

A Novel Player in Atherosclerotic Diseases in Renal Patients: Tumor Necrosis Factor-like Weak Inducer of Apoptosis (TWEAK)

Böbrek Hastalarında Ateroskleroz Gelişiminde Yeni Bir Oyuncu: Tumor Necrosis Factor-like Weak Inducer of Apoptosis (TWEAK)

ABSTRACT

Cardiovascular disease is common in patients with chronic kidney disease. Atherosclerosis has a very important role in pathogenesis of cardiovascular diseases. Tumor Necrosis factor- Like Weak Inducer of Apoptosis (TWEAK) is a glycoprotein that belongs to the TNF superfamily. TWEAK plays important roles in cellular proliferation, growth, migration, osteoclastogenesis, angiogenesis and apoptosis. In the recent years, TWEAK has been suggested to have a role in atherosclerosis. While it is known that TWEAK levels are decreased in patient with renal failure, its association with atherosclerosis is not well-defined. This review focuses on the association of TWEAK with atherosclerosis in patients with renal patients.

KEY WORDS: Kidney, TWEAK, Atherosclerosis

ÖZ

Kronik böbrek yetmezliği hastalarında kardiyovasküler olaylar sık görülür. Ateroskleroz, kardiyovasküler olayların patogeneğinde önemli bir yere sahiptir. Tumor Necrosis factor- Like Weak Inducer of Apoptosis (TWEAK) TNF süper familyasına ait bir glikoproteindir. TWEAK organizmada hücrel büyüme, proliferasyon, migrasyon, osteoklastogenezis, anjiogenezis ve apoptoziste rol oynar. Son zamanlarda TWEAK'ın ateroskleroz gelişiminde de rol oynayabileceği ileri sürülmüştür. Böbrek yetmezliği durumlarında TWEAK düzeylerinin azaldığı bilinirken renal hasta popülasyonunda TWEAK-ateroskleroz ilişkisi netlik kazanmamıştır. Bu derlemede böbrek hastalarında TWEAK-ateroskleroz ilişkisi gözden geçirilmiştir.

ANAHTAR SÖZCÜKLER: Böbrek, TWEAK, Ateroskleroz

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INTRODUCTION

Chronic renal failure (CRF) is a clinical table that develops secondary to the gradual impairment of renal functions in patients with chronic renal disease, and it is associated with permanent reduction of the glomerular filtration rate (1). Generally, CRF is a process which starts with reduction of glomerular filtration rate below 60 ml/min. Patients with renal failure suffer cardiovascular system problems in addition to other systems and the cardiovascular problems are among the most significant causes of death for this group of patients (2). Advanced age, hypervolemia, hypertension, diabetes, uremia, atherosclerosis and

vascular calcification make significant contributions to cardiovascular death in this group of patients. It is known that correction of hypervolemia and hypertension reduces the frequency of cardiovascular events. Following a successful renal transplantation to patients with chronic renal failure, rate of cardiovascular diseases decreases, although cardiovascular events are still among the most significant factors which influence the survival in this group of patients.

Atherosclerosis is a condition characterized with formation of plaques, also referred as atheroma, on the intima layer of vessels. Pathogenesis of the atherosclerosis is poorly understood; however, the view of damage-



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repair is more strongly advocated (3). Introduced first by Ross, this theory emphasizes that the events are triggered by endothelial dysfunction. It has been known for long time that somewhat preparatory causes are present that facilitate operation of the mechanism pertaining to the development of atherosclerosis. Many studies have been conducted to reveal the endothelial dysfunction that develops in the course of chronic renal disease (4). Age, hypertension, diabetes, smoking and family history are among principal factors. Other risk factors include abdominal obesity, insulin resistance, high serum C-reactive protein levels, high leukocyte-hematocrit levels and high serum lipoprotein (a) and homocysteine levels (5). It is known that chronic renal failure accelerates development of the atherosclerosis.

Tumor Necrosis Factor-like Weak Inducer of Apoptosis (TWEAK)

TNF-like weak induced of apoptosis (TWEAK) is a Type 2 trans-membrane glycoprotein that is a member of the TNF super family and has a molecular weight of 18 kilo-dalton. The human TWEAK gene is located at chromosome 17. TWEAK can be synthesized in many tissues, particularly pancreas, intestines, heart, brain, lung, ovary, liver and kidney (6). TWEAK binds Fn 14, the relevant receptor at cellular level, and undertakes different functions in many physiological systems. The Fn 14 gene is located at chromosome 16 (7). It is believed that the recently discovered CD163 have roles in Fn 14-free cells which function as receptor for TWEAK (8). The TWEAK-Fn14 complex plays role in cellular growth, proliferation, migration, osteoclastogenesis, angiogenesis and apoptosis (7). Moreover, the TWEAK plays role also in the inflammation by increasing release of adhesion molecules and pro-inflammatory cytokines via the activation of nuclear factor kappa beta (Nf-kB) (9).

TWEAK and the Kidney

The potential source of TWEAK in kidney includes infiltration of monocytes and T-lymphocytes. In addition, tubular epithelial cells and mesangial cells produce TWEAK and Fn14. Experimental studied demonstrated that TWEAK leads to the activation of NF-kB in rat tubular epithelial cells resulting in induction of inflammation by increasing production of IL-6 and monocyte chemo-attractant protein-1 (MCP-1) (10). Thus, it is considered that TWEAK leads to tubulointerstitial inflammation (11). Yet, TWEAK has been found to cause glomerular damage, although there is no consensus. Apoptosis is known to result in the death of the renal cell. We believe that a co-stimulant such as interferon gamma is required in order to ensure that TWEAK leads to apoptosis in kidneys.

TWEAK and Atherosclerosis

The relationship between TWEAK and atherosclerosis has not been clarified yet. Rat studies have determined that TWEAK mRNA levels reduce in tissues and peritoneal macrophages in case of acute and chronic inflammation (12). Moreover, it was

demonstrated that release of TWEAK from atherosclerotic arteries reduces in comparison with that of healthy arteries. It is determined that low TWEAK levels are related with subclinical atherosclerosis (13), while the level of TWEAK increases in several inflammatory conditions such as experimental autoimmune encephalitis (9).

Recently, the relation of TWEAK with atherosclerosis and endothelial dysfunction has been investigated in both renal and non-renal patient populations. However, results are contradictory. The observation that increased TWEAK level plays a dominant role in inflammatory events and that the level decreases in atherosclerosis suggests that the event may vary depending on the interaction at receptor level or it may have dual effects.

It is known that TWEAK induces release of MCP-1 by human smooth muscle cells. Moreover, TWEAK is also released from macrophages located on atherosclerotic plaques in human carotid arteries. Blanco-Colio et al. compared 30 atherosclerotic (diabetic) and 28 healthy subjects and demonstrated that plasma TWEAK levels were significantly low in the atherosclerotic population and there was negative correlation between TWEAK level and carotid artery intima-media thickness (CA-IMT) (14). The authors reported that the results were surprising as TWEAK enhances proinflammatory activity and a positive relation is expected between TWEAK and atherosclerosis under normal conditions. However, it has recently been suggested that TWEAK may play a protective role against severe inflammatory conditions and that the production and release of TWEAK may decrease under atherosclerotic conditions.

In a study conducted by Kralish et al., 60 patients with creatinine clearance >50 ml/min (the control group) and 60 chronic hemodialysis patients were enrolled. Thirty diabetic patients from the control group and 32 diabetic patients from the hemodialysis group were compared with respect to TWEAK level and it was found that the TWEAK level is significantly reduced in the diabetic + dialysis group and the deficiency of this marker may be a risk factor for atherosclerosis (13).

Yilmaz et al. evaluated 295 non-diabetic patients with chronic renal failure at different stages and aimed to investigate the relationship between plasma TWEAK level and endothelial dysfunction. In conclusion, it was found that the higher renal failure stages were associated with lower TWEAK levels and more severe endothelial dysfunction. In addition, it was determined that TWEAK is an independent predictor of endothelial dysfunction (15). It was reported that the receptor of TWEAK, Fn 14, increased in pathological processes and thus serum levels of TWEAK reduced; however, the mechanism could not be clearly understood.

In a study conducted by Carrero et al., it was demonstrated that in contrast to reduction, increases in TWEAK levels and inflammatory markers (IL-6) contributed to the mortality in

208 hemodialysis patients (16). Again, Jain et al. found that increased serum TWEAK levels were responsible for dilated cardiomyopathy and cardiac dysfunction (17). Those studies demonstrated that TWEAK level is negatively correlated with Hs-CRP, blood pressure and insulin resistance determinants and positively correlated with the creatinine clearance.

In a study conducted by Gungor et al. on 131 hemodialysis patients, there was a weak negative correlation between serum TWEAK level and CA-IMT (18), while in another study that enrolled 117 renal transplant patients, a strong positive correlation was found between TWEAK level and CA-IMT (19). Those studies found that TWEAK levels were closely related with renal functions.

In conclusion, as the above referenced studies demonstrate, TWEAK levels may exert different effects at different clinical conditions. Most studies were cross-sectional and it was found that both high and low values were associated with negative outcomes since serum and plasma levels of TWEAK were used. The studies also demonstrated that TWEAK levels decrease when renal functions are impaired. It is obvious that new studies conducted with larger patient populations, which investigate particularly the interaction at the receptor level, are required in order to better clarify the role of TWEAK in the pathogenesis of the atherosclerosis.

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