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# Leukocyte Function in High-Flux Hemodialysis

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## 1. Introduction

Patients with chronic kidney disease and patients on renal replacement therapy, such as hemodialysis and peritoneal dialysis, have an increased susceptibility to infectious diseases compared with healthy subjects (Sarnak & Jaber 2000; Allon et al. 2003). Infection is also the second most common cause of morbidity and mortality in patients with end-stage renal disease (Bloembergen & Port 1996; Powe et al. 1999; Graff et al. 2002).

One contributing factor could be the chronic inflammatory activation seen in patients with chronic kidney disease and patients on dialysis, which causes a refractoriness of leukocytes when confronted with invading microorganisms.

### 1.1 The innate and adaptive immune responses

The immune system is designed to defend us from invading microorganisms, such as viruses and bacteria. The first response is called the innate immune response, mostly dependent on recruitment and activation of neutrophils (Parkin & Cohen 2001). Complement activation occurs on the bacterial cell surface, triggering a cascade of proteolytic reactions that are specific in so far as they act on microbial surfaces but not on host cells. Neutrophils have receptors both for common bacterial constituents and for complement. Neutrophils become activated through complement (C3b and C5a) but can also get activated directly by bacterial peptides, such as lipopolysaccharide, lipoteichoic acid, mannans and fMLP (N-formylmethionyl leucyl phenylalanine) (Parkin & Cohen 2001).

Activation of neutrophils occurs in several steps, comprising both priming and further activation, and is necessary for neutrophils to perform their specific actions at the inflammatory sites: phagocytosis and release of inflammatory mediators (Swain et al. 2002). Neutrophils are effector cells of great importance in the innate immune system. An impaired neutrophil function leads to several dysfunctions in the defense against invading microorganisms. Neutrophils have previously been regarded as wholly differentiated and static cells whose function is based on preformed receptors and soluble factors, and solely part of the innate immune system. This idea has been challenged by publications that show a high gene transcriptional activity following both activation and extravasation (Theilgaard-Monch et al. 2006). The transcriptional activation occurs at the inflammatory site and engages genes involved in multiple neutrophil functions, such as production of reactive oxygen species, hydrogen peroxide, cytokines and chemokines (Theilgaard-Monch et al. 2004; Coldren et al. 2006). Neutrophils direct both innate and adaptive immune responses,

by interacting with immune modulating cells (Cohen et al. 2001; Yamashiro et al. 2001; Cohen et al. 2003; Theilgaard-Monch et al. 2004). Neutrophil cytokine and chemokine production can be an important link between the innate and the adaptive immune responses. Cytokine-activated neutrophils produce and release multiple proinflammatory cytokines and chemokines, including IL-1, IL-8, monocyte chemoattractant protein-1 (MCP-1/CCL2) and macrophage inflammatory protein-1 $\alpha$  and 1 $\beta$  (MIP-1 $\alpha$ /MIP-1 $\beta$ ). MCP-1 and MIP-1 $\alpha$  act as chemotactic and activating signals for mononuclear cells, especially monocytes, and for mobilization of other cell surface molecules involved in the adaptive immune response (Yamashiro et al. 2001; Kobayashi 2008).

Chemokines attract neutrophils and monocytes from the circulation to the inflammatory/infectious site by first making the endothelium more adhesive to the circulating cells and then through a chemokine gradient through the tissue leading the way to the site of inflammation (Janeway & Travers 2005). Circulating monocytes that extravasate and get activated rapidly develop into mature macrophages with the principal function of phagocytosing microorganisms (Janeway & Travers 2005).

### 1.2 Adhesion molecules

The recruitment and accumulation of monocytes and neutrophils at inflammatory sites is an essential step in the defense against invading microorganisms. The process of extravasation, when leukocytes slip through the endothelial cells and basement membrane into the underlying interstitium and further to the inflammatory site requires the expression of adhesion molecules on the endothelium. This serves to initiate leukocyte adherence by interaction between adhesion molecules on leukocytes and vascular endothelial cells (Johnson-Leger et al. 2000; van Buul & Hordijk 2004). The main families of adhesion molecules are the intercellular adhesion molecules (ICAMs); integrins, selectins and cadherins (calcium-dependent adherins) (Parkin & Cohen 2001).

The selectins, P-selectin (PADGEM, CD62P) and E-selectin (ELAM-1, CD62E), are membrane glycoproteins with a lectin-like domain that binds transiently to oligosaccharide molecules on passing leukocytes after cytokine-mediated activation of the endothelial cells. CD62L is present on circulating leukocytes (Janeway & Travers 2005). Selectin binding leads to tethering, which allows leukocytes to search the endothelium for the presence of activating factors. In a second step, leukocytes bind firmly to the endothelium, followed by the process of diapedesis (Albelda et al. 1994). The tighter adhesion is mediated by  $\beta_2$ -integrins CD11a/CD18 (LFA-1) and CD11b (Mac-1 or CR3) expressed on leukocytes after a chemokine-mediated conformational change in the integrins.  $\beta_2$ -integrins bind to intercellular adhesion molecules (ICAM-2 on resting endothelium and ICAM-1 on activated endothelium) (Adams & Shaw 1994; Gonzalez-Amaro & Sanchez-Madrid 1999; Janeway & Travers 2005). The  $\beta_1$ - integrin very late antigen-4 (VLA-4) is present principally on mononuclear cells, mediating monocyte transmigration by binding to vascular adhesion molecules (VCAM-1) on activated endothelial cells (Chuluyan & Issekutz 1993).

### 1.3 Leukocyte adhesion and extravasation

Leukocyte adhesion is made possible by the action of chemokines: small, structurally related molecules that interact with G-protein-coupled receptors. They perform activation of integrins in order to confer tight adhesion between leukocytes and endothelial cells, and promote the migration of adherent leukocytes across the endothelium and through the extracellular matrix (Adams & Shaw 1994). Chemokines are small molecules, divided into

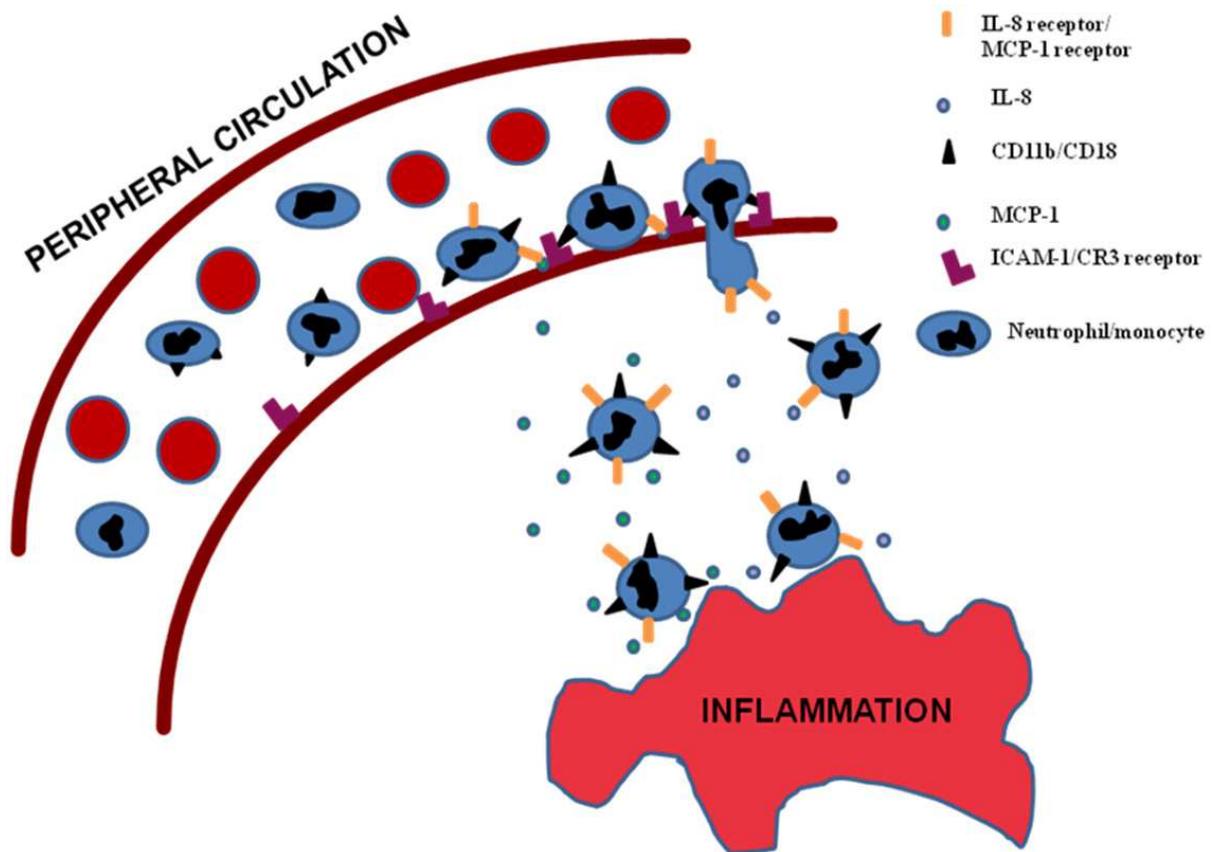


Fig. 1. Leukocyte adhesion to the endothelium, subsequent extravasation and transmigration through a chemotactic gradient in the interstitium towards a site of inflammation.

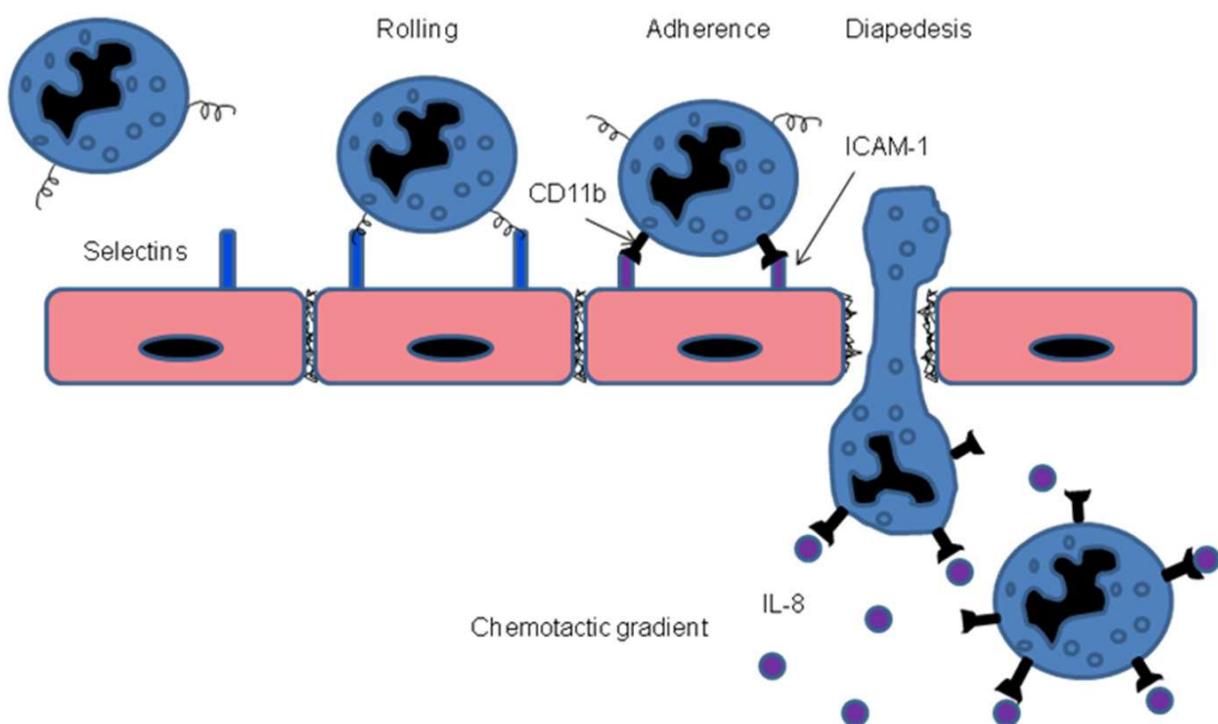


Fig. 2. Neutrophil adhesion, extravasation and transmigration.

CXC ( $\alpha$ -chemokines) and CC ( $\beta$ -chemokines) depending on the positions of two cysteine residues (C) relative to other amino acids (X) (Charo & Ransohoff 2006). Chemokines are produced by inflammatory cells after stimulation with proinflammatory cytokines or bacterial products, and there are both soluble and membrane-bound chemokines, with various functions (Parkin & Cohen 2001). Some of the chemokines and cytokines analyzed in our study, and their respective functions, are listed in Table 1 and Table 2.

Leukocyte binding to endothelial cells induces production of signaling molecules in the endothelial cells and activation of NADPH oxidase in leukocytes. NADPH oxidase promotes production of reactive oxygen species that break down the barrier to leukocyte passage between the endothelial cells and through the basement membrane (van Buul & Hordijk 2004). PECAM-1 plays an important role in transendothelial migration of leukocytes, by inducing phosphorylation of tyrosine in junctional proteins which leads to loss of cell-cell adhesion (van Buul & Hordijk 2004).

When neutrophils extravasate, they produce enzymes (i.e. elastase and other proteases such as matrix metalloproteinase-9, MMP-9) that break down extracellular matrix proteins and in this way promote leukocyte migration through the interstitium (Hermant et al. 2003).

The final step of the transmigration is the chemokine concentration gradient, which guides leukocytes through the interstitium and towards the inflammatory site. CXCL8 (IL-8) and CCL2 (MCP-1) act as chemotactic factors for neutrophils and monocytes, respectively. They bind to proteoglycans in the extracellular matrix and to similar molecules on the leukocytes (Janeway & Travers 2005).

Neutrophils and monocytes in blood normally express a low amount of CD11b on their surface. Following chemokine-mediated activation of the cells, CD11b is mobilized on the cell surface and the molecules are activated in order to display their functions (Adams & Shaw 1994; Albelda et al. 1994; Adams & Lloyd 1997; Gonzalez-Amaro & Sanchez-Madrid 1999). Mobilization of CD11b is important in the process of leukocyte transmigration, phagocytosis and complement activation as a response to inflammation/infection (Bainton et al. 1987; Borregaard et al. 1987; Miller et al. 1987).

#### **1.4 Respiratory burst**

The enzyme complex NADPH oxidase promotes the generation of reactive oxygen species (e.g. superoxide anions) in leukocytes, in a process referred to as the respiratory burst. Respiratory burst is a central mechanism for the leukocyte function of phagocytosis and elimination of invading microorganisms (Babior 1999). Superoxide anions are converted to hydrogen peroxide in the phagolysosome by the action of superoxide dismutase. In the absence of superoxide dismutase, superoxide anions can form the highly aggressive oxidative substance peroxynitrite (by reacting with nitric oxide) and hydroxyl radicals (Dahlgren & Karlsson 1999; Johnson & Giulivi 2005).

#### **1.5 Apoptosis**

In early apoptosis, there is a reformation of the cell membrane, with phosphatidyl serine (PS) translocated from the inner surface to the outer leaflet of the cell membrane. Fluorescein-conjugated Annexin V binds to PS with high affinity and identifies early apoptotic cells. Propidium iodide enters through damaged cell membranes after loss of membrane integrity and stains DNA, identifying late stages of apoptosis and secondary necrotic cells. PS is identified by phagocytes in the extracellular milieu in order to remove the dying cells by phagocytosis.

| Chemokines  | Receptor     | Functions                          | References   |   |
|---|--------------|------------------------------------|--|---|
| <b>IL-8 (interleukin-8)</b>   | <b>CXCL8</b> | IL-8 receptor $\alpha$ and $\beta$ | Induces neutrophil CD11b/CD18 up-regulation, transmigration and activation. Stimulates the release of MMP-9/NGAL. Binding to the receptor causes a reconfiguration of integrins, which allows neutrophils to bind to the endothelial cells.  | (Zeilhofer & Schorr 2000; Drost & MacNee 2002; Adams & Lloyd 1997)  |
| <b>MCP-1 (monocyte chemotactic protein-1)</b>   | <b>CCL2</b>  | CCR2                               | Chemotactic factor and activator of monocytes and macrophages. Produced by many different inflammatory cells. Induces up-regulation of CD11b/CD18 and facilitates monocyte adhesion to endothelial cells. Associated with chronic and acute inflammation, as well as with the acute coronary syndrome. | (Adams & Lloyd 1997; Jiang et al. 1992; Jiang et al. 1994; Ikeda et al. 2002; de Lemos et al. 2003; Pawlak et al. 2004) |
| <b>MIP-1<math>\alpha</math> (macrophage inflammatory protein-1<math>\alpha</math>)</b>                    | <b>CCL3</b>  | CCR1 and CCR5                      | Released from monocytes after triggering of CD11b/CD18. Promotes the recruitment of inflammatory cells. Chemotactic factor for both monocytes and neutrophils. Activates macrophages by up-regulation of CD11b/CD18.   | (Rezzonico et al. 2001; Adams & Lloyd 1997; Ramos et al. 2005; Weber et al. 2000)                                       |
| <b>MMP-9/NGAL (matrix metalloproteinase-9 in complex with neutrophil gelatinase-associated lipocalin)</b> |              |                                    | MMP-9 and proteolytic enzymes degrade the extracellular matrix and promote leukocyte transmigration. Marker of neutrophil activation and release of reactive oxygen species. Regulates chemokine activity by cleaving of chemokines and cytokines.   | (Yan et al. 2001; Alberts et al. 2002; Brogden & Guthmiller 2002; Van Den Steen et al. 2003)                            |

Table 1. Chemokines analyzed in our study and their respective functions.

| Cytokines  | Functions   | References  |
|--|---|---|
| TNF- $\alpha$ (tumor necrosis factor- $\alpha$ ) | Produced by macrophages and monocytes in acute and chronic inflammation. Pro-apoptotic. Up-regulates adhesion molecules on endothelial cells. Chemotactic factor for monocytes and primes cells for phagocytosis. Increases vascular permeability and vasodilatation, promotes intravascular coagulation, and causes the septic syndrome and failure of vital organs. | (Idriss & Naismith 2000; Janeway & Travers 2005)  |
| IL-6   | Inflammatory marker, important role in acute inflammation and production of acute phase proteins from the liver.  | (Adams & Lloyd 1997; Pupim et al. 2004; Pecoits-Filho et al. 2002; Panichi et al. 2004) |

Table 2. Cytokines analyzed in our study and their respective functions.

### 1.6 Leukocyte dysfunction in chronic kidney disease

There is a complex state of leukocyte dysfunction in chronic kidney disease patients. The most important contributing factors are metabolic and functional abnormalities of leukocytes caused by the accumulation of uremic toxins that inhibit leukocyte function. In patients on dialysis, another factor influencing leukocyte function is bioincompatibility of the dialysis procedure resulting in a dysfunctional inflammatory activation (Lundberg et al. 1994; Vanholder et al. 1996; Cohen et al. 2001; Horl 2001; Cohen et al. 2003; Cheung et al. 2008).

In chronic kidney disease, there is an altered leukocyte adherence to endothelial cells, decreased activation of inflammatory cells, impaired phagocytosis and chemotaxis and an altered generation of reactive oxygen species and hydrogen peroxide (Gibbons et al. 1990; Haag-Weber & Horl 1996b; Horl 2001). Chemokine and cytokine dysregulation in chronic kidney disease gives rise to a dysfunctional activation of the immune system (Descamps-Latscha 1993; Malaponte et al. 2007; Carrero et al. 2008).

The comorbidity of the patient, such as a state of malnutrition and other chronic diseases, also plays an important role in this non-physiological inflammatory activity (Cohen et al. 1997; Stenvinkel et al. 2000; Pecoits-Filho et al. 2002). A study from our group has demonstrated that neutrophils and monocytes from patients with advanced chronic kidney disease have an impaired expression of CD11b in the interstitium compared with the corresponding cells from healthy subjects (Dadfar et al. 2004b, 2004a). The same result has been demonstrated for patients on peritoneal dialysis (Dadfar et al. 2004c).

#### 1.6.1 Uremic toxins with effects on leukocytes

There are several uremic toxins that inhibit neutrophil functions, e.g. guanidino compounds, granulocyte inhibitory protein I and II, degranulation inhibitory protein I and II (identified

as angiogenin and complement factor D),  $\kappa$ - and  $\lambda$ -light chains and chemotaxis inhibitory protein (Vanholder et al. 1994b; Haag-Weber & Horl 1996a; Kaysen 2001; Horl 2002; Kaysen & Kumar 2003; Cohen & Horl 2009b, 2009a).

### 1.6.2 Patients on hemodialysis

Historically, dialysis has contributed to saving many lives over the years. Without dialysis, a uremic patient unavoidably goes towards death. However, the life quality of patients on dialysis still has to be improved to develop an optimal treatment. In spite of the process in the last years to strive towards more biocompatible materials and methods, including high-flux dialysis treatment, patients on hemodialysis still display a high morbidity and mortality in infections (Bloembergen & Port 1996; Powe et al. 1999; Graff et al. 2002). Neutrophil dysfunction in dialysis patients is manifested by reduced chemotaxis, adherence, respiratory burst and glucose consumption in response to an inflammatory stimulus (Vanholder et al. 1993b; Vanholder et al. 1993a).

The dysfunctional state of inflammatory activation seen in dialysis patients could be caused by several different factors (Cheung et al. 1989; Haag-Weber et al. 1991; Descamps-Latscha 1993; Schindler et al. 2001; Carracedo et al. 2002; Horl 2002; Raj et al. 2002; Kosch et al. 2003; Koller et al. 2004). Fragments of bacterial products can be present in small amounts in the dialysate and enter the circulation by diffusion through the dialysis membrane (Horl 2002). These bacterial fragments activate proinflammatory cytokines such as IL-6, TNF- $\alpha$  and IL-1. There is also direct activation of complement factors and of leukocytes by contact with the dialysis membrane. Another aspect is the removal of cytokines and other inflammatory markers (lipopolysaccharide fragments, granulocyte inhibitory proteins 1 and 2, IL-1, TNF- $\alpha$ ) and complement factors (C3a, C5a) by the hemodialysis procedure as well as the adsorption of substances to the hydrophobic high-flux membrane (e.g. factor D) (Clark et al. 1999; Schindler et al. 2006). Dialysis can reduce leukocyte-endothelial interactions and impair transmigration (Thylen et al. 1997). In patients on hemodialysis with cuprophane or polysulfone membranes, a significantly higher serum level of MCP-1 is seen compared with healthy subjects both before and after the hemodialysis session, independent of the membrane used (Jacobson et al. 2000; Thylen et al. 2000).

Biocompatibility of dialysis membranes probably plays an important role in determining leukocyte function in patients on hemodialysis (Himmelfarb et al. 1991; Himmelfarb et al. 1993; Hernandez et al. 2004; Schindler et al. 2006). High serum levels of cytokines and chemokines have been observed in patients on hemodialysis with modified cellulose membranes (Descamps-Latscha 1993; Pawlak et al. 2004; Muniz-Junqueira et al. 2005). High-flux hemodialysis causes lower levels of IL-6 and IL-1 $\beta$  than low-flux hemodialysis or dialysis with cuprophane membranes (Schindler et al. 2006). Our group has previously demonstrated that neutrophils and monocytes recruited to an induced interstitial inflammatory site in patients treated with low-flux bioincompatible hemodialysis have an impaired capacity of mobilizing CD11b in response to the induced inflammation, compared with the corresponding cells from healthy subjects (Thylen et al. 2000; Jacobson et al. 2002).

Chronic kidney disease is a state that induces apoptosis, but this is normalized with continuous and high-flux hemodialysis modalities (D'Intini et al. 2004; Bordoni et al. 2006). This is in accordance with studies showing that dialysis membrane characteristics affect leukocyte cell apoptosis (Martin-Malo et al. 2000; Sela et al. 2005; Sardenberg et al. 2006). The degree of spontaneous apoptosis of leukocytes is higher when bioincompatible membranes

are used for hemodialysis, than when biocompatible membranes are used (Martin-Malo et al. 2000). This higher apoptotic activity in leukocytes is probably due to an antibody-dependent activation of the complement system caused by the material or structure of the dialysis filters. It has been shown that heat-inactivation of complement components results in significantly lower apoptosis rates and that bioincompatible membranes cause a higher degree of apoptosis than biocompatible membranes (Koller et al. 2004).

The dialysis membrane permeability and flux are also of importance in determining the acute and chronic effects of hemodialysis on the inflammatory system. High-flux polysulfone dialysis, as opposed to low-flux polysulfone and cuprophane treatment, has been shown to improve the transmigration of circulating neutrophils (Moshfegh et al. 2002). High-flux dialysis membranes decrease the levels of the two degranulation inhibitory proteins (angiogenin and complement factor D), which could contribute to the maintained respiratory burst and phagocytic capacity seen in patients on high-flux hemodialysis (Horl 2002). There are several molecules, mainly middle-sized molecules, that are cleared to a greater extent by convective therapies, such as hemofiltration or hemodiafiltration (Clark et al. 1999). Postdilution hemofiltration was the first convective therapy used, and this method provides a high clearance of middle- and large-sized molecules but a lower clearance of small molecules. Through predilution hemofiltration, with on-line ultrafiltration, the clearance of small molecules increased substantially. In hemodiafiltration, convection is combined with diffusion, and with this mechanism the clearance of small-, middle- and large-sized molecules can be achieved to more or less the same extent (Ledebø 1998).

A number of previous studies have suggested that the type of dialysis membrane (low-flux or high-flux) is associated with differences in long-term outcome of patients undergoing hemodialysis, both in terms of morbidity and mortality (Hornberger et al. 1992; Woods & Nandakumar 2000; Cheung et al. 2003; Locatelli 2003; Chauveau et al. 2005; Canaud et al. 2006). However, the results have been conflictive regarding different outcomes.

The HEMO study, which was the first large randomized clinical trial on patient outcome depending on membrane permeability, failed to show any difference in all-cause mortality between high-flux and low-flux hemodialysis, except in some subgroups of patients (Eknoyan et al. 2002; Cheung et al. 2003; Rocco et al. 2005). Some criticism regarding the generalizability of the results from the HEMO study has been raised (Locatelli 2003). Important results from the HEMO study indicate that middle-sized molecules, e.g. parathyroid hormone,  $\beta_2$ -microglobulin, advanced glycosylation end products, granulocyte inhibitory proteins, advanced lipoxidation end products, advanced oxidation protein products and leptin (Horl 2002) are associated with systemic toxicity and that their accumulation predisposes dialysis patients to severe infections. An increased clearance of these molecules, e.g.  $\beta_2$ -microglobulin, by high-flux hemodialysis is associated with a lower mortality by infectious disease (Cheung et al. 2008). An increased removal of middle-sized molecules could also have positive effects of the cardiovascular system (Vanholder et al. 2001; Vanholder et al. 2008).

In a Cochrane database review by Rabindranath et al. in 2006, the authors were unable to demonstrate a significant advantage with convective therapies over low-flux hemodialysis with regard to clinical outcomes such as mortality, dialysis-related hypotension and hospitalization (Rabindranath et al. 2006).

The DOPPS study (Dialysis Outcomes and Practice Patterns Study) revealed that patients on high-flux hemodiafiltration had a 35 % lower mortality rate than patients on low-flux hemodialysis (Canaud et al. 2006; Canaud et al. 2008).

The MPO-study (Membrane Permeability Outcome) was a European randomized clinical trial on the effect of high-flux treatment in a large hemodialysis population. It was a prospective study which analyzed the long-term effects of membrane permeability on clinical outcomes such as mortality, morbidity, vascular access survival and nutritional status. The authors of the MPO-study did not find any significant survival benefit overall by high-flux hemodialysis versus low-flux hemodialysis. However, for some dialysis populations with low serum albumin and for patients with diabetes mellitus, a significantly lower mortality rate was observed using high-flux hemodialysis as compared with low-flux hemodialysis (Locatelli et al. 2009).

## 2. Leukocyte functional studies in patients on high-flux biocompatible hemodialysis

Our research group has described functions of *in vivo* extravasated monocytes and neutrophils from patients on high-flux hemodialysis/hemodiafiltration and healthy subjects (Olsson et al. 2007). The objective was to study leukocyte function and specifically, to study the up-regulation of CD11b, production of hydrogen peroxide and apoptosis of *in vivo* extravasated monocytes and neutrophils at the site of an induced interstitial inflammation in patients on high-flux hemodialysis/hemodiafiltration, compared with healthy subjects. Our group has also described the concentrations of important inflammatory mediators for neutrophils (IL-8 and MMP-9/NGAL) and monocytes (MCP-1 and MIP-1 $\alpha$ ) in the peripheral circulation and at sites of interstitial inflammation in patients on high-flux hemodialysis/hemodiafiltration, compared with healthy subjects (Olsson et al. 2009).

### 2.1 Methods for leukocyte functional studies

The method used was the skin chamber technique, which is well documented and has been used by a number of investigators to study transmigration and recruitment of leukocytes at the inflammatory site (Scheja & Forsgren 1985; Follin 1999; Thylen et al. 2000; Jacobson et al. 2002; Theilgaard-Monch et al. 2004; Dadfar et al. 2007; Paulsson et al. 2007). With the skin chamber technique, we measured leukocyte functions at time 0 (before the high-flux hemodialysis/hemodiafiltration session) and after 10 hours (within which time the high-flux hemodialysis/hemodiafiltration treatment was performed). The terms intermediate and intense inflammation were used to designate the blister stimulated with buffer and with autologous serum, respectively.

Leukocytes were measured with flow cytometry or FACS (fluorescence-activated cell sorting) a method in which cells are scanned by a laser and recognized as different cell populations through their light-scattering properties. Different leukocyte populations (lymphocytes, monocytes and neutrophils) can thus be counted and expressed as a percentage of the total leukocyte population. Mean fluorescence intensity (MFI) values for the different analyses of cell functions (CD11b expression, hydrogen peroxide formation and apoptosis) can also be measured and quantified.

The CD11b expression on leukocytes, both unstimulated and after stimulation with fMLP, was studied through immunostaining. Analysis of leukocyte hydrogen peroxide formation, after stimulation with fMLP or PMA, was performed using the 2', 7'-dichlorofluorescein diacetate (DCFH-DA) method. We also stained leukocytes with Annexin V and propidium iodide (PI) to identify cells that were in an early or late apoptotic state.

Chemokines in skin blister fluids and serum from the peripheral circulation were analyzed with commercially available immunoassays (Quantikine®, R&D Systems Inc. Minneapolis, MN, USA). All immunoassays were used in accordance with the manufacturer's instructions. For further details, please review publications (Olsson et al. 2007 & Olsson et al. 2009).

## 2.2 Results

### 2.2.1 CD11b

There was a similar expression of CD11b on monocytes and neutrophils in patients on high-flux hemodialysis/hemodiafiltration and healthy subjects, both in the peripheral circulation and at the three sites of interstitial inflammation. *In vitro* activation with fMLP induced a significant increase in the expression of CD11b on monocytes and neutrophils in the peripheral circulation and at the sites of interstitial inflammation, both in patients on high-flux hemodialysis/hemodiafiltration and healthy subjects.

The preserved capacity of both monocytes and neutrophils to express CD11b at the sites of interstitial inflammation in patients on high-flux hemodialysis/hemodiafiltration, as shown by our findings, may have important biological consequences in terms of an adequate performance of leukocyte functions in which the CD11b molecule plays a key role (Thylen et al. 1997; Moshfegh et al. 2002). Extravasated neutrophils and monocytes from patients on high-flux hemodialysis/hemodiafiltration showed a maintained response to fMLP as a second inflammatory stimulus after extravasation.

The mechanism behind this preserved leukocyte function in patients on high-flux biocompatible hemodialysis/hemodiafiltration could be the removal of small and middle-sized leukocyte inhibitory molecules by high-flux hemodialysis/hemodiafiltration (Vanholder et al. 1994a), but membrane compatibility could also play an important role.

### 2.2.2 Hydrogen peroxide formation

Results for hydrogen peroxide production in neutrophils and monocytes are displayed in Figures 3-6. The findings indicate the presence of a dose-response phenomenon in terms of leukocyte function at the site of interstitial inflammation in patients on high-flux hemodialysis/hemodiafiltration, which could be due to leukocyte refractoriness when encountered with an intense inflammatory stimulus. Refractoriness of leukocytes could be caused by previous priming, giving rise to an impaired response to a second activating stimulus.

### 2.2.3 Apoptosis and cell counts

There was no significant difference in the total number of leukocytes at the inflammatory sites between patients on high-flux hemodialysis/hemodiafiltration and healthy subjects.

In our study of leukocytes from patients on high-flux hemodialysis/hemodiafiltration, leukocytes were studied at their actual site of action, namely after *in vivo* extravasation. This is advantageous, since leukocyte function in patients with chronic kidney disease or on dialysis has previously almost exclusively been studied on cells collected from the peripheral circulation.

In both the neutrophil and monocyte populations, we observed no significant differences in the percentage of apoptotic cells (Annexin V+ and Annexin V+ PI+) in the peripheral circulation or at the sites of interstitial inflammation between patients on high-flux hemodialysis/hemodiafiltration and healthy subjects.

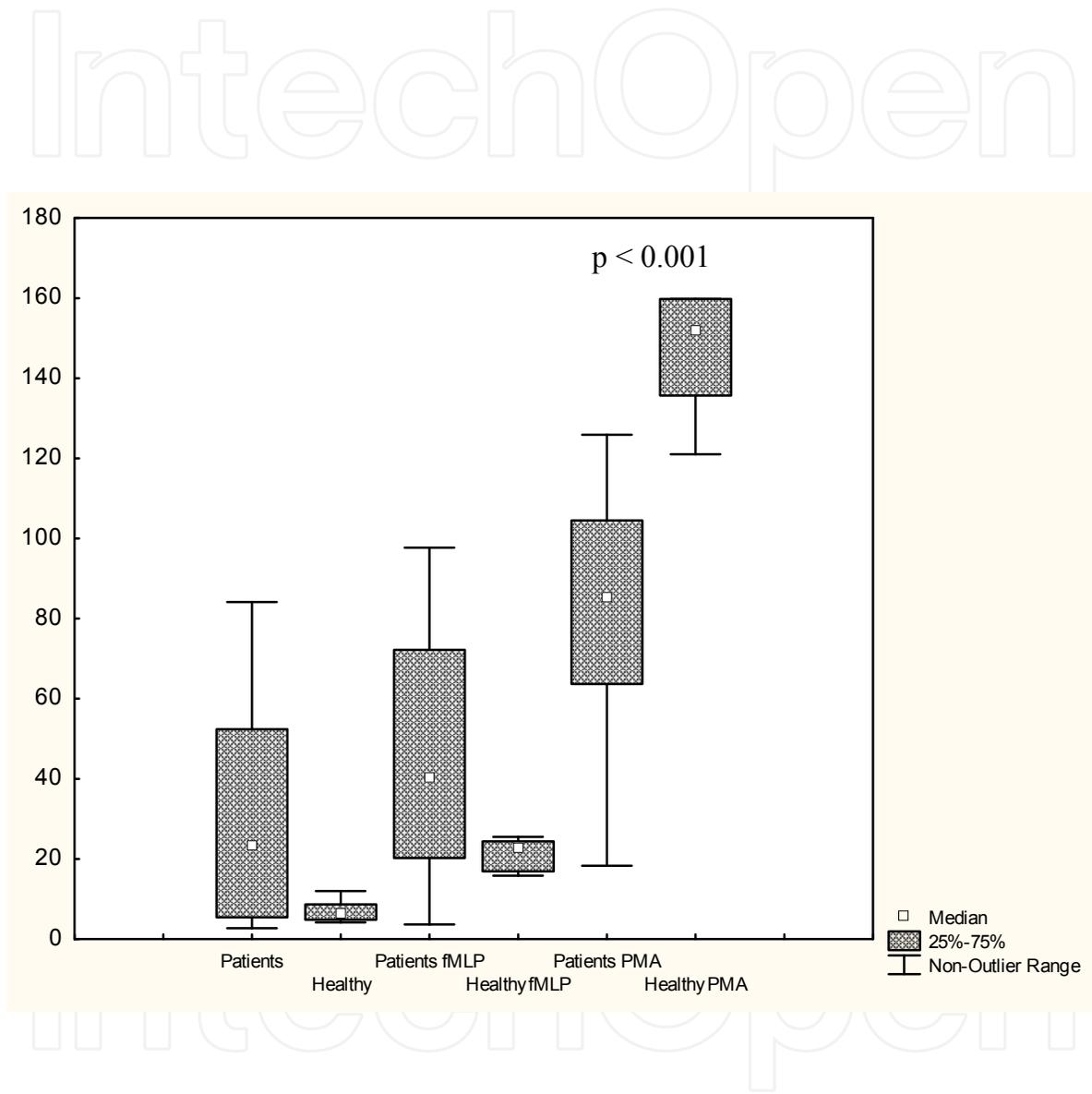


Fig. 3. Respiratory burst in neutrophils at the site of an intermediate interstitial inflammation expressed as mean fluorescence intensity (MFI). P is indicated where a significant difference is present.

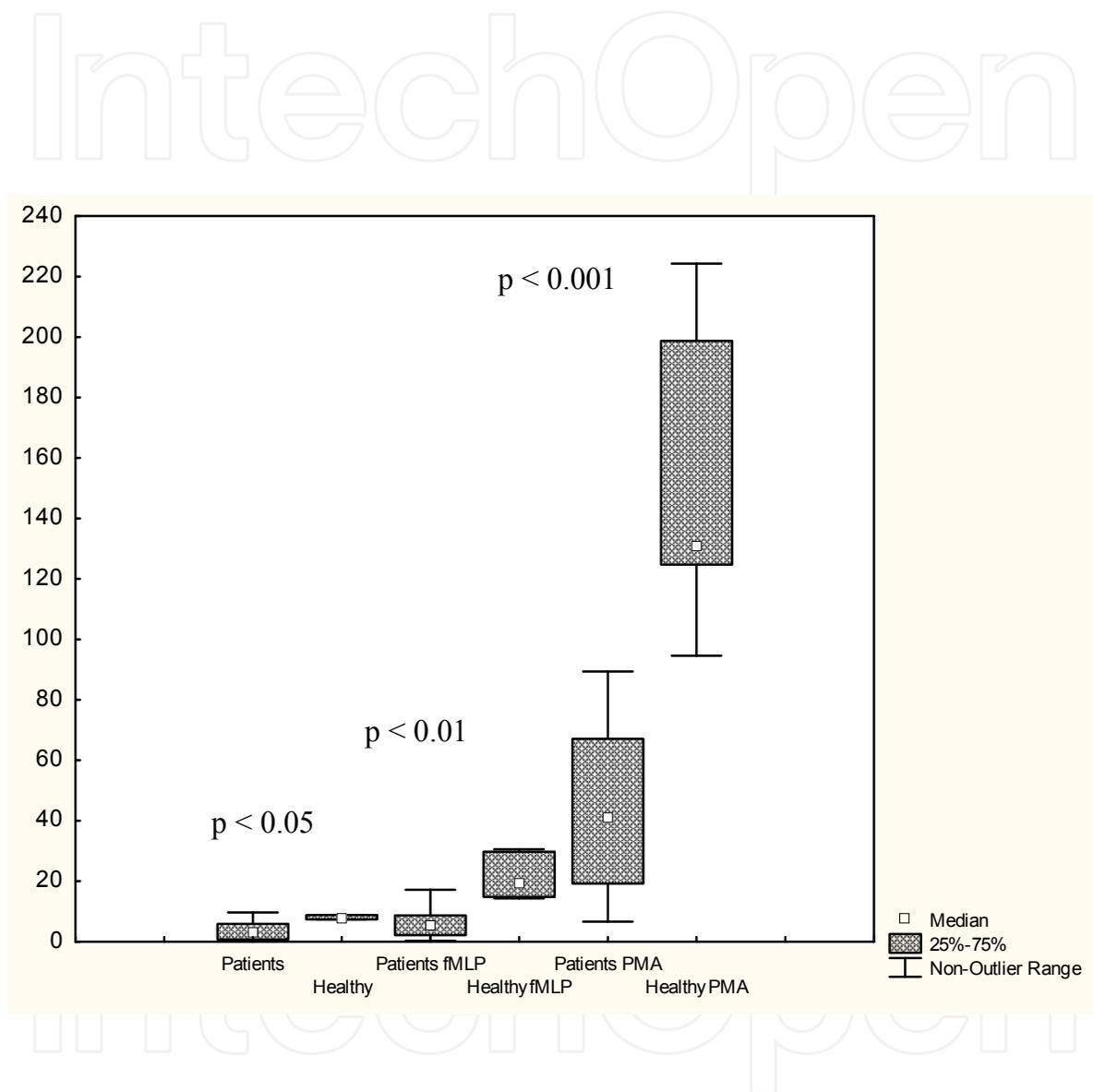


Fig. 4. Respiratory burst (MFI) in neutrophils at the site of intense interstitial inflammation.

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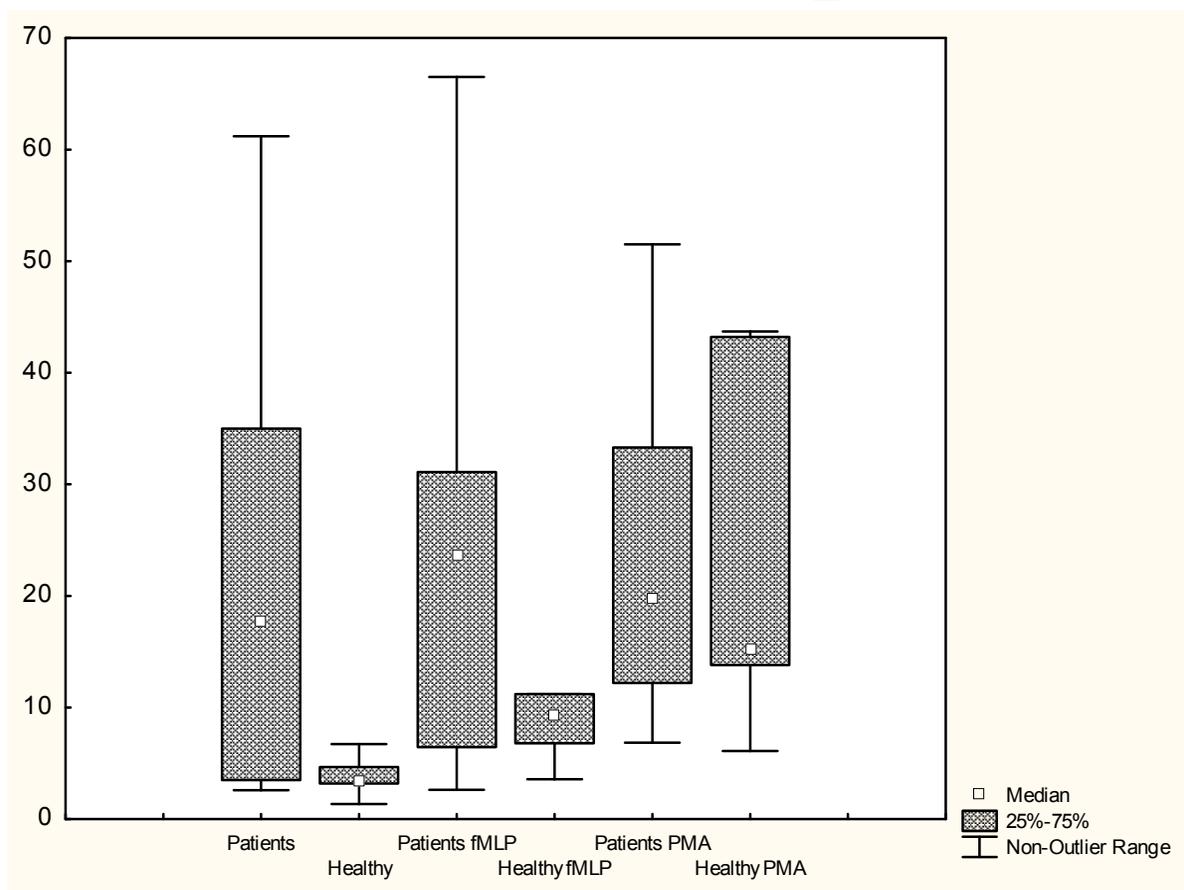


Fig. 5. Respiratory burst (MFI) in monocytes at the site of intermediate interstitial inflammation. No significant difference for any comparison.

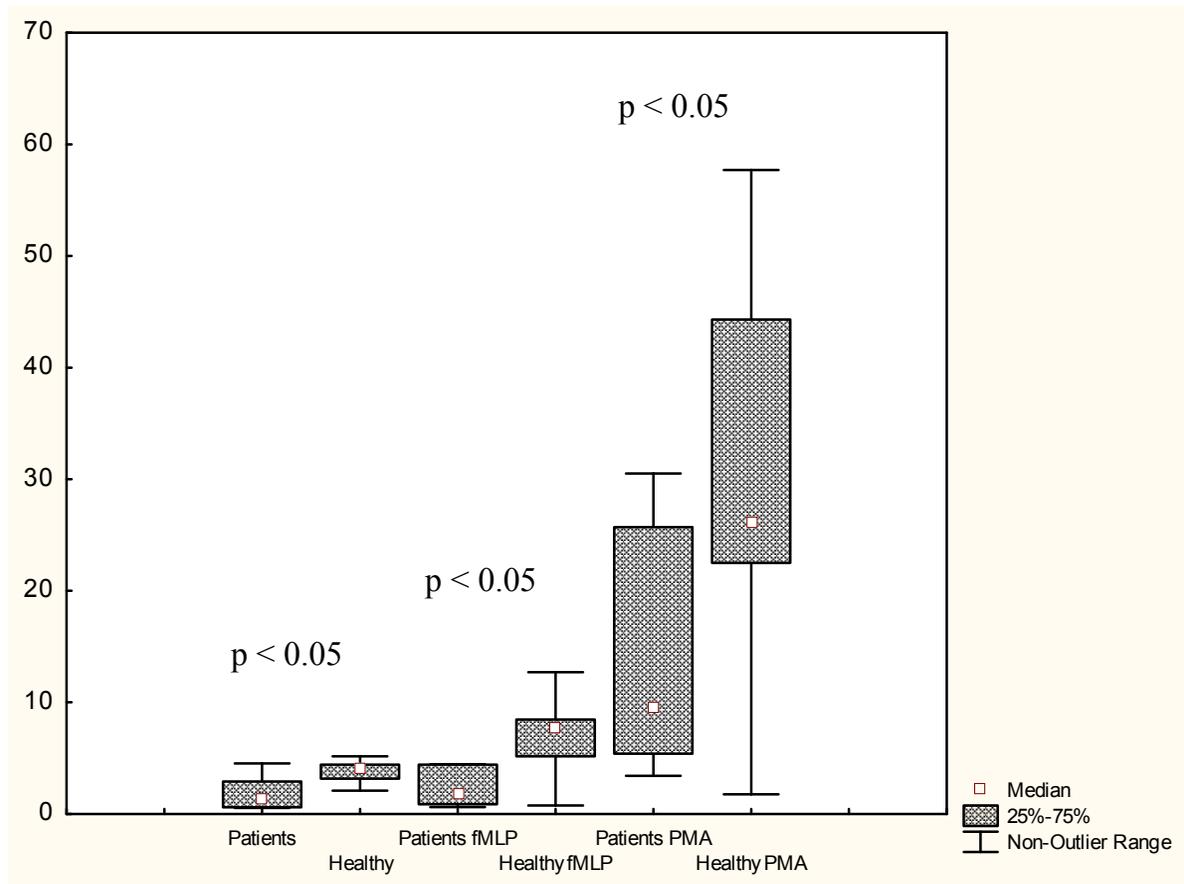


Fig. 6. Respiratory burst (MFI) in monocytes at the site of intense interstitial inflammation.

#### 2.2.4 Concentrations of chemokines

Patients on high-flux hemodialysis/hemodiafiltration had significantly higher concentrations of MCP-1, MIP-1 $\alpha$ , IL-6, IL-8, TNF- $\alpha$  and high-sensitivity CRP (hsCRP) in the peripheral circulation, prior to dialysis treatment, compared with healthy subjects (Olsson et al. 2009). MMP-9/NGAL serum concentration was similar in patients on high-flux hemodialysis/hemodiafiltration and healthy subjects (Olsson et al. 2009). Significantly higher serum levels of  $\beta$ 2-microglobulin and serum amyloid A (SAA) were observed in patients on high-flux hemodialysis/hemodiafiltration, compared with healthy subjects. The serum concentrations of chemokines, hsCRP, SAA and oxidized LDL were not influenced by the high-flux hemodialysis/hemodiafiltration session, while the concentration of  $\beta$ 2-microglobulin was significantly reduced (unpublished data).

The concentrations of MIP-1 $\alpha$ , MMP-9/NGAL and IL-8 at the sites of intermediate and intense inflammation were similar in patients and healthy subjects, and the concentration of MCP-1 at the sites of intermediate and intense inflammation was significantly higher in patients on high-flux hemodialysis/hemodiafiltration, compared with healthy subjects (Olsson et al. 2009). At the site of intermediate inflammation, the concentration of IL-6 and TNF- $\alpha$  was significantly higher in patients compared with healthy subjects, reflecting a high inflammatory activity (unpublished data). There were no significant correlations between the concentrations of chemokines or the gradient between the concentration in the peripheral circulation and the interstitium, and the recruitment of neutrophils and monocytes and their expression of CD11b at the site of interstitial inflammation (unpublished data).

### 3. Conclusion

*In vivo* extravasated monocytes and neutrophils from patients on high-flux hemodialysis/hemodiafiltration have a preserved capacity to mobilize CD11b, compared with the corresponding cells from healthy subjects (Olsson et al. 2007). Furthermore, monocytes and neutrophils were able to respond to a second signal (fMLP) at the site of interstitial inflammation, indicating an adequate response to bacterial peptides (Olsson et al. 2007). After the most potent stimulation, both monocytes and neutrophils that had extravasated *in vivo* and been recruited to the site of intense inflammation showed a lower capacity to produce hydrogen peroxide in response to activation, compared with the corresponding cells from healthy individuals (Olsson et al. 2007). The apoptotic rates of neutrophils and monocytes were similar in patients and in healthy subjects (Olsson et al. 2007). Clearance of leukocytes from the site of infection via apoptosis is essential for the coordinated resolution of inflammation. The balance between pro-apoptotic and anti-apoptotic factors is necessary for the maintenance of an effective immune response without the harmful side effects of an excessive neutrophil activation.

The higher concentration of MCP-1 and equal concentration of IL-8, MMP-9/NGAL and MIP-1 $\alpha$  at the sites of intermediate and intense inflammation in patients on high-flux hemodialysis/hemodiafiltration (Olsson et al. 2009) could be of importance for the maintained capacity of leukocytes to extravasate and mobilize CD11b compared with healthy subjects (Olsson et al. 2007). These data contrast with our previous studies on patients with chronic kidney disease or patients on peritoneal dialysis, in which the concentrations of MCP-1 and IL-8 are significantly lower, coupled with an impaired capacity to up-regulate CD11b on neutrophils at sites of interstitial inflammation (Dadfar et al. 2004c; Dadfar et al. 2004b, 2004a).

The results of our study support a preserved neutrophil and monocyte function in terms of extravasation and activation at the inflammatory focus. One possible explanation for the preserved capacity of monocytes and neutrophils to express CD11b in response to an interstitial inflammation in patients on high-flux hemodialysis/hemodiafiltration may be that the cells extravasate into a milieu which contains equal or higher concentrations of factors involved in transmigration and CD11b expression (MCP-1, IL-8, MIP-1 $\alpha$  and MMP-9/NGAL) compared with healthy subjects. The maintained capacity to produce chemokines in the interstitium in patients on high-flux hemodialysis/hemodiafiltration may be due to an increased intradialytic removal of uremic substances that inhibit leukocyte function.

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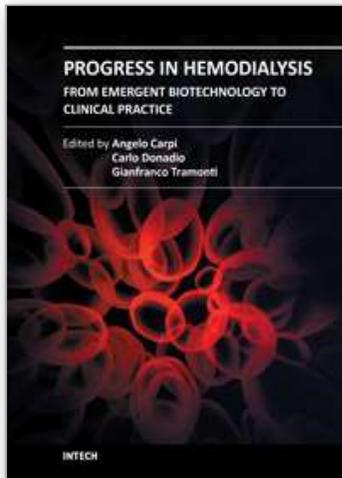
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Hemodialysis (HD) represents the first successful long-term substitutive therapy with an artificial organ for severe failure of a vital organ. Because HD was started many decades ago, a book on HD may not appear to be up-to-date. Indeed, HD covers many basic and clinical aspects and this book reflects the rapid expansion of new and controversial aspects either in the biotechnological or in the clinical field. This book revises new technologies and therapeutic options to improve dialysis treatment of uremic patients. This book consists of three parts: modeling, methods and technique, prognosis and complications.

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