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editorial

Chronic microinflammation and endothelial damage in uremia

R. Ojeda and P. A. Aljama

Servicio de Nefrología. Hospital Universitario Reina Sofía. Córdoba.

Nefrología 2008; 28 **(6)** 583-586

Chronic kidney disease (CKD) patients have a higher rate of cardiovascular morbidity and mortality than the general population from early stages of the disease, and this rate may increase by 1000-fold in advanced stages of CKD (stages 4-5 and on renal replacement therapy)[1]. This high rate of morbidity and mortality cannot be explained only by traditional cardiovascular risk factors (diabetes, hypertension, smoking, hypercholesterolemia, and age); CKD patients have additional nontraditional risk factors directly related to their disease such as uremia, hyperhomocysteinemia, malnutrition, altered calcium and phosphorus metabolism, increased oxidative stress and chronic microinflammation.[2]

Among nontraditional risk factors, the chronic microinflammation state present in uremia currently has a very significant role in the development of endothelial damage in CKD patients. This is shown by the large number of studies published in the literature reporting an association between the microinflammation state and development of endothelial dysfunction from the early stages of chronic kidney disease. It is known that endothelial dysfunction is the first step for subsequent development of atherosclerosis, which can help us to explain in part the high rate of cardiovascular disease in this group of patients.[3-7]

OXIDATIVE STRESS AND ENDOTHELIAL DYSFUNCTION

The vascular endothelium regulates vessel tone by releasing vasoactive substances such as nitric oxide (NO). Therefore, the deficiency in NO that CKD patients are known to have from the early stages of the disease[11] will lead to signs of endothelial dysfunction from impaired endothelium-dependent vasodilation, thus promoting the development of atherosclerosis and subsequent appearance of cardiovascular events.

Several mechanisms have been proposed to cause the endothelial damage associated with the chronic microinflammation state of uremic patients and the excessive oxidative stress manifested by a reduction in NO levels. One of the mechanisms that has been studied in greater depth is the production of reactive oxygen species (ROS) in areas of inflammation, such as the superoxide anion released by phagocytes recruited in areas of inflammation due to this increased oxidative stress.[8] ROS release is the result of an imbalance between proinflammatory and antiinflammatory mechanisms in favor of the former; which is known to occur in uremic patients.[9] Endothelial cells are damaged by ROS despite the fact that the endothelium has antioxidant mechanisms against these deleterious products. If the number of ROS is high and if the release of these ROS persists over time, the defense mechanisms of the endothelial cell may be insufficient and endothelial damage is produced with subsequent development of atherosclerosis.[10] Overproduction of ROS will result in a reduced availability of NO, whose main role in the vascular endothelium is known to be to cause endothelium-dependent vasodilation, and therefore its reduction contributes to the development of endothelial dysfunction.[11]

Together with ROS production, which will be a determining factor in the reduction of plasma NO levels, another of the mechanisms that influences the development of endothelial damage/dysfunction and which also produces a reduction in plasma NO levels in uremic patients is the increase in asymmetric dimethylarginine (ADMA). ADMA is a competitive inhibitor of endothelial nitric oxide synthetase (eNOS), so the increase in ADMA observed in CKD patients as a result of reduced renal clearance causes plasma NO levels to decrease. Therefore, the increase in ADMA observed in uremia is another mechanism that explains the development of endothelial dysfunction from the early stages of chronic kidney disease, causing like ROS a dysfunc-

Correspondence: *Raquel Ojeda López*
Servicio de Nefrología
Hospital Universitario Reina Sofía
Avda. Menéndez Pidal, s/n
14004 Córdoba
raqojeda@hotmail.com

tion of endothelium-dependent vasodilation due to decreased NO.[12]

INFLAMMATION AND ENDOTHELIAL DAMAGE

Although several studies have been published in the literature that show the relationship between endothelial damage, oxidative stress and inflammation in CKD patients, the mechanism by which the microinflammation state of uremic patients causes endothelial damage it is still not fully clear; it is thought to be due to an alteration of the immune system related to the persistence of chronic inflammation.[13-15]

The inflammatory response plays a very important role in defending the body against external aggressions. Its main objective is to eliminate agents that can cause tissue damage. But if this inflammatory state persists over time, as occurs in uremia, the chronic inflammatory state may be harmful for the body, changing from a mechanism of defense to a mechanism of damage.[16] Therefore, the chronic microinflammation state present in uremia has been proposed as one of the mechanisms causing endothelial dysfunction, the first step for subsequent development of atherosclerosis, although the way in which this damage is produced is not fully understood.[7]

In vitro studies with endothelial cells have shown that endothelial cells cultured in contact with a uremic medium are characterized by increased adhesion molecule expression. This increase in vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) was found to the expression of increased inflammatory activity. These same findings were shown in studies conducted in vivo with uremic patients, where it was observed that an increase in these adhesion molecules coincided with an increase in inflammatory activity, and that this was related to a higher number of cardiovascular events[17,18]. Consequently, it is thought that the increase in these adhesion molecules in the vascular endothelium is one of the possible mechanisms of endothelial damage related to the microinflammation state in uremia.

Another of the mechanisms recently proposed to explain the relationship between microinflammation and the development of endothelial damage is activation of the immune system in CKD, which is shown in peripheral blood by determination of a subpopulation of activated monocytes in the serum of uremic patients, CD14+/CD16+ monocytes,[19] described in recent publications in relation to the chronic inflammation state in uremia. These cells have been found to be increased in peripheral blood of uremic patients, even when there is no clinical evidence of an active inflammatory process or an increase in peripheral blood of other inflammatory markers, such as C-reactive protein or proinflammatory cytokines.[19] Recently published studies have observed a direct relationship between this monocyte subpopulation and the development of cardiovascular events.[20] CD14+/CD16+ monocytes are a subpopulation of this cell group that exhibits special phenotypical characteristics, with a shorter telomere than unactivated CD14++/CD16- monocytes. CD14+/CD16+ monocytes show an increase in proinflammatory cytokines in their cytoplasm, which are released to the bloodstream after being stimulated by an external aggression.[19,20]

The role that this monocyte subpopulation plays in the production of endothelial damage in CKD patients is unclear. Studies have recently been published of an experimental model in which these cells are cultured with HUVEC endothelial cells (an endothelial cell line derived from human umbilical vein endothelial cells). This experiment placed activated monocytes in contact with endothelial cells to see what effect the CD14+/CD16+ monocytes caused on endothelial cells. ROS activity and apoptosis were determined by flow cytometry to measure endothelial damage in the HUVEC.[21] Increased ROS activity in endothelial cells is thought to play a very important role in the endothelial damage associated with CKD, as previously described. In this study, ROS activity was measured in three different HUVEC cocultures: with total monocytes (CD14++/CD16- together with CD14+/CD16+), with unactivated monocytes (CD14++/CD16-) and activated monocytes (CD14+/CD16+). Only the HUVEC cells cocultures with this latter subset of activated monocytes showed increased ROS activity. Similarly, when apoptosis was measured, only this last culture of HUVEC cells with activated monocytes was increased, which supports the idea that oxidative stress induced by microinflammation in the endothelial cells plays a very important role in the production of endothelial damage in CKD patients.[5] This study supports the hypothesis that independently of uremia, microinflammation mediated by CD14+/CD16+ cells induces endothelial damage in CKD patients and thus may contribute significantly to subsequent development of atherosclerosis and therefore to cardiovascular events, the leading cause of morbidity and mortality in CKD patients.

In the same line of this study, another study has been recently published in which the HUVEC cells and the different subpopulations of monocytes were placed in bacterial DNA cocultures, the authors again determined that only in the coculture of activated monocytes (CD14+/CD16+) from uremic patients and not in mononuclear cells from healthy subjects

was there increased apoptosis of endothelial cells (HUVEC) and increased release of proinflammatory cytokines.[21] These results support the hypothesis of development of endothelial dysfunction in uremia from increased endothelial cell apoptosis as well as the presence of a subpopulation of activated monocytes.

Finally, we would mention that a study has recently been published that goes one step further in knowledge of the mechanisms of endothelial damage in uremia. This study used proteomics to elucidate which are the proteins damaged in the endothelial cells that will promote subsequent development of endothelial dysfunction. This study measured in vitro the proteins from HUVEC cells that are damaged when they are cultured in a uremic medium, taking as controls these same proteins measured in HUVEC cells after performing the same experiment in a nonuremic medium. The results of this in vitro study help to understand even better the mechanisms of endothelial damage in uremic patients by determining the increase in proteins associated with oxidative stress and inflammation,[22] both of which are mechanisms implicated in the development of endothelial damage from the early stages of CKD.

CONCLUSION

We know that the vascular endothelium is a metabolically active organ with multiple functions, including protection against the development of atherosclerosis and blood pressure control. The appearance of endothelial damage and/or dysfunction has been shown to be the first step for subsequent development of atherosclerosis. Evidence of endothelial dysfunction has been detected in uremic patients from early stages of the disease, which can help to explain the high rate of cardiovascular morbidity and mortality in this group of patients. In this study, we have attempted to analyze the possible mechanisms implicated in the early development of endothelial dysfunction, but much data still remains to be known and many questions to be answered.

A good knowledge of all the mechanisms by which endothelial damage is produced in CKD patients is important because of the high rate of morbidity and mortality caused by cardiovascular events in this population. A complete knowledge of these mechanisms is very important to be able to propose different therapeutic strategies to prevent the development of endothelial damage/dysfunction or slow its progression once it has developed, thus preventing subsequent development of atherosclerosis and the appearance of cardiovascular events.

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