Kidney & Blood Pressure Research

Kidney Blood Press Res 2017;42:209-219
DOI: 10.1159/000476017
Published online: May 04, 2017
Accepted: February 07, 2017

© 2017 The Author(s)
Published by S. Karger AG, Basel
www.karger.com/kbr

This article is licensed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (CC BY-NC-ND) (http://www.karger.com/Services/OpenAccessLicense). Usage and distribution for commercial purposes as well as any distribution of modified material requires written permission.

Review

Angiogenesis and Inflammation in Peritoneal Dialysis: The Role of Adipocytes

Jun Shi Manshu Yu Meixiao Sheng

Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing, China

Key Words
Adipocytes • Peritoneal dialysis • Angiogenesis • Inflammation

Abstract
Chronic inflammation and angiogenesis are the most common complications in patients undergoing maintenance peritoneal dialysis (PD), resulting in progressive peritoneum remolding and, eventually, utrafiltration failure. Contributing to the deeper tissue under the peritoneal membrane, adipocytes play a neglected role in this process. Some adipokines act as inflammatory and angiogenic promoters, while others have the opposite effects. Adipokines, together with inflammatory factors and other cytokines, modulate inflammation and neovascularization in a coordinated fashion. This review will also emphasize cellular regulators and their crosstalk in long-term PD. Understanding the molecular mechanism, targeting changes in adipocytes and regulating adipokine secretion will help extend therapeutic methods for preventing inflammation and angiogenesis in PD.

© 2017 The Author(s)
Published by S. Karger AG, Basel

Introduction

Continuous ambulatory peritoneal dialysis (CAPD) is a well-established renal replacement therapy for patients with end-stage renal disease (ESRD). Peritoneal dialysis (PD) is a life-sustaining therapy used by 100,000 patients worldwide, accounting for approximately 10 to 15% of the dialysis population [1]. PD has several advantages over hemodialysis (HD), including a simpler and less invasive procedure and a more continuous removal of waste products. Additionally, it contributes to retention of residual renal function, which results in an improved quality of life. Patients who undergo CAPD have lower mortality than HD after the first 2 years of PD therapy [2]. Unfortunately, recurrent peritonitis and progressive peritoneal tissue remodeling, as well as angiogenesis, ultimately

Meixiao Sheng
Affiliated Hospital of Nanjing University of Chinese Medicine,155 Hanzhong Road, Qinhuai District, Nanjing 210029 (China)
Tel. +86-25-8661-7141, Fax +86-25-8650-6055, E-Mail jsszyysmx@163.com

leads to utrafiltration failure (UFF), which results in discontinuation of PD therapy. Frail PD patients are more likely to be hospitalized, and they require a long stay for each hospital admission [3]. In developed countries, the proportion of dialysis patients undergoing PD significantly declined in the last 15 years [4]. Thus, overcoming complications and UFF have become key issues that require urgent solutions to maintain the longevity and efficiency of PD.

In PD, the peritoneum is used as a semi-permeable membrane, allowing for diffuse exclusion of uremic toxins and exchange of solutes between the circulation and PD fluid (PDF) [5]. The peritoneum consists of three layers. The most superficial layer is a mesothelial monolayer, which covers a basement membrane and submesothelial compact zone. This zone contains extracellular matrix (ECM), collagen and a few fibroblasts. The deepest layer comprises loose adipose tissue with peritoneal capillaries and peritoneal lymphatic vessels [6]. Long-term instillation of PDF causes morphological alterations in the peritoneal membrane, which are characterized by detachment of the mesothelial layer, increased ECM deposition, fibrosis and angiogenesis.

As the local blood circulation is supplied by mesenteric and celiac arteries, peritoneal microvessels play a crucial role in PD. Although PMCs directly contact the PDF, microvessels are an important location for the exchange of water, toxins, oxygen, and inflammatory mediators between the peritoneal membrane and cavity [7]. Angiogenesis increases the effective surface area for exchange and lymphangiogenesis raises the lymphatic absorption rates. The enhanced vascular network decreases the glucose-driven osmotic pressure of the PDF, leading to UF loss. Furthermore, vascular wall changes, such as thickening and increased permeability, increase small solute transport and thus reduce the time spent on exchanging waste products [8]. Furthermore, inflammation and angiogenesis occur simultaneously in the peritoneum, and efforts to alleviate inflammation also reduce angiogenesis [9].

Interestingly, a new study suggested that peritoneal adipocytes could also contribute to this pathological process. Manipulating crosstalk among adipose tissue, macrophages, mesothelial cells (MCs), and endothelial cells (ECs) may represent a novel therapeutic strategy for preventing the peritoneal inflammation and angiogenesis that lead to UFF [10]. In this review, the focus will be on the role of adipocytes on inflammation and accompanying angiogenesis in PD.

Molecular network of angiogenesis, fibrosis and inflammation in PD

Angiogenesis is an event induced by almost all injury and repair processes. PD-induced angiogenesis is mediated by inducing cytokines, such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), as well as inhibitors, including angiogenesis inhibin, endostatin (ES) and others [11, 12]. Local VEGF production during PD seems to play a central role in the processes leading to peritoneal neoangiogenesis and functional decline. One study showed VEGF is widely expressed in PMCs and has much lower expression in other cells [13]. Vascular endothelial growth factor receptor 2 (VEGFR2) is the specific receptor distributed on the surface of ECs. It binds VEGF and recruits EC migration to anoxic and avascular areas. As the ECs proliferate and differentiate, angiogenic remodeling occurs where the vessels enlarge and mature.

Various exogenous factors strengthen peritoneal angiogenesis. Local catheter repetitive stimulation and bacterial peritonitis are considered extrinsic factors. Intriguingly, a study found that VEGF, bFGF, and ES expression as well as the number of neocapillaries were increased in pre-dialysis uremics and PD patients compared to control subjects [14], which indicates that uremia is an independent risk factor for microvessel formation.

Normally, the human peritoneal cavity contains approximately 100 ml of fluid, which works as a lubricating liquid. During CAPD, approximately 2 liters of PDF is instilled with 5 exchanges per day, which is approximately 20 times the baseline level of fluid. Conventional PDFs have a low pH value, a high glucose concentration in lactate-buffered solution, and contain glucose degradation products (GDPs), which are formed during heat sterilization of

the fluids. GDPs cause the formation of advanced glycation end-products (AGEs), which are critical to determining the biocompatibility of different PDFs. Prolonged exposure to GDP solutions enhances cytotoxic damage and proangiogenic responses in PMCs [15], stimulating the release of VEGF, which in turn enhances vascular permeability and angiogenesis [16, 17]. Meanwhile, GDPs could also reduce the expression of intercellular tight junction proteins, including ZO-1, occludin and claudin-1, in MCs [18]. Exogenous VEGF suppresses ZO-1 expression, while neutralizing the anti-VEGF antibody reverses the effect of GDPs on ZO-1 expression in PMCs. These findings suggest that the action of GDPs on ZO-1 expression is regulated through VEGF. It is more important to realize ZO-1 is one of the biomarkers of EMT, a process by which MCs undergo a progressive loss of the epithelial phenotype and acquire fibroblast-like characteristics. MCs that have undergone EMT augment the ability to invade and migrate into the submesothelial zone, leading to angiogenesis, fibrosis and ultrafiltration failure. In addition to undergoing morphological changes, the non-epithelioid MCs produce higher levels of VEGF than the non-EMT cells [13]. MCs that undergo EMT promote angiogenesis via VEGF and fibrosis via ECM formation [19]. TGF-β1, the vital induced factor of EMT and subsequent fibrosis, is up-regulated among EMT progress [20], which participates in a positive feedback loop and enhances the production of ECM, leading to further neovascularization [13, 21]. AGE receptor (RAGE) activation also participates in VEGF-induced angiogenesis and TGF-β-induced EMT [22]. The receptor has been considered a scavenger receptor in AGE removal and clearance with binding of AGE to the receptor. The anti-RAGE antibody partially prevents blood tube formation and submesothelial fibrosis in vivo [23], demonstrating the pivotal interaction between AGEs/GDPs and RAGE in neoangiogenesis.

Inflammation, the most common complication in ESRD patients, may be progressively exacerbated upon initiation of PD. This process is well recognized as alleviated secretion of C-reactive protein (CRP) and inflammatory factors, such as interleukins (ILs) and TNF-a. Notably, the microinflammatory state in PD patients may potentially trigger the pro-angiogenesis response [24]. A sequence of molecules or inflammatory factors produced by different cells compose the angiogenic network (Table 1). Among all cytokines, IL-6 plays a key role in modulating inflammation and angiogenesis. First, it is positively associated with other inflammatory factors, such as TNF-α, IL-10, and IL-18 [25]. Second, IL-6 also induces the

Table 1. Pro-angiogenic cytokines in PD

Types of cytokines	Cytokines	Cellular source in peritoneum	Relevance to PD	References
Angiogenic factors	VEGF	Mast cells ECs MCs	VEGF and VEGFR are decisive molecules for angiogenesis.	[26, 27]
	Angiopoietin2	ECs	Angiopoietin2 signaling involved in TNF-α induced peritoneal angiogenesis.	[28, 29]
Inflammatory factors	IL-6	Macrophages ECs MCs	IL-6 is positively correlated with VEGF in plasma and dialysate.	[30-33]
	IL-1	Macrophages MCs	IL-1 increases vessel-like structures by enhancing VEGF production, and augments proliferation when added to ECs.	[34-36]
	IL-8	Macrophages Mast cells MCs	IL-8 enhances EC proliferation and capillary tube formation.	[37, 38]
	TNF-α	Macrophages Mast cells MCs	TNF-α causes neoangiogenesis both in vitro and in vivo.	[29, 39]
Chemokines	MCP-1	Macrophages ECs	MCP-1-induced protein enhances endothelial cell proliferation, migration, and other pro-angiogenic genes, leading to capillary-like tube formation.	[40, 41]
Adhesion molecules	ICAM-1 VCAM-1	ECs	Induced by IL-6 and TNF-a after EC injury, promoting new capillary formation.	[32, 42] [32, 43]
Growth factors	TGF-β	Mast cells MCs	TGF-β triggers the expression of VEGF via EMT and conversely amplifies its own secretion.	[26, 44, 45]

expression of chemokines and adhesion molecules, such as monocyte chemotactic protein-1 (MCP-1), intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), as well as angiogenic markers, such as VEGF and angiotensin-2 (Ang-2).

Adipocytes become activated in PD

Compared with hemodialysis, there is an increasing trend in the body mass, BMI, muscle mass and visceral fat percentage in PD patients [46]. Body mass starts to increase after 6 months of PD therapy, and most of the increased body mass consists of visceral fat [47]. A new explanation to consider is that PD-induced obesity is significantly related to the BMI, duration of dialysis, and whether patients received dialysis and is less related to glucose absorption [48]. Although some studies of PD patients have reported an inverse relationship between weight and mortality [49-51], the visceral fat content increases in long-term PD.

A nest of mature adipocytes and a stromal-vascular fraction compose the adipose tissue. Anatomically, these features are abundant in mesenteric or omental peritoneum, but they contribute less to the parietal, intestinal and diaphragmatic peritoneum. As above, the peritoneal adipose tissue is deeply buried under a mesothelial monolayer and submesothelial layer. However, when the mesothelial monolayer is injured, dialysate could also reach the adipose tissue. An ultrastructural study revealed that some omental adipocytes stretch out from the mesothelial surface and directly contact the dialysate [10]. Adipose tissue is not only an energy storage depot, it has autocrine, paracrine, and endocrine functions. Adipocytes secrete various cytokines and adipokines, including leptin, adiponectin, resistin, TNF-a, IL-6, visfatin, TGF-β, VEGF and other molecules [52], which form a network that regulates various physiological processes. Chronic PD patients are characterized by elevated plasma levels of adipokines [53]. Although a majority of previous work has focused on peritoneal mesothelial cells, more attention has been paid to the role of peritoneal adipocytes during PD therapy. It is reasonable to speculate that during direct or indirect contact with dialysate, peritoneal adipocytes will be "activated" and are associated with angiogenesis and inflammation.

Adipokines primarily promote angiogenesis via regulating VEGF

The pro-angiogenic function of adipocyte-derived cytokines involves VEGF. Inflammatory adipokines, such as TNF-a, IL-6, and MCP-1, are strongly related to VEGF as explained in Table 1. TNF-α has been shown to mediate endothelial dysfunction and promote calcification of vascular cells. Increased TNF-α level results in a dose-dependent VEGF in peritoneal mesothelium [54]. IL-6 and soluble IL-6 receptor (sIL-6R) not only directly promote VEGF, but also induce the synthesis and secretion of MCP-1, which in company with VEGF, recruits monocytes and lymphocytes [55].

Among all other adipokines, leptin receives substantial attention because it is the most abundant hormone secreted by adipocytes, and it is also known as a pro-inflammatory cytokine. This 16-kDa protein is a uremic toxin because the serum leptin concentration is markedly higher in patients with chronic renal failure or undergoing dialysis [56]. Moreover, it cannot be removed by hemodiafiltration. Leptin could directly phosphorylate VEGFR2 and activate the p38 mitogen-activated protein kinase/protein kinase B/cyclooxygenase-2 (p38MAPK/Akt/COX-2) signal axis to stimulate angiogenesis [57]. In addition, as it is a positive modulator of IL-1α, TNF-α and IL-6 secretion [58, 59], leptin has emerged as an indirect pro-angiogenic mediator. Leptin receptor, Ob-Rb, has been found in MCs. Glucose notably increases the synthesis of adipocyte-derived leptin and Ob-Rb in a dose-dependent manner [54].

TGF-β, a VEGF associated inflammatory factor, is directly released by adipocytes via up-regulating proto-oncogene c-Fos [35]. Additionally, it is amplified by adipocyte-derived leptin, activating the Janus kinase-signal transducers and activation (JAK-STAT) signal transduction pathway [60]. Resistin also promotes the expression of VEGF via phosphatidylinositol 3 kinase/protein kinase B-Sp1 (PI3K/Akt-Sp1) pathway activation [61]. Visfatin influences vasodilatation and promotes the proliferation of ECs independent of VEGF [62].

Adipocytes bridge inflammation and angiogenesis in PD

As mentioned above, peritoneum failure could be induced by infectious or non-infectious inflammation. Despite being in clinical remission, PD patients still suffer from prolonged systemic chronic inflammation [63]. A series of studies have focused on its mechanisms, however, the cause of systematic inflammation in PD is not completely understood [64]. Patients undergoing CAPD have increased levels of pro-inflammatory cytokines, including IL-1β, IL-6, TNF-α, and TGF-β, in both PD effluent and plasma [65]. The serum leptin level increases during acute infection, and even after apparent remission of peritonitis, in response to IL-1 and TNF-α [66]. Hyperleptinemia also induces IL-6 and TNF-α protein production by monocytes [58]. It may be posited that low-grade inflammation in the peritoneum activates fat cells, releases pro-inflammatory adipokines and accelerates angiogenesis. The positive feedback from the inflammatory response may cause a vicious cycle for angiogenesis.

Intriguingly, not all the adipokines destroy vascular function. The vascular protector inhibits capillary formation by restraining the inflammation reaction. Omentin inhibits norepinephrine synthesis and promotes EC-derived NO release via 5-AMP-activated protein kinase (AMPK)-mediated eNOS phosphorylation, inducing down-regulation of TNF-α [62].

Contrary to leptin, adiponectin has anti-angiogenic, anti-inflammatory and insulin-sensitizing functions [67]. It is negatively related to the adipose tissue mass [68] and a low plasma adiponectin level is associated with coronary artery disease and type-2 diabetes. Adiponectin inhibits adhesion molecule production by ECs, suppressing the attachment of monocytes, a precursor in the angiogenic process [69]. Moreover, adiponectin reduces the TNF-α-induced activation of NF-κB; in turn, TNF-α downregulates adiponectin production [70]. This negative reciprocal interaction on their local production in adipose tissue suggests that adiponectin decreases in the peritoneum may aggravate local inflammation, creating a "vicious cycle" that lowers adiponectin release [71]. In vivo, neointimal thickening of injured arteries is accelerated in adiponectin-KO mice [72] and inhibited by exogenous adiponectin [73], revealing the key role of adiponectin in anti-angiogenesis.

Crosstalk among adipocytes, macrophages and endothelial cells

To better understand the molecular mechanism of inflammation and angiogenesis during PD, it is important to identify the different cell types that are involved and their potential cross-talk (Figure 1).

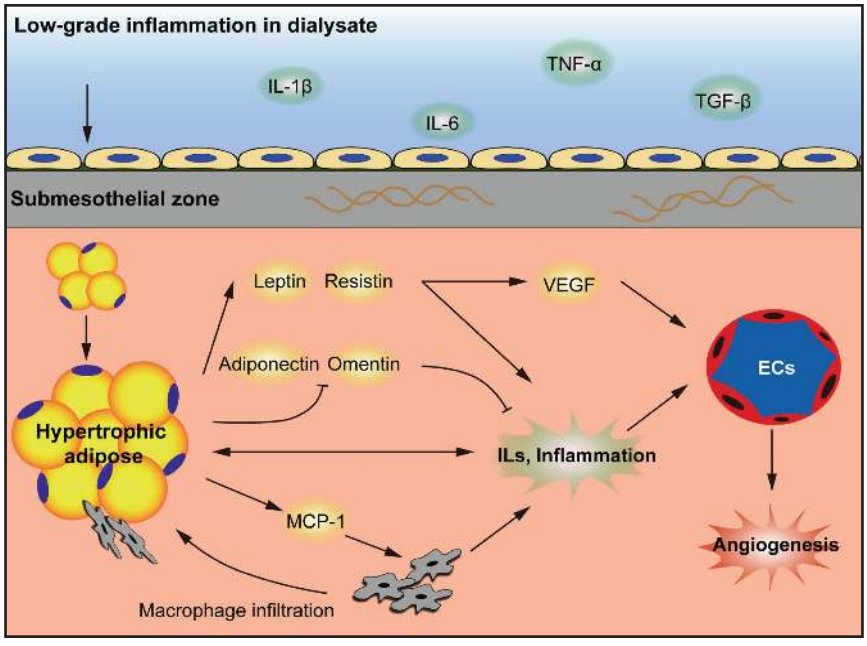

Fig. 1. Adipocytes in inflammation and angiogenesis during PD. Adipocytes lie deep beneath the monolayer peritoneal mesothelial cells and submesothelial zone, which contains collagen and fibroblasts. PD patients undergo chronic low-grade inflammation in dialysate and plasma. The adipocytes enhance and regulate adipokine secretion. On the one hand, they produce

pro-inflammatory and pro-angiogenic cytokines (e.g., leptin and resistin). On the other hand, anti-inflammatory cytokines are suppressed (e.g., adiponectin and omentin). Meanwhile, hypertrophic adipose directly releases inflammatory factors (e.g., IL-6 and TNF-a). The adipose-derived MCP-1 propagates inflammation by stimulating macrophage infiltration to interstitial space in fat tissue. The pro-angiogenic function focuses on VEGF, which acts on endothelial cells with inflammatory factors, inducing angiogenesis.

Hypertrophic adipocytes initiate inflammation

As mentioned above, with decreased residual renal function, the fat mass index increases, while the non-fat content decreases [74]. As mature fat cells account for 50–85% of the total cellular components in adipose tissue, obese patients seem to have a higher total adipocyte number than individuals who are not obese [75]. Approximately 10% of adipocytes are renewed annually, regardless of the BMI levels and ages. Beyond altering the quantity, it is more important to target the enlarged fat cells (hypertrophy) and then the increased fat storage in fully differentiated adipocytes and adipokine overproduction. They were found not only in the context of PD, but also in individuals with obesity-related metabolic disorders [76]. First, the adipocyte size is hyper-responsive to disordered adipokine secretion. Second, the hypertrophic adipocytes shift their balance towards producing cytokines, regulating the subsequent immune response [77]. Larged cells are more lipolytic, release more inflammatory promotors (ILs, leptin, resistin) and less inhibitors (adiponectin, omentin). Chemoattractants, such as MCP-1, are released for subsequent macrophage infiltration. Thus, the relative number of hypertrophic adipocytes might be the most pivotal determinant in the originating of inflammation. Additionally, these highly sensitive larged adipocytes were mediated by the NF-κB pathway and could be prevented by NF-κB inhibitors [78, 79], which indicates the activation would occur before or after inflammation events.

Macrophage infiltration into adipocytes spreads inflammation

There are two types of macrophages in adipose tissue: M1 (classically activated) macrophages and M2 (resident or alternatively activated) macrophages. M1 macrophages are characterized by expression of CD11c surface marker, inducible nitric oxide synthase (iNOS) and pro-inflammatory cytokines such as TNF-α, IL-6, while M2 macrophages produce arginase and anti-inflammatory cytokines such as IL-10 and IL-1Ra [80]. Macrophage infiltration is correlated with both adipocyte size and BMI [81]. Hypertrophic adipocytes initiate the infiltration of monocytes/macrophages. The enlarged adipoctyes are related to IL-6, MCP-1, free fatty acid (FFA) and oxidative stress conditions [82]. In PD, circulating mononuclear cells and MCP-1 play a vital role in endothelial cell dysfunction. Monocytes from dialysate or circulating blood persist in a pro-inflammatory state and transmigrate to peritoneal adipose tissue by promoting adherent molecules, which are secreted by both monocytes and vascular endothelial cells. After this process, the monocytes differentiate into inflammatory (M1) macrophages.

Infiltrating inflammatory macrophages produce inflammatory cytokines and synergistically act with adipocytes, leading to massive amplification of the inflammatory process. Resident macrophages can be activated with reinforced monocytes recruitment; however, they express a low level of pro-inflammatory molecules. It seems that PD-related inflammation causes a shift in the polarized state of adipose tissue macrophages from M2, which has anti-inflammatory function, to M1, which contributes to a pro-inflammatory state [83]. Intriguingly, over 90% of all macrophages in adipose tissue from obese mice or humans surround dead adipocytes [84]. In line with this view, conversion of the M1/M2 balance relies on the recruitment of inflammatory monocytes from the circulation to macrophage clusters that surround dead adipocytes instead of on the resident M2 macrophages that are directly transformed to M1 in situ, where there are interstitial spaces among adipocytes [85]. Inhibition of M1 cell differentiation or permeation through adipocytes offers a therapeutic approach for PD-related complications.

Activation of ECs amplifies the inflammatory response and promotes angiogenesis

Endothelial cells could be activated by inflammatory cytokines, VEGF, and the aforementioned adipose-derived secretions. This is much more an immune response than a process of ECs and macrophages feeding each other. A series of signaling pathways in ECs are invoked, and downstream cytokines, such as adhesion molecules and chemokines, are excreted. These factors, in a synergistic model, drive local macrophages into deep-seated adipose tissue and induce full activation of ECs. Therefore, peripheral blood monocytes are closely absorbed to ECs or even seep out of vessels and are thus polarized to different macrophage phenotypes among adipocytes, which provide sources for spreading inflammation [86]. Adipose tissue inflammation cross talks with endothelial cells via adipocyte-derived cytokines and promotes NF-κB-dependent endothelial dysfunction [87]. Moreover, ECs are recruited to anoxic zones to form neovascularization via VEGF, which is partially enhanced by EC activation as well as a stimulus for inflammation factors and adipokines.

Conclusions

Patients in long-term PD undergo progressive inflammation and accompanying angiogenesis. Chronic local or systemic inflammatory responses promote new blood vessel formation. During this process, adipocytes participate in two-way regulating actions by producing substantial adipokines, inflammatory factors, and other molecules. On the one hand, inflammatory response and angiogenesis are stimulated by adipose-derived ILs, VEGF, leptin, and resistin. On the other hand, some adipokines participate as inflammatory inhibitors and vascular function protectors, such as adiponectin and omentin. Inflammation is initiated by enlarged adipose, propagated by macrophage infiltration and amplified by EC activation. All the multiple cytokines and cellular components compose a complex network. Targeting the changes in adipocytes as well as the regulated secretion of adipokines (or their activation/receptors) offers a therapeutic approach for suppressing inflammation and angiogenesis in PD. Further studies that aim to illustrate the molecular mechanisms of diverse adipokines and cells in the context of PD should be performed.

Disclosure Statement

The authors of this manuscript state that they do not have any conflict of interests and nothing to disclose.

Acknowledgments

This work was supported by grants from the National Natural Science Foundation of China (No.81473606), Six Talent Peaks Project in Jiangsu Province (WS-033) and Research Innovation Program for College Graduates of Jiangsu Province (KYZZ16-0407).

References

1 Davies SJ: Peritoneal dialysis--current status and future challenges. Nat Rev Nephrol 2013;9:399-408.
2 Collins AJ, Foley RN, Chavers B, Gilbertson D, Herzog C, Johansen K, Kasiske B, Kutner N, Liu J, St Peter W, Guo H, Gustafson S, Heubner B, Lamb K, Li S, Li S, Peng Y, Qiu Y, Roberts T, Skeans M, Snyder J, Solid C, Thompson B, Wang C, Weinhandl E, Zaun D, Arko C, Chen SC, Daniels F, Ebben J, Frazier E, Hanzlik C,

Johnson R, Sheets D, Wang X, Forrest B, Constantini E, Everson S, Eggers P, Agodoa L: 'United States Renal Data System 2011 Annual Data Report: Atlas of chronic kidney disease & end-stage renal disease in the United States. Am J Kidney Dis 2012;59:A7, e1-420.

3 Ng JKC, Kwan BCH, Chow KM, Cheng PMS, Law MC, Pang WF, Leung CB, Li PKT, Szeto CC: Frailty in Chinese Peritoneal Dialysis Patients: Prevalence and Prognostic Significance. Kidney Blood Press Res 2016;41:736-745.

4 Jain AK, Blake P, Cordy P, Garg AX: Global trends in rates of peritoneal dialysis. J Am Soc Nephrol 2012;23:533-544.

5 Vlahu CA, Aten J, de Graaff M, van Veen H, Everts V, de Waart DR, Struijk DG, Krediet RT: New Insights into the Effects of Chronic Kidney Failure and Dialysate Exposure on the Peritoneum. Perit Dial Int 2016;36:614-622.

6 Krediet RT, Struijk DG: Peritoneal changes in patients on long-term peritoneal dialysis. Nat Rev Nephrol 2013;9:419-429.

7 Lee CC, Weng CH, Huang WH, Yen TH, Lin JL, Lin-Tan DT, Chen KH, Hsu CW: Association Between Blood Cadmium Levels and Mortality in Peritoneal Dialysis. Medicine (Baltimore) 2016;95:e3717.

8 Stavenuiter AW, Schilte MN, Ter Wee PM, Beelen RH: Angiogenesis in peritoneal dialysis. Kidney Blood Press Res 2011;34:245-252.

9 Fabbrini P, Schilte MN, Zareie M, ter Wee PM, Keuning ED, Beelen RH, van den Born J: Celecoxib treatment reduces peritoneal fibrosis and angiogenesis and prevents ultrafiltration failure in experimental peritoneal dialysis. Nephrol Dial Transplant 2009;24:3669-3676.

10 Aoki S, Udo K, Morimoto H, Ikeda S, Takezawa T, Uchihashi K, Nishijima-Matsunobu A, Noguchi M, Sugihara H, Toda S: Adipose tissue behavior is distinctly regulated by neighboring cells and fluid flow stress: a possible role of adipose tissue in peritoneal fibrosis. J Artif Organs 2013;16:322-331.

11 Nakao A, Nakao K, Takatori Y, Kojo S, Inoue J, Akagi S, Sugiyama H, Wada J, Makino H: Effects of icodextrin peritoneal dialysis solution on the peritoneal membrane in the STZ-induced diabetic rat model with partial nephrectomy. Nephrol Dial Transplant 2010;25:1479-1488.

12 Tanabe K, Maeshima Y, Ichinose K, Kitayama H, Takazawa Y, Hirokoshi K, Kinomura M, Sugiyama H, Makino H: Endostatin peptide, an inhibitor of angiogenesis, prevents the progression of peritoneal sclerosis in a mouse experimental model. Kidney Int 2007;71:227-238.

13 Aroeira LS, Aguilera A, Selgas R, Ramirez-Huesca M, Perez-Lozano ML, Cirugeda A, Bajo MA, del Peso G, Sanchez-Tomero JA, Jimenez-Heffernan JA, Lopez-Cabrera M: Mesenchymal conversion of mesothelial cells as a mechanism responsible for high solute transport rate in peritoneal dialysis: role of vascular endothelial growth factor. Am J Kidney Dis 2005;46:938-948.

14 Gao D, Zhao ZZ, Liang XH, Li Y, Cao Y, Liu ZS: Effect of peritoneal dialysis on expression of vascular endothelial growth factor, basic fibroblast growth factor and endostatin of the peritoneum in peritoneal dialysis patients. Nephrology (Carlton) 2011;16:736-742.

15 Lai KN, Leung JC, Chan LY, Li FF, Tang SC, Lam MF, Tse KC, Yip TP, Chan TM, Wieslander A, Vlassara H: Differential expression of receptors for advanced glycation end-products in peritoneal mesothelial cells exposed to glucose degradation products. Clin Exp Immunol 2004;138:466-475.

16 Yuan J, Guo Q, Qureshi AR, Anderstam B, Eriksson M, Heimburger O, Barany P, Stenvinkel P, Lindholm B: Circulating vascular endothelial growth factor (VEGF) and its soluble receptor 1 (sVEGFR-1) are associated with inflammation and mortality in incident dialysis patients. Nephrol Dial Transplant 2013;28:2356-2363.

17 Perez-Lozano ML, Sandoval P, Rynne-Vidal A, Aguilera A, Jimenez-Heffernan JA, Albar-Vizcaino P, Majano PL, Sanchez-Tomero JA, Selgas R, Lopez-Cabrera M: Functional relevance of the switch of VEGF receptors/co-receptors during peritoneal dialysis-induced mesothelial to mesenchymal transition. PLoS One 2013;8:e60776.

18 Lai KN, Tang SC, Leung JC: Mediators of inflammation and fibrosis. Perit Dial Int 2007;27:S65-71.

19 Morishita Y, Ookawara S, Hirahara I, Muto S, Nagata D: HIF-1alpha mediates Hypoxia-induced epithelial-mesenchymal transition in peritoneal mesothelial cells. Ren Fail 2016;38:282-289.

20 Strippoli R, Moreno-Vicente R, Battistelli C, Cicchini C, Noce V, Amicone L, Marchetti A, Del Pozo MA, Tripodi M: Molecular Mechanisms Underlying Peritoneal EMT and Fibrosis. Stem Cells Int 2016;2016:3543678.

21 Pletinck A, Van Landschoot M, Steppan S, Laukens D, Passlick-Deetjen J, Vanholder R, Van Biesen W: Oral supplementation with sulodexide inhibits neo-angiogenesis in a rat model of peritoneal perfusion. Nephrol Dial Transplant 2012;27:548-556.
22 Kim YL: Update on mechanisms of ultrafiltration failure. Perit Dial Int 2009;29:S123-127.
23 Boulanger E, Grossin N, Wautier MP, Taamma R, Wautier JL: Mesothelial RAGE activation by AGEs enhances VEGF release and potentiates capillary tube formation. Kidney Int 2007;71:126-133.
24 de Lima SM, Otoni A, Sabino Ade P, Dusse LM, Gomes KB, Pinto SW, Marinho MA, Rios DR: Inflammation, neoangiogenesis and fibrosis in peritoneal dialysis. Clin Chim Acta 2013;421:46-50.
25 Lee CT, Ng HY, Hsu CY, Tsai YC, Yang YK, Chen TC, Chiou TT, Kuo CC, Lee WC, Hsu KT: Proinflammatory cytokines, hepatocyte growth factor and adipokines in peritoneal dialysis patients. Artif Organs 2010;34:E222-229.
26 Carter JG, Gammons MV, Damodaran G, Churchill AJ, Harper SJ, Bates DO: The carboxyl terminus of VEGF-A is a potential target for anti-angiogenic therapy. Angiogenesis 2015;18:23-30.
27 Dong A, Seidel C, Snell D, Ekawardhani S, Ahlskog JK, Baumann M, Shen J, Iwase T, Tian J, Stevens R, Hackett SF, Stumpp MT, Campochiaro PA: Antagonism of PDGF-BB suppresses subretinal neovascularization and enhances the effects of blocking VEGF-A. Angiogenesis 2014;17:553-562.
28 Umikawa M, Umikawa A, Asato T, Takei K, Matsuzaki G, Kariya K, Zhang CC: Angiopoietin-like protein 2 induces proinflammatory responses in peritoneal cells. Biochem Biophys Res Commun 2015;467:235-241.
29 Yuan J, Fang W, Lin A, Ni Z, Qian J: Angiopoietin-2/Tie2 signaling involved in TNF-alpha induced peritoneal angiogenesis. Int J Artif Organs 2012;35:655-662.
30 Gopinathan G, Milagre C, Pearce OM, Reynolds LE, Hodivala-Dilke K, Leinster DA, Zhong H, Hollingsworth RE, Thompson R, Whiteford JR, Balkwill F: Interleukin-6 Stimulates Defective Angiogenesis. Cancer Res 2015;75:3098-3107.
31 Feurino LW, Zhang Y, Bharadwaj U, Zhang R, Li F, Fisher WE, Brunicardi FC, Chen C, Yao Q, Min L: IL-6 stimulates Th2 type cytokine secretion and upregulates VEGF and NRP-1 expression in pancreatic cancer cells. Cancer Biol Ther 2007;6:1096-1100.
32 Pecoits-Filho R, Araujo MR, Lindholm B, Stenvinkel P, Abensur H, Romao JE, Jr., Marcondes M, De Oliveira AH, Noronha IL: Plasma and dialysate IL-6 and VEGF concentrations are associated with high peritoneal solute transport rate. Nephrol Dial Transplant 2002;17:1480-1486.
33 Yang X, Lin A, Jiang N, Yan H, Ni Z, Qian J, Fang W: Interleukin-6 trans-signaling induces VEGF synthesis partly via Janus kinases-STAT3 pathway in human mesothelial cells. Nephrology (Carlton) 2016, DOI 10.1111/nep.12746.
34 Carmi Y, Voronov E, Dotan S, Lahat N, Rahat MA, Fogel M, Huszar M, White MR, Dinarello CA, Apte RN: The role of macrophage-derived IL-1 in induction and maintenance of angiogenesis. J Immunol 2009;183:4705-4714.
35 Bonder CS, Ebert LM: Fos-icking for control of angiogenesis: increasing the longevity of peritoneal dialysis. Kidney Int 2013;84:1065-1067.
36 Rosell A, Arai K, Lok J, He T, Guo S, Navarro M, Montaner J, Katusic ZS, Lo EH: Interleukin-1beta augments angiogenic responses of murine endothelial progenitor cells in vitro. J Cereb Blood Flow Metab 2009;29:933-943.
37 Wang L, Tang C, Cao H, Li K, Pang X, Zhong L, Dang W, Tang H, Huang Y, Wei L, Su M, Chen T: Activation of IL-8 via PI3K/Akt-dependent pathway is involved in leptin-mediated epithelial-mesenchymal transition in human breast cancer cells. Cancer Biol Ther 2015;16:1220-1230.
38 Li A, Dubey S, Varney ML, Dave BJ, Singh RK: IL-8 directly enhanced endothelial cell survival, proliferation, and matrix metalloproteinases production and regulated angiogenesis. J Immunol 2003;170:3369-3376.
39 Oviedo-Socarras T, Vasconcelos AC, Barbosa IX, Pereira NB, Campos PP, Andrade SP: Diabetes alters inflammation, angiogenesis, and fibrogenesis in intraperitoneal implants in rats. Microvasc Res 2014;93:23-29.
40 Cakmak H, Basar M, Seval-Celik Y, Osteen KG, Duleba AJ, Taylor HS, Lockwood CJ, Arici A: Statins inhibit monocyte chemotactic protein 1 expression in endometriosis. Reprod Sci 2012;19:572-579.
41 Niu J, Azfer A, Zhelyabovska O, Fatma S, Kolattukudy PE: Monocyte chemotactic protein (MCP)-1 promotes angiogenesis via a novel transcription factor, MCP-1-induced protein (MCPIP). J Biol Chem 2008;283:14542-14551.

42 Mosbah A, Nabiel Y, Khashaba E: Interleukin-6, intracellular adhesion molecule-1, and glycodelin A levels in serum and peritoneal fluid as biomarkers for endometriosis. Int J Gynaecol Obstet 2016;134:247-251.
43 Schlesinger M, Bendas G: Vascular cell adhesion molecule-1 (VCAM-1)--an increasing insight into its role in tumorigenicity and metastasis. Int J Cancer 2015;136:2504-2514.
44 Jang YH, Shin HS, Sun Choi H, Ryu ES, Jin Kim M, Ki Min S, Lee JH, Kook Lee H, Kim KH, Kang DH: Effects of dexamethasone on the TGF-beta1-induced epithelial-to-mesenchymal transition in human peritoneal mesothelial cells. Lab Invest 2013;93:194-206.
45 Krishnan S, Szabo E, Burghardt I, Frei K, Tabatabai G, Weller M: Modulation of cerebral endothelial cell function by TGF-beta in glioblastoma: VEGF-dependent angiogenesis versus endothelial mesenchymal transition. Oncotarget 2015;6:22480-22495.
46 Bal Z, Uyar ME, Tutal E, Guliyev O, Sezer S, Haberal M: Body composition analysis of patients on waiting list for cadaveric renal transplantation: a comparison of hemodialysis and peritoneal dialysis patients. Transplant Proc 2013;45:3489-3493.
47 Choi SJ, Kim NR, Hong SA, Lee WB, Park MY, Kim JK, Hwang SD, Lee HK: Changes in body fat mass in patients after starting peritoneal dialysis. Perit Dial Int 2011;31:67-73.
48 Miyamoto T, Rashid Qureshi A, Heimburger O, Barany P, Carrero K, Sjoberg B, Lindholm B, Stenvinkel P, Carrero JJ: Inverse relationship between the inflammatory marker pentraxin-3, fat body mass, and abdominal obesity in end-stage renal disease. Clin J Am Soc Nephrol 2011;6:2785-2791.
49 Lo WK: Metabolic syndrome and obesity in peritoneal dialysis. Kidney Res Clin Pract 2016;35:10-14.
50 Jin H, Shin JY, Lee SH, Song JH, Kim MJ, Lee SW: Abdominal Obesity and Mortality in Continuous Ambulatory Peritoneal Dialysis Patients. Electrolyte Blood Press 2015;13:22-29.
51 Zhou H, Cui L, Zhu G, Jiang Y, Gao X, Zou Y, Yang M, Liu H, Di J, Zong Y, Pan J: Survival advantage of normal weight in peritoneal dialysis patients. Ren Fail 2011;33:964-968.
52 Achike FI, To NH, Wang H, Kwan CY: Obesity, metabolic syndrome, adipocytes and vascular function: A holistic viewpoint. Clin Exp Pharmacol Physiol 2011;38:1-10.
53 Rodriguez-Carmona A, Perez-Fontan M, Guitian A, Peteiro J, Garcia-Falcon T, Lopez-Muniz A, Garcia-Buela J, Cordido F: Effect of low-GDP bicarbonate-lactate-buffered peritoneal dialysis solutions on plasma levels of adipokines and gut appetite-regulatory peptides. A randomized crossover study. Nephrol Dial Transplant 2012;27:369-374.
54 Catar R, Witowski J, Wagner P, Schramm IA, Kawka E, Philippe A, Dragun D, Jörres A: The proto-oncogene c-Fos transcriptionally regulates VEGF production during peritoneal inflammation. Kidney Int 2013;84:1119-1128.
55 Avraham-Davidi I, Yona S, Grunewald M, Landsman L, Cochain C, Silvestre JS, Mizrahi H, Faroja M, Strauss-Ayali D, Mack M, Jung S, Keshet E: On-site education of VEGF-recruited monocytes improves their performance as angiogenic and arteriogenic accessory cells. J Exp Med 2013;210:2611-2625.
56 Briley LP, Szczech LA: Leptin and renal disease. Semin Dial 2006;19:54-59.
57 Garonna E, Botham KM, Birdsey GM, Randi AM, Gonzalez-Perez RR, Wheeler-Jones CP: Vascular endothelial growth factor receptor-2 couples cyclo-oxygenase-2 with pro-angiogenic actions of leptin on human endothelial cells. PLoS One 2011;6:e18823.
58 Leung JC, Chan LY, Lam MF, Tang SC, Chow CW, Lim AI, Lai KN: The role of leptin and its short-form receptor in inflammation in db/db mice infused with peritoneal dialysis fluid. Nephrol Dial Transplant 2012;27:3119-3129.
59 Fang TC, Lee CJ, Wang CH, Liou HH, Hsu BG: Fasting serum leptin level correlates with mid-arm fat area in peritoneal dialysis patients. Ther Apher Dial 2010;14:583-588.
60 Leung JC, Chan LY, Tang SC, Chu KM, Lai KN: Leptin induces TGF-beta synthesis through functional leptin receptor expressed by human peritoneal mesothelial cell. Kidney Int 2006;69:2078-2086.
61 Pang L, Zhang Y, Yu Y, Zhang S: Resistin promotes the expression of vascular endothelial growth factor in ovary carcinoma cells. Int J Mol Sci 2013;14:9751-9766.
62 Yamawaki H: Vascular effects of novel adipocytokines: focus on vascular contractility and inflammatory responses. Biol Pharm Bull 2011;34:307-310.
63 Lai KN, Leung JC: Inflammation in peritoneal dialysis. Nephron Clin Pract 2010;116:c11-18.

64 Szeto CC, Lai KB, Chow KM, Kwan BC, Cheng PM, Kwong VW, Choy AS, Leung CB, Li PK: Plasma mitochondrila DNA level is a prognostic marker in peritoneal dialysis patients. Kidney Blood Press Res 2016;41:402-412.
65 Velloso MS, Otoni A, de Paula Sabino A, de Castro WV, Pinto SW, Marinho MA, Rios DR: Peritoneal dialysis and inflammation. Clin Chim Acta 2014;430:109-114.
66 Wolf G, Chen S, Han DC, Ziyadeh FN: Leptin and renal disease. Am J Kidney Dis 2002;39:1-11.
67 Costacou T, Orchard TJ: Adiponectin: good, bad, or just plain ugly? Kidney Int 2008;74:549-551.
68 Ahima RS: Adipose tissue as an endocrine organ. Obesity (Silver Spring) 2006;14:242S-249S.
69 Teta D, Maillard M, Halabi G, Burnier M: The leptin/adiponectin ratio: potential implications for peritoneal dialysis. Kidney Int Suppl 2008;108:S112-118.
70 He Y, Lu L, Wei X, Jin D, Qian T, Yu A, Sun J, Cui J, Yang Z: The multimerization and secretion of adiponectin are regulated by TNF-alpha. Endocrine 2016;51:456-468.
71 Guerre-Millo M: Adiponectin: an update. Diabetes Metab 2008;34:12-18.
72 Ouchi N, Walsh K: Adiponectin as an anti-inflammatory factor. Clin Chim Acta 2007;380:24-30.
73 Parker-Duffen JL, Nakamura K, Silver M, Kikuchi R, Tigges U, Yoshida S, Denzel MS, Ranscht B, Walsh K: T-cadherin is essential for adiponectin-mediated revascularization. J Biol Chem 2013;288:24886-24897.
74 Kang SH, Cho KH, Park JW, Yoon KW, Do JY: Change in body composition in accordance with residual renal function in patients on peritoneal dialysis. J Ren Nutr 2013;23:438-444.
75 Arner P, Bernard S, Salehpour M, Possnert G, Liebl J, Steier P, Buchholz BA, Eriksson M, Arner E, Hauner H, Skurk T, Ryden M, Frayn KN, Spalding KL: Dynamics of human adipose lipid turnover in health and metabolic disease. Nature 2011;478:110-113.
76 Gustafson B: Adipose tissue, inflammation and atherosclerosis. J Atheroscler Thromb 2010;17:332-341.
77 Laforest S, Labrecque J, Michaud A, Cianflone K, Tchernof A: Adipocyte size as a determinant of metabolic disease and adipose tissue dysfunction. Crit Rev Clin Lab Sci 2015;52:301-313.
78 Turner JJ, Foxwell KM, Kanji R, Brenner C, Wood S, Foxwell BM, Feldmann M: Investigation of nuclear factor-kappaB inhibitors and interleukin-10 as regulators of inflammatory signalling in human adipocytes. Clin Exp Immunol 2010;162:487-493.
79 Maury E, Noel L, Detry R, Brichard SM: In vitro hyperresponsiveness to tumor necrosis factor-alpha contributes to adipokine dysregulation in omental adipocytes of obese subjects. J Clin Endocrinol Metab 2009;94:1393-1400.
80 Jetten N, Verbruggen S, Gijbels MJ, Post MJ, De Winther MP, Donners MM: Anti-inflammatory M2, but not pro-inflammatory M1 macrophages promote angiogenesis in vivo. Angiogenesis 2014;17:109-118.
81 Michaud A, Pelletier M, Noel S, Bouchard C, Tchernof A: Markers of macrophage infiltration and measures of lipolysis in human abdominal adipose tissues. Obesity (Silver Spring) 2013;21:2342-2349.
82 Isakson P, Hammarstedt A, Gustafson B, Smith U: Impaired preadipocyte differentiation in human abdominal obesity: role of Wnt, tumor necrosis factor-alpha, and inflammation. Diabetes 2009;58:1550-1557.
83 Maury E, Brichard SM: Adipokine dysregulation, adipose tissue inflammation and metabolic syndrome. Mol Cell Endocrinol 2010;314:1-16.
84 Cinti S, Mitchell G, Barbatelli G, Murano I, Ceresi E, Faloia E, Wang S, Fortier M, Greenberg AS, Obin MS: Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans. J Lipid Res 2005;46:2347-2355.
85 Vinchi F, Costa da Silva M, Ingoglia G, Petrillo S, Brinkman N, Zuercher A, Cerwenka A, Tolosano E, Muckenthaler MU: Hemopexin therapy reverts heme-induced proinflammatory phenotypic switching of macrophages in a mouse model of sickle cell disease. Blood 2016;127:473-486.
86 Gerhardt T, Ley K: Monocyte trafficking across the vessel wall. Cardiovasc Res 2015;107:321-330.
87 Lee MY, Wang Y, Mak JC, Ip MS: Intermittent hypoxia induces NF-kappaB-dependent endothelial activation via adipocyte-derived mediators. Am J Physiol Cell Physiol 2016;310:C446-455.