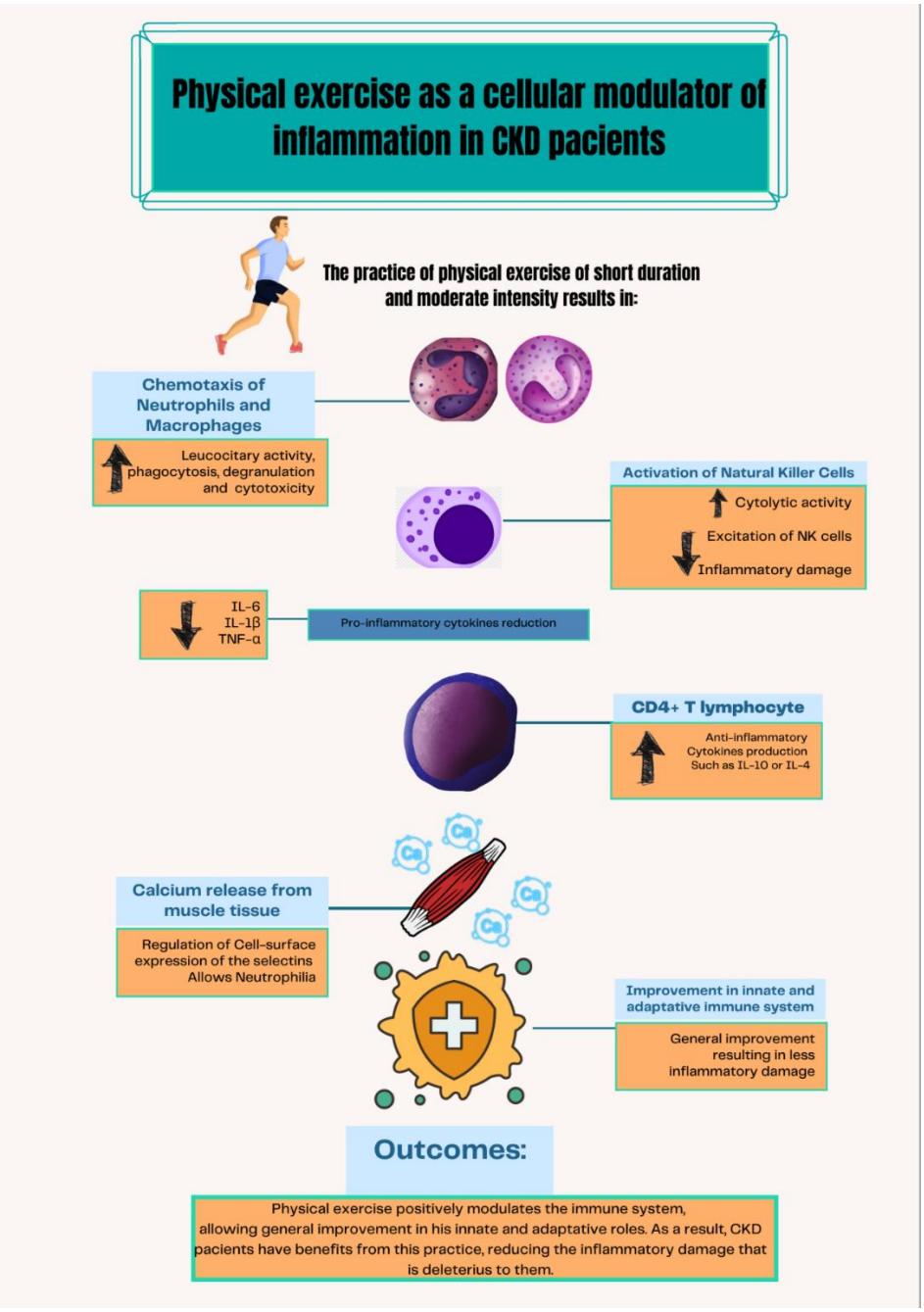

Figure 4. Physical exercise, especially when practiced with short duration and medium intensity, acts as a modulator of inflammation in CKD patients. Therefore, the major modifications are: 1- chemotaxis of neutrophils and macrophages, which occurs by the raise of leucocitary activity, phagocytosis, degranulation and cytotoxicity. 2- Activation of Natural Killer Cells, represented by the growth of cytolytic activity and the reduction of inflammatory damage and excitation of natural killer cells. 3- Pro-inflammatory cytokines reduction, such as IL-6, IL-1β and TNF- α. 4- Elevation of anti-inflammatory cytokines (IL-10 and IL-4). 5- Calcium release from the muscular tissue. 6- Improvement in innate and adaptative imune system. The main outcomes of this practice are improvements of the innate and adaptative roles, resulting in reduction of inflammation that is deleterius to CKD patients.

Patients affected by CKD tend to suffer from a series of extra-renal disorders, mainly cardiovascular, in addition to infections developed as a result of a compromised immune system and the dialysis process, in both cases, there is an increase in morbidity and mortality levels. of this population and these conditions are directly influenced by the chronic inflammation to which individuals with CKD are subjected. Inflammation levels in CKD progressively increase with the loss of kidney function and, although it is known

that inflammation is an important defense process against infections, in the case of CKD, this unregulated inflammation creates a series of harmful effects on health. of the patient, due to a very large increase in these pro-inflammatory mediators. Therefore, regulating or reducing levels of chronic inflammation in patients with CKD is essential for the treatment of these individuals (Rapa *et al.,* 2019).

Systemic inflammation deregulates the response of the renal microvasculature, thus enabling the formation of toxins, damage to the nephron and the progression of CKD. This process occurs from pro-inflammatory cytokines that reach the nephron and activate, mainly, leukocytes and endothelial cells, producing inflammatory mediators at a local level, thus causing a series of changes in space, such as changes in the glycocalyx, activation of coagulation and cell adhesion, which can cause irreversible damage to the tubules and the functioning of the nephron as a whole. Accordingly, the greater the loss of kidney function, the more easily inflammatory markers, such as TNF-α and fibrinogen, are found. Thus, it is possible to establish a correlation between the development of inflammation and CKD concomitantly (Mihai *et al.,* 2018).

The benefits of physical exercise have been extensively researched, and it has been found to have significant anti-inflammatory effects that are advantageous for the body. This effect occurs primarily through the regulation of inflammatory cytokines such as IL-6 and IL-10, helping to modulate the immune system in response to infections or chronic diseases. Exercise, therefore, exerts an anti-inflammatory influence by triggering hormones like adrenaline and cortisol, which are released during physical activity and play a key role in immunosuppression and regulating pro-inflammatory cytokines. Additionally, muscle contractions during exercise lead to the production of myokines, which actively contribute to anti-inflammatory processes (Scheffer & Latini, 2020).

Considering the benefits provided by regular physical exercise, we realize that this benign effect is also seen in patients with CKD. Most of these patients have reduced physical fitness, which is closely related to mortality rates, in addition to impacting the quality of life and independence of individuals. Probably the greatest beneficial effect of physical exercise for patients with CKD is an improvement in cardiovascular capacity, mainly the reduction in blood pressure and consequent reduction in the use of medications to control it, a decrease in heart rate and well-visualized modulation of the levels of inflammation, as well as the control of comorbidities frequently associated with CKD, such as diabetes and systemic arterial hypertension. Furthermore, physical exercise is capable of increasing strength and physical capacity, mitigating the occurrence of muscular atrophy, that is, loss of muscle mass or cachexia, which is very common in patients with CKD, especially those undergoing hemodialysis. Finally, physical exercise in pre-dialysis patients significantly reduces the loss of kidney function, delaying the progression of the disease (Wilkinson *et al.,* 2016).

The chronic inflammation present in CKD is the result of the accumulation of acute phase proteins such as C-reactive protein and interleukins, especially the pro-inflammatory cytokine IL-6, which plays a significant role in the development of chronic inflammation in this condition. In most cases, IL-6 can be found in high concentrations in blood plasma, serving as a parameter for leveling the risk of heart problems in patients with CKD, which often lead to death. Several studies indicate that regular physical exercise, therefore, is essential to limit chronic inflammation in these patients, especially in relation to the decrease in plasma IL-6 levels, both in pre-dialysis patients and in patients undergoing hemodialysis (Wu *et al.,* 2021).

Likewise, in addition to the reduction in IL-6 levels and concomitant increase in IL-10 levels, thus showing a decrease in the IL-6:IL-10 ratio that illustrates the patient's inflammatory condition, there is a reduction in leukocyte activity, especially T lymphocytes and monocyte activation in patients with CKD, thus showing the great importance of regular physical exercise in modulating the immune system and inflammatory levels of these patients together (Viana *et al.,* 2014).

On the other hand, there are still several open factors, meaning that the real effectiveness of physical exercise in HD patients with CKD is not as effective as expected and believed. Firstly, most studies involving the practice of physical exercise in this population end up carrying out lower intensity activities depending on the clinical condition of these patients, thus reducing the final benefits. Added to this is the fact that most studies are carried out intradialytically, making it even more difficult to practice at greater intensity. Another relevant point to be discussed is the time of the studies, which to present satisfactory results generally needs to be very long, a fact that becomes incompatible with this group due to the high rates of

morbidity and mortality and consequent withdrawal or reduction in the quality of practicing exercise protocols. In addition to the fact that, in the case of a progressively debilitating disease, the objective should probably be to maintain the health of these patients, given that effective improvement would be difficult to achieve (Wilund *et al.,* 2019).

Furthermore, the large burden of comorbidities that these patients present may be responsible for generating a type of resistance to the effects of resistance physical exercise. In particular, the chronic inflammation of these patients is a factor that hinders their anabolism. Therefore, it is believed that conflicting or less relevant data are due to these factors that make data analysis and interpretation difficult, possibly masking the potential of physical exercise in this population, thus ending up not generating clinically significant results (Wilund *et al.,* 2019).

Therefore, the practice of regular moderate-intensity physical exercise can be vitally important for patients with CKD, although new analyzes are needed to fully elucidate this practice in this specific population, thus serving as an adjuvant treatment for patients with CKD. It is clear that the lifestyle of these patients, shaped by the practice of physical exercise, can be extremely relevant for health, treatment and reduction of the progression of the disease, as through anti-inflammatory mechanisms, the risk can be reduced. of mortality and morbidity in this population, in addition to modulating the immune system, improving the capacity of the cardiovascular system and mitigating the occurrence of cachexia in these individuals. However, it is still difficult to say exactly the ideal amount of physical exercise that should be practiced by each patient, in addition to questioning the ability of this population to perform physical exercises that are effectively beneficial, with conflicting information on these issues, and therefore it is necessary further studies to verify this information more precisely (Wilkinson *et al.,* 2016; Wu *et al.,* 2021).

6. Conclusion

LEP and ADP are proteins produced by mature adipocytes and are involved in the signaling process between the adipocyte and other tissues and cells, in order to modulate the cell division process and the inflammatory cascade. Associated with this, physical exercise is capable of improving metabolic biomarkers, regulating the inflammatory mechanism in favor of anti-inflammatory cytokines and interleukins, as well as through the reduction of pro-inflammatory adipokines. Furthermore, physical exercise reduces resistance to LEP and ADP.

Therefore, the practice of moderate-intensity physical exercise in patients with CKD is responsible for altering the process of loss of muscle mass resulting from the underlying disease, as well as modulating the immune system in favor of anti-inflammatory mediators, contributing to the reduction the morbidity and mortality of these individuals, given that it improves their cardiovascular, immunological, endocrine and metabolic condition. However, it is noted that the clinical results of this practice are not yet completely clear, meaning that more studies are needed to determine how we can achieve the greatest possible benefit from physical exercise in patients with CKD.

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The authors declare that there was no conflict of interest.

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E. G., M.R.B., K.E.T.S., M.E.S., J.C.E., A.C., B.D., K.P., R.C.R., D.T.R.S. contributed to the conception of the manuscript. E. G., M.R.B., K.E.T.S., and DTRS. Contributed to formal analysis, research and methodology. All authors contributed to writing and translating the original draft. And D.T.R.S. revised the final work. All the authors read and approved the final version of the manuscript.

Does this article pass screening for similarity?
Yes