Immune System Dysfunction and Inflammation in Hemodialysis Patients

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Biocompatibility in hemodialysis (HD) has considerably improved, but remains an open issue to be solved, appearing essential to reduce systemic inflammation and enhance patients' clinical outcomes. Clotting prevention, reduction in complement and leukocyte activation, and improvement of antioxidant effect represent the main goals. Platelet activation is one of the first steps occurring in HD patients, determining several events causing chronic sub-clinical inflammation and immune dysfunction involvement. Moreover, oxidative stress processes, resulting from a loss of balance between pro-oxidant factors and antioxidant mechanisms, have been described, highlighting the link with inflammation.

Keywords: hemodialysis ; immune system dysfunction ; inflammation

1. Introduction

Ten percent of the world population suffers from chronic kidney diseases, with 2.6 million people undergoing hemodialysis (HD), which will reach about 5.4 million in 2030 [1]. During the past 50 years, HD techniques have progressively improved, with a consequent strong impact on patients' outcomes and quality of life [2].

Nevertheless, these patients are still chronically exposed to systemic stress related both to hemodynamic and non-hemodynamic factors, with increased risk for cardiovascular, neoplastic, and infection diseases [3][4].

In addition to established cardiovascular risk factors frequently observed in HD patients, such as dyslipidemia, blood hypertension, or diabetes mellitus, the additional activation of the immune system, involving both innate and adaptive responses, contribute to maintaining a condition of chronic systemic inflammation [5].

The concept of "inflammaging" identifies a "persistent, low-grade, sterile, non-resolving inflammatory state, associated with the senescence of the immune system" [6]. Thus, HD "per se" contributes to the morbidity and mortality of these patients inducing a systemic stress condition, resulting from hemodynamic management (weight loss, ultrafiltration), treatment schedules, solute fluxes, electrolytic shifts, and interaction between blood and the extracorporeal circuit [7].

The term "biocompatibility" was firstly used in 1970, although its first official definition was presented in 1986 when it was described as "the ability of a material to perform with an appropriate host response in a specific application" [8][9].

In the following years, this definition was modulated, pointing out the "interaction" between devices and human tissues [10], and taking into account the concepts of "bioactivity" [11][12].

During each HD session, the patient's flowing blood leaves the physiological protection of the endothelial cells in the vessels and comes into contact with the extracorporeal circuit, with consequent physical and chemical stimulations.

2. Innate Immune System

2.1. Complement

Complement is one of the major components of the innate immune system and bridges the adaptive response of the body to abnormal stimuli, as well as being induced by hemodialysis, with consequent inflammation and pro-coagulant effects [13][14].

All the three pathways of the complement activation (classical pathway (CP), lectin pathway (LP), and alternative pathway (AP)) are involved; it is known that they all converge on C3 convertase, an enzymatic complex that generates C3a and

C3b factors through C3 cleavage, and they can be activated by different triggers, such as acetylated compounds, carbohydrate structures, proteins adsorbed on biomaterials, and immunoglobulin G [15].

During the first 10–15 min of the HD session, C3a levels increased, indicating C3 activation, and subsequently C5a and C5b levels also raised, with an increase of up to 70% of soluble C5b9 levels and plasmatic C3d/C3 ratios during a single treatment of HD [16].

However, this complement activation effect is active in the early stages of HD and gradually decreases during long-term dialysis, as revealed by the negative correlation between C3 levels and dialysis duration [17].

The first studies, conducted on cellulose-based HD membranes, revealed the activation of the alternative pathway of the complement system. However, the lectin and classical pathways are also activated by HD, respectively, by the binding of mannose-binding-lectin and ficolin-2 (for LP) and properdine and/or C3b (for CP) to the dialysis membrane [18][19]. Moreover, polysulfone membranes can adsorb some complement inhibitors, such as factor H and clusterin, significantly reducing their circulating amount, further complementing activation [18][20].

Conversely, the use of medium cut-off filters decreased the levels of many complement components, including C4B, when compared to polyamix membranes [21].

Interventions targeting the complement system could improve biocompatibility, dialysis efficacy, and long-term outcomes. As observed for the platelet activation, citrate inhibits complement activity through calcium chelation in the HD circuit [22].

Complement inhibitors could represent other attractive therapeutic options to reduce complement activation and inflammation. Poppelaars observed that the addition of C1-inhibitor to an ex vivo HD model significantly reduced the complement activation and the induction of pro-inflammatory cytokines, such as TNF-α, IL-6, and von Willebrand factor [17]. In an ex vivo model of HD, Kourtzelis used compstatin to block complement activation at the C3 level, improving the biocompatibility of hemodialysis membranes [23].

A modified polysulfone membrane with a direct thrombin inhibitor, Argatroban, was chemically grafted to enhance the hydrophilicity and induced protein adsorption, coagulation, and platelet and complement activation [24].

2.2. Neutrophils and Monocyte Macrophages

The interaction between blood and biomaterials during the HD session also stimulates the cellular components of the innate immune system, mostly neutrophils and monocytes macrophages. Their recruitment and the subsequent release of pro-inflammatory cytokines contribute to maintaining the pro-inflammatory status and thus increasing cardiovascular risk in HD patients [25].

Many studies analyzed the changes in leukocyte count induced by dialysis sessions, although the results have sometimes been inconstant. Fukushi examined peripheral leukocytes and neutrophils counts in HD patients treated with polysulfone membranes, revealing a decrease in neutrophils number at the end of the HD session and a significant increase in apoptosis-positive cells among neutrophils and monocytes, but not among lymphocytes. The activation of the complement system and the increased apoptotic cell levels mainly caused this transient leukopenia [26].

Bieber confirmed this datum, measuring high levels of neutrophil activation and death markers, such as calprotectin, peroxidase activity, and neutrophil extracellular traps (NETs), in HD patients treated with polysulfone membranes [27].

Moreover, Koga assessed the effects of five different polysulfone membranes on blood cells in vitro, showing considerable differences in platelet adhesion and reactive oxygen species production by neutrophils. The number of adherent platelets and reactive oxygen species production increased with the amount of fibrinogen adsorbed on the membranes, suggesting that the use of dialyzers with lower fibrinogen adsorption may reduce cell activation, microvascular inflammation, and oxidative stress during HD [28].

Whereas neutrophil numbers could transitory change, qualitative alterations characterized monocytes, with modifications of phenotype and functions, contributing to their dysfunction.

Monocytes are highly plastic cells able to modify their initial phenotype when facing environmental modifications, such as those in HD patients, with important consequences on their ability to interact with vascular structures, causing chronic inflammation [29].

Monocytes can be classified into three subpopulations (Mo1, Mo2, and Mo3) based on the expression of different surface markers. Mo1 monocytes show a “classical” pattern expressing lipopolysaccharide (CD14), but not the Immunoglobulin Fc Segment Receptor (CD16), while Mo2 and Mo3 monocytes express both CD14 and CD16 [30].

Mo2 monocytes act as antigen-presenting cells showing an “inflammatory pattern”, since they produce inflammatory factors, such as tumor growth factor (TGF)-β1.

Dialyzed patients have abnormally high proportions of intermediate ($CD14^{++}/CD16^{+}$) Mo2 and Mo3 monocytes, with pro-inflammatory and atherogenic features, and a strong ability to attach to endothelial cells, thus contributing to endothelial damage, and are consequently associated with atherosclerotic disease and cardiovascular events [31][32].

Liakopoulos analyzed the surface-marker profile of monocytes from HD patients treated with polysulfone membranes, confirming a skewed distribution of pro-inflammatory Mo2 and Mo3 monocytes. Moreover, behind this atypical pattern, monocyte had phenotype alterations inducing a functional impairment after a single dialysis session. In particular, the researchers described a significant reduction in the chemokine receptor CX3CR1 expression in all monocyte subpopulations, impairing their adhesion to the endothelium during hemodialytic treatment. In vitro analyses confirmed the significant decrease in CX3CRI surface expression on monocytes after incubation with foreign uremic serum, suggesting a uremia-related impaired immune response. Finally, supporting the previous observations, HD patients’ monocytes showed an impaired response to lipopolysaccharide stimulation, mirroring the immune dysfunction [33].

The potential role of different dialysis techniques in modulating monocytes’ phenotype and function has been investigated with conflicting results. Some researchers reported a reduction in the Mo2 population in patients treated with online hemodiafiltration, when compared to standard HD, without differences between pre-, mixed, or post-dilution [34][35].

However, a prospective trial based on hemodialysis with high cut-off membranes or surface modification of cuprophane dialyzers with the antioxidant vitamin E failed to reduce pre-dialysis levels of inflammatory monocytes and related markers, notwithstanding high amounts of pro-inflammatory cytokines cleared [36][37].

These conflicting data could be related to the differences between the membranes analyzed, with different cellular activation signals. Measuring monocytes before and after a dialysis session can be influenced by the dialysis-induced sequestration of cells, which may considerably change the cell population distribution in peripheral blood. However, the more biocompatible membranes remove more Mo2 and Mo3 cell populations from circulation during dialysis than Mo1 cells, as a measure of dialyzer membrane biocompatibility [38].

The Mo3 cells reach a nadir at about 15–30 min of a dialysis session and return to pre-dialysis levels until the end of treatment at 4–5 h [39].

Impairment and activation are two sides of the same coin involving the immune natural cells in HD patients, with reduced defense mechanisms, such as phagocytic capabilities or impairment of antigen presentation function, and, on the other side, increased synthesis of inflammatory cytokines.

3. Acquired Immune System

T and B Cells

The dysfunction of the adaptive immune response characterizes HD patients with negative implications for morbidity and mortality. Many studies described a reduced number and functional alterations of naïve T cells, Th2, and regulatory T cells [40], while highly differentiated memory T cells increase [41]; these cells show a pro-inflammatory phenotype destabilizing atherosclerotic plaques and enhancing the inflammatory state [42].

T-cell lymphopenia observed in HD patients seems to be due to impaired thymic output, increased apoptosis, and reduced proliferation [43][44].

Starting from these assumptions, the HD treatment “per se” can contribute to adaptive immune system dysfunction [45].

Borges reported that HD procedure contributes to the development of T-cell lymphopenia, at least in part, by apoptosis induction, with negative effects on $CD4^{+}$ T cells also mediated by recombinant erythropoietin (rhuEPO) therapy, often administered in these patients [46]. Moreover, an increased $CD4^{+}/CD8^{+}$ T-cell ratio, after a single hemodialysis session [47], and a weakened response of $CD4^{+}$ T cells to mitogen-mediated stimulation, have been revealed [48].

All these conditions, characterized by a loss of telomere length, reduced expression of activation antigens, and impaired proliferative capacity, could be related to a stress-induced premature senescence (SIPS) process, involving changes in the function and morphology of cells in response to the chronic inflammatory process [49].

$CD4^+$ T lymphocytes of HD patients are characterized by impaired proliferation parameters, such as a reduced number of cell divisions, a longer period required by these cells to enter the first (G1) phase of the first cell cycle, and a decreased percentage of cells able to divide [48].

Adaptive immune response dysregulation in HD patients also involves B lymphocytes. As for T cells, an increase in high differentiated forms and a reduction in naïve cells has been described [50].

One of the possible explanations could be found in the increased levels of soluble CD40 in patients undergoing hemodialysis. CD40 and its ligand (CD40L) regulate several cellular functions, including T- and B-cell activation, but their interaction is antagonized by the soluble form of CD40 [51].

4. Inflammation and Oxidative Stress

HD patients are affected by an inflammatory state with multifactorial pathogenesis, resulting in increased morbidity and mortality [52].

Inflammation is due to HD-related factors, such as dialysate quality, membrane compatibility, dialytic age, and vascular access, by oxidative stress, infections, and patient-related factors (comorbidities) [5].

Oxidative stress results from a loss of balance between pro-oxidant factors and antioxidant mechanisms. In HD patients, higher plasmatic levels of pro-inflammatory cytokines, such as tumor necrosis factor α (TNFα) and interleukin 6 (IL-6), have been reported, and intracellular levels of reactive oxygen species (ROS) are also increased in this patient population [53][54].

Similar results were obtained in the HD children population, whose IL-6 levels were significantly higher when compared to subjects affected by stage 5 CKD and healthy children. Moreover, IL-6 levels rose with increased time of dialysis [55].

Plasma levels of endothelin-1 (ET-1), a potent coronary vasoconstrictor, are also increased and they are associated with adverse clinical events in HD patients. ET-1, acting as a mediator for leukocyte recruitment, induces the expression of leukocyte adhesion molecules and the synthesis of inflammatory mediators, enhancing neutrophil adhesion to endothelial cells [56].

In a recent study, Hirayama evaluated the effects of hemodialysis with high-flux polysulfone membranes on multiple ROS using electron spin resonance-based methods. They concluded that ROS scavenging activities deteriorate after a single HD session, suggesting an uncontrolled production of these radicals during HD [57].

This “pro-oxidant” environment results in the formation of oxidized lipids or advanced oxidation protein products (AOPPs) and the expression of pro-inflammatory cytokines and recruitment of pro-inflammatory cells mainly through Nuclear Factor Kappa B (NF-κB) stimulation [58].

The presence of bacterial DNA in the dialysate can induce C-reactive protein (CRP) and IL6 production, further increasing oxidative stress. In HD patients, a decreased intracellular pH value, due to a lower concentration of pre-dialysis plasma bicarbonate, contributes to the creation of a pro-oxidative environment [59].

Many other pro-oxidative factors, such as anemia and iron administration, should be taken into account. On the other hand, chronic kidney disease is characterized by a progressive impairment of the antioxidant systems [60].

Vascular access also plays a role in inducing HD patients’ inflammatory state. Previous studies have reported an increased mortality ratio in patients with central venous catheters compared to those with native AV fistula, due to the worst dialysis quality, increased infection incidence, and inflammatory state [61][62].

In a recent study, the researchers compared inflammation and micro-inflammation parameters in patients with AV fistula and with central venous catheters: the latter showed a higher degree of inflammation independently from catheter infections, while the vascular access was not associated with higher mortality rates [63]. Finally, many studies have reported a positive correlation between oxidative stress and mortality in HD patients [64].

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