Review

Hormones and Arterial Stiffness in Patients with Chronic Kidney Disease

Ozkan Gungor¹, Fatih Kircelli¹, Luminita Voroneanu², Adrian Covic² and Ercan Ok¹

¹Ege University School of Medicine, Division on Nephrology, Izmir, Turkey
²Gr. T. Popa University Hospital, Division on Nephrology, Lasi, Romania

Cardiovascular disease constitutes the major cause of mortality in patients with chronic kidney disease. Arterial stiffness is an important contributor to the occurrence and progression of cardiovascular disease. Various risk factors, including altered hormone levels, have been suggested to be associated with arterial stiffness. Based on the background that chronic kidney disease predisposes individuals to a wide range of hormonal changes, we herein review the available data on the association between arterial stiffness and hormones in patients with chronic kidney disease and summarize the data for the general population.


**Key words:** Hormones, Arterial stiffness, Renal patients

---

**Introduction**

The diagnosis, prevention and management of cardiovascular disease constitute one of the major challenges in chronic kidney disease (CKD) patients. Despite extensive research on cardiovascular outcomes, dialysis patients continue to face increased rates of cardiovascular morbidity and mortality compared to the general population. Arterial stiffness (AS) is one of the most important contributors to this high cardiovascular burden. Hypertension, hypervolemia, increased sympathetic activity, inflammation and the renin-angiotensinogen-aldosterone system have also been identified to be risk factors for AS. However, there is much more to be clarified from the point of view of the etiopathogenesis and pathophysiology of CKD, considering the complex nature of the disease.

Although several studies have reported significant effects of hormonal disturbances on AS in the general population, data are limited in CKD patients. In addition, uremia is associated with disturbance of the hypothalamic-hypophyseal and gonadal axis that leads to a wide spectrum of hormonal changes.

In this review, we focus on the importance of AS, changes in the hormonal profile of CKD patients and the effects of hormonal disturbance on AS.

**Arterial Stiffness and CKD: General Considerations**

Arterial stiffness is one of the earliest manifestations of adverse structural and functional injuries within the vessel wall. AS results from the complex interplay between several independent and interdependent factors. Aging is considered to be the most important risk factor for the development of AS alongside other various changes in hemodynamic forces, salt intake, glycemic control and the overall decline in the cellular function. In the arterial wall, aging and increased blood pressure leads to stiffening via medial degeneration that presents with fractures and fragmentation of the elastic lamellae, increased collagen and calcium content, dilation and hypertrophy of the large arteries. In CKD patients, the uremic milieu predisposes the vascular bed to more pronounced injuries, including capillary rarefaction, an increased wall to lumen ratio of the small arterioles and decreased endothelium-mediated vasodilation. Consequently, CKD patients have stiffer arteries than controls of the same age and blood pressure. The
underlying mechanisms of the development of AS in patients with CKD remain unclear; however, elevated levels of oxidative stress and inflammatory markers, hypervolemia, arterial calcification, activation of the renin-angiotensin-aldosterone system, overactivity of the sympathetic nervous system and hormones are anticipated to play a role.  

AS has been associated with numerous comorbidities and, most importantly, shown to independently predict all-cause and cardiovascular mortality, fatal and nonfatal coronary events and fatal strokes, both in the general and CKD populations. Increased left ventricular stress and reduced coronary perfusion, both caused by AS, lead to cardiac hypertrophy and myopathy, thus resulting in congestive heart failure and sudden death in CKD patients. In hemodialysis patients, a 1 m/s increase in PWV index has been associated with a 15% increase in the adjusted CV and overall mortality. Sipahioglu et al. reported that, among 156 PD patients of Caucasian origin, a 23% increase was observed in cardiovascular mortality, but not with all-cause mortality, following a 1-m/s increase in PWV index. In a Chinese PD population, a high baseline carotid-femoral PWV (CF-PWV) was found to be associated with a lower overall survival, although the prognostic value of the CF-PWV disappeared after adjusting for confounding factors. Whether this difference is due to differences in racial backgrounds or other risk factors requires further study.

Reversing the detrimental effects of uremia following successful renal transplantation can result in the attenuation of AS. Indeed, several studies have confirmed this hypothesis. The recipient age, graft function, proteinuria, donor age and cold ischemia time have been reported to be predictors of arterial stiffness after renal transplantation.

### Hormonal Changes in CKD: General Considerations

The kidneys not only secrete, but also play a role in the metabolism of, a wide spectrum of hormones. Therefore, once the kidneys fail, the hormonal balance in the human body is very much disturbed. The primary hormones affected in patients with CKD include insulin and the thyroid, sex, growth and parathyroid hormones. Changes in these hormones and the resulting associations with various outcomes are presented in Table 1.

#### Thyroid Hormones

CKD affects thyroid metabolism at all levels of the hypothalamic-pituitary-thyroid axis, including hormone production, distribution and excretion, in the absence of underlying intrinsic thyroid disor-

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Disease (patient number)</th>
<th>Hormonal change</th>
<th>Determinants</th>
<th>Change in AS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peleg et al. (2008)</td>
<td>Subclinic hypothyroidism (30)</td>
<td>Subclinic hypothyroidism</td>
<td>Aortic AS</td>
<td>Increase</td>
</tr>
<tr>
<td>Nagasaki et al. (2007)</td>
<td>Hypothyroidism (46)</td>
<td>Hypothyroidism</td>
<td>Carotid AS</td>
<td>Increase</td>
</tr>
<tr>
<td>Dage et al. (2005)</td>
<td>Hypothyroidism (65)</td>
<td>Hypothyroidism</td>
<td>Aortic AS</td>
<td>Increase</td>
</tr>
<tr>
<td>Bodlaj et al. (2007)</td>
<td>Graves Disease (59)</td>
<td>Hyperthyroidism</td>
<td>Aortic AS</td>
<td>Increase</td>
</tr>
<tr>
<td>Yaron et al. (2009)</td>
<td>Hypogonadism (18)</td>
<td>Low testosterone</td>
<td>Aortic AS</td>
<td>Increase</td>
</tr>
<tr>
<td>Fukui et al. (2007)</td>
<td>Diabetes (268)</td>
<td>Low testosterone</td>
<td>Carotid AS</td>
<td>Increase</td>
</tr>
<tr>
<td>Dockery et al. (2003)</td>
<td>Aging (55)</td>
<td>Low testosterone</td>
<td>Aortic AS</td>
<td>Increase</td>
</tr>
<tr>
<td>Hougaku et al. (2006)</td>
<td>Aging (901)</td>
<td>Low testosterone</td>
<td>Carotid AS</td>
<td>Increase</td>
</tr>
<tr>
<td>Moreau et al. (2012)</td>
<td>Postmenopause (24)</td>
<td>Low estradiol</td>
<td>Carotid AS</td>
<td>Increase</td>
</tr>
<tr>
<td>Georgiopulos et al. (2009)</td>
<td>Postmenopause (76)</td>
<td>Hyperprolactinemia</td>
<td>Carotid AS</td>
<td>Increase</td>
</tr>
<tr>
<td>Urbina et al. (2012)</td>
<td>Healthy young adults (343)</td>
<td>Insulin resistance</td>
<td>Aortic AS</td>
<td>Increase</td>
</tr>
<tr>
<td>Okada et al. (2011)</td>
<td>Non-diabetics (260)</td>
<td>Hyperinsulinemia and low insulin levels</td>
<td>Cardio-ankle index</td>
<td>Increase</td>
</tr>
<tr>
<td>Pirro et al. (2012)</td>
<td>Postmenopause (150)</td>
<td>Hyperparathyroidism</td>
<td>Aortic AS</td>
<td>Increase</td>
</tr>
<tr>
<td>Rosa et al. (2011)</td>
<td>Primary hyperparathyroidism (28)</td>
<td>Hyperparathyroidism</td>
<td>Aortic AS</td>
<td>Increase</td>
</tr>
<tr>
<td>Smith et al. (2002)</td>
<td>Hypopituitarism (32)</td>
<td>Growth hormon deficiency</td>
<td>Aortic AS</td>
<td>Increase</td>
</tr>
<tr>
<td>Fukui et al. (2007)</td>
<td>Diabetes (268)</td>
<td>Low DHEA-S</td>
<td>Aortic AS</td>
<td>Increase</td>
</tr>
</tbody>
</table>

AS: Arterial stiffness, DHEA-S: Dehydroepiandrosterone sulfate
Serum TSH level is frequently in the normal range, the free and total T4 (thyroxine) concentrations may be normal or slightly reduced and the free triiodothyronine (fT3) level is usually reduced due to diminished conversion of T4 to T3 in the periphery. The incidence and prevalence of these hormonal changes are affected by the declining glomerular filtration rate. Low T3 syndrome (characterized by a reduced fT3 level in the presence of normal TSH and fT4 levels) is more common in the mild to moderate CKD stages. Previous studies have reported increased morbidity and mortality in the presence of thyroid abnormalities in CKD patients.

**Sex Hormones**

Disturbances in the sexual function, primarily in the form of testosterone and/or estrogen deficiency, are common features of CKD. The total and free testosterone levels are typically reduced, although the binding capacity and concentration of sex hormone-binding globulin are normal. Disturbances in the levels of sex hormones are associated with decreased fertility and libido in addition to increased morbidity and mortality.

**Prolactin**

In CKD patients, the prolactin levels are significantly elevated, with a prevalence ranging from 30% to 65%. The major risk factors for an increased level of prolactin are reduced renal clearance and increased production of the hormone. Hyperprolactinemia is associated with infertility, gynecomastia, galactorrhea, loss of libido and mortality in CKD patients.

**Growth Hormone**

The fasting growth hormone (GH) levels are increased in patients with CKD due to decreased hormone degradation and increased hormone secretion. However, measurements of the growth hormone level may not be reliable considering the rapid changes in this hormone observed in CKD patients, and it has been suggested that the insulin-like growth factor-1 (IGF-1) level may be a better marker. While growth hormone disturbances in adult CKD patients are not well defined, children with CKD are reported to have normal/elevated levels of the hormone, but with less effectiveness. Several mechanisms, including decreased hepatic synthesis and bioavailability of IGF-1 and end organ resistance to GH, have been proposed for the GH alterations observed in patients with CKD. The clinical manifestations of a high level of GH are ambiguous. The use of growth hormone replacement with recombinant GH has been extensively tested in clinical studies.

**Parathyroid Hormone**

The parathyroid hormone levels are increased in nearly 60% of CKD patients. Serum calcium, phosphorus, vitamin D and FGF23 levels each influence PTH levels. Although the association between the phosphorus level and mortality is well defined, such a finding has not been fully confirmed for PTH.

**Insulin**

The kidneys play an important role in insulin metabolism. CKD is associated with decreased insulin degradation and insulin resistance (IR) at the postreceptor level, leading to hyperinsulinemia. The complex interplay between metabolic abnormalities, such as vitamin D deficiency, obesity, metabolic acidosis, inflammation and the accumulation of "uremic toxins," is believed to contribute to the etiology of IR in CKD patients. Disturbed insulin metabolism and increased insulin resistance are well-known contributors to morbidity in mortality in both the general and CKD population.

**Associations between Hormones and Arterial Stiffness in Patients with and without CKD**

**Thyroid Hormones**

Thyroid hormones are important regulators of the cardiovascular functions due to their direct effects on cardiac myocytes and endothelial and vascular smooth muscle cells, stimulation of vasodilatatory molecule production and inhibition of the angiotensin II receptor expression and its downstream signaling.

Hyperthyroidism is associated with an increased heart rate, cardiac output, pulse pressure and blood pressure and decreased systemic vascular resistance. Consequently, hyperthyroidism results in a hyperdynamic circulation and reduced vascular stiffness. The reversal of the effects of thyroid hormones on the vascular bed observed in patients treated for thyrotoxicosis further confirms the role of these hormones in vascular hemodynamics and functions. Impaired cardiac contractility, a reduced heart rate, a reduced cardiac output, increased vascular resistance and a consequently greater prevalence of hypertension predispose hypothyroidic patients to a higher cardiovascular burden. Increased AS with a higher central augmentation pressure has been reported in hypothyroidic patients, whereas the PWV is lowered and AS is reversed following L-thyroxine treatment.

There are relatively few data on the association...
between thyroid hormones and the cardiovascular function in CKD patients compared to that observed in patients without CKD. In two recently published articles, our group demonstrated that the levels of thyroid hormones are inversely related to arterial stiffness in both hemodialysis and peritoneal dialysis patients. There are several potential pathways by which thyroid hormones may affect the vascular bed, including alteration of tissue oxygen consumption, blood volume, cardiac contractility and heart rate and dilation of the peripheral resistance arterioles. Another potential confounding factor for the effects of the thyroid hormone levels on the vascular bed is the high inflammatory burden observed in dialysis patients. The FT3 level is affected by inflammation, which decreases this parameter by inhibiting the 5′-deionidase enzyme. Inflammatory cytokines, such as tumor necrosis factor, interferon-α and interleukin-6, have been implicated in the inhibition of this enzyme. To conclude, inflammation is likely the major element involved in the association between the levels of thyroid hormones and arterial stiffness.

**Sex Hormones**

Hypogonadism has been reported to be a risk factor for cardiovascular disease in patients with and without CKD. However, only a few studies have investigated the associations between sex hormones and arterial stiffness.

**Testosterone**

In the general population, the pathophysiological mechanisms of the role of testosterone within the cardiovascular system are unclear. Several mechanisms have been proposed. Testosterone has been shown to exert direct vasodilatory effects on the vascular endothelium by acting on specific testosterone receptors and receptor-independent non-genomic pathways that regulate the opening of calcium and potassium channels. Therefore, the reduced AS observed in men with higher testosterone levels may be due to the continuous beneficial effects of testosterone on the arterial bed. Although it has not been investigated, it may be proposed that exogenous testosterone supplementation prevents endothelial dysfunction by reducing inflammatory factors, increasing the endothelial progenitor cell activity and improving the coagulation process. Testosterone may also affect the vascular bed by regulating structural elements of the arterial wall, including collagen, elastin and fibrillin-1.

In the Baltimore Longitudinal Study of Aging, a low serum testosterone level was found to be a risk factor for AS, suggesting a cause and effect relationship between a low testosterone level and the evolution of subsequent increased arterial wall rigidity. Similarly, Dockery and Hougaku et al. demonstrated a negative association between serum testosterone levels and AS. In a subsequent study, Dockery et al. found that patients who received testosterone suppression had higher levels of AS (14.1 (10.1-21.8) vs. 12.4 (9.6-17.4) m/s, p=0.03, median) Similarly, Yaron et al. observed very rapid (evident by day 48) improvements in AS in 18 men with hypogonadism treated with transdermal testosterone replacement therapy.

Regarding CKD patients, in the one and only relevant study, Kyriazis et al. reported a negative association between the testosterone level and AS in male HD patients. Considering the effects of testosterone on the vascular bed, further research on this issue may provide important data with respect to the cardiovascular outcomes.

**Estradiol**

Endogenous sex hormones play a role in the cardiovascular risk profile of postmenopausal women by inducing hemodynamic, metabolic and immunological changes (indirect effects), as well as by acting on steroid receptors in the vascular bed (direct effects). Estrogen is capable of inducing vasodilation in the arterial bed by stimulating endothelial nitric oxide (NO) and prostacyclin synthesis. NO is important for arterial compliance, and the inhibition of NO synthesis is responsible for increased aortic stiffness. Furthermore, arterial wall compliance can be altered by the effects of estrogen on lipid metabolism and atherogenesis, arterial blood pressure, endothelial repair and smooth muscle proliferation. Additionally, estrogen has been shown to modulate the proportion of collagen and elastin in the arterial wall and directly affect smooth muscle cell proliferation.

More pronounced age-related increases in AS have been reported in women compared to that observed in men of similar age (45-60 years old). Nagai et al. successfully reduced the incidence of AS early after menopause by administering hormone replacement therapy. In contrast, Rodriguez-Macias et al. did not find any differences in AS when comparing women on long-term hormone replacement therapy to those not treated with these medications.

In CKD patients, low estrogen levels are associated with worsening of osteoporosis and a decreased quality of life. A similar deteriorative outcome on mortality was reported in 147 postmenopausal prevalent female HD patients with low levels of estrogen (HR=4.49, 95%CI 1.59-12.6, p=0.004), although high levels of estrogen were also found to have a dele-
terious effect compared to the middle tertile (HR = 4.32, 95% CI 1.59–11.7, \( p = 0.004 \)). However, there are no data regarding the association between the estrogen level and arterial stiffness. It is probable that the lack of definition of a “normal” estrogen level in CKD patients and other confounding factors, such as the lack of consensus on how and when to initiate hormone replacement therapy in this patient population, are a deterrent.

**Dehydroepiandrosterone Sulfate (DHEA-S)**

Data regarding the association between DHEA-S (a precursor of more potent androgens) and AS are limited. In a study by Fukui et al., low levels of both DHEA-S and testosterone were found to be independent predictors for AS in 268 male diabetic patients without CKD. Similar outcomes were reported only in men in a study that included 494 prevalent HD patients (313 men and 181 women).

**Prolactin**

Hyperprolactinemia is related to endothelial dysfunction and adverse cardiovascular outcomes in the general population, possibly as a result of the vasoconstrictive properties of prolactin. Therefore, an elevation of the prolactin levels is observed in patients with essential hypertension, acute coronary syndrome, ischemic stroke, preeclampsia and heart failure that accompanies postpartum cardiomyopathy. In patients with advanced atherosclerosis, an increased expression of prolactin receptors has been reported. In vitro studies have also established the modulatory role of prolactin in the inflammatory response, stimulation of adhesion of mononuclear cells to the endothelium and vascular smooth muscle cell proliferation.

As the vascular effects of prolactin remain to be clarified, data remain scarce with regard to the association between the prolactin level and AS. In one study, Georgiopoulos et al. demonstrated a positive relationship between the prolactin level and AS in 76 postmenopausal women. Prolactin may increase AS by inducing changes in vascular tone, low-grade inflammation and smooth muscle cell proliferation, thereby influencing central and peripheral hemodynamics.

Hyperprolactinemia is common in CKD patients due to both reduced renal clearance and increased production of prolactin. In patients with CKD, the prolactin levels appear substantially elevated, with a prevalence of hyperprolactinemia ranging from 30% to 65%. Carrero et al. studied 457 non-CKD and 173 CKD 5D patients and found a positive association between the prolactin levels and flow-mediated dilatation in the non-CKD patients and pulse wave velocity in the CKD 5D patients. The authors suggested that prolactin retention in CKD patients may be a contributing factor to vascular derangement and worse cardiovascular outcomes.

**Insulin**

Studies conducted in recent decades have demonstrated that hyperinsulinemia is a risk factor for cardiovascular disease. Okada et al. found that hyperinsulinemia is associated with an elevated cardio-ankle vascular index in the general population. Similarly, insulin resistance is related to AS in adolescents, adults with metabolic syndrome, diabetes and hypertension and healthy nondiabetic women. The mechanisms linking insulin resistance to AS remain unclear; however, many potential mechanisms have been suggested, including increased sympathetic tone, promotion of sodium reabsorption, activation of the renin-angiotensin-aldosterone system and increased systemic and vascular inflammation.

Zhou et al. showed a positive relationship between the insulin levels and carotid stiffness in 80 nondiabetic CKD patients. In a more recent article, we demonstrated that insulin resistance is a risk factor for cardiovascular disease in nondiabetic patients older than 50 years of age. Of the 53 patients enrolled in that study, 48 were on continuous ambulatory peritoneal dialysis (PD) and five were on automated PD. Age and MAP, but not HOMA-IR, were found to be independent predictors of arterial stiffness after adjusting for age, gender, PD duration, HOMA-IR, body mass index and mean arterial pressure. However, when the patients were divided into two groups according to the median age (≤49 and >50), the mean arterial pressure, male gender and age were found to be predictors of the c-f PWV in the patients ≤49 years of age, whereas HOMA-IR was found to be the only predictor of the c-f PWV in the patients >50 years of age.

Stimulation of the sympathetic nervous system, activation of proinflammatory factors, endothelial dysfunction, renal sodium absorption, activation of the renin-angiotensin-aldosterone system, release of advanced glycation end products and lipid peroxidation have been proposed to be responsible for the IR-induced vascular changes observed in this patient population. Age is an important risk factor for insulin resistance. Declines in muscle mass and muscle oxidative capacity associated with aging have been shown to cause IR in CKD patients.

**Other Hormones**

High PTH levels are also considered to be involved in the pathogenesis of increased AS. How-
Hormones and Arterial Stiffness in Renal Disease Patients

The association between the ACTH-cortisol axis and AS in CKD patients is unclear. In patients without CKD, only one study has addressed this issue, which found no associations in 25 patients with Cushing’s disease94).

A summary of the associations between the levels of these hormones and arterial stiffness in non-renal and CKD patients are presented in Table 1 and 2.

Conflicts of Interest

None.

References

2) Safar ME, Blacher J, Jankowski P: Arterial stiffness, pulse pressure, and cardiovascular disease-is it possible to break the vicious circle? Atherosclerosis, 2011; 218: 263-271
4) London GM, Marchais SJ, Guerin AP, Pannier B: Arterial...


48) Biondi B: Cardiovascular effects of mild hypothyroidism. Thyroid, 2007; 17: 625-630


60) Dockery F, Bulpitt CJ, Agarwal S, Rajkumar C: Testosterone suppression in men with prostate cancer is associated with increased arterial stiffness. Aging Male, 2002; 5: 216-222


63) Lekontseva O, Jiang Y, Schleppe C, Davidge ST: Altered neuronal nitric oxide synthase in the aging vascular sys-


76) Leanos-Miranda A, Marquez-Acosta J, Cardenas-Mon-
growth hormone deficiency. Pol Arch Med Wewn, 2007; 117: 221-226