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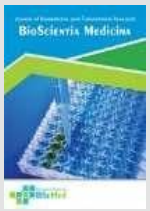

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Diurnal Variation of Blood Pressure and Arterial Stiffness in Chronic Kidney Disease

Kgs M Yusuf Arief Akbar[1*], Novadian Suhaimi[1], Zulkhair Ali[1], Suprapti Slamet[1], Ian Effendi[1], Syahpri Putra Wangsa[1], Deddy Primadona Mulia[1]

[1]Division of Nephrology and Hypertension, Department of Internal Medicine, Faculty of Medicine, Universitas Sriwijaya/Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia

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***Corresponding author:**
Kgs M Yusuf Arief Akbar

E-mail address:
kgs.myusufariefakbar@yahoo.com

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A B S T R A C T

Hypertension and chronic kidney disease (CKD) are interrelated public health problems throughout the world. Hypertension accompanied by CKD is mostly difficult to control. Difficulty in controlling blood pressure (BP) is known from changes in the diurnal variation of BP over 24 hours in CKD patients with a pattern of non-dipping and reverse dipping at night and an increase in pulse pressure due to arterial stiffness that occurs in CKD, resulting in a high incidence of nocturnal hypertension and masked hypertension. Nocturnal hypertension in CKD has a significant prognostic risk of increased risk of cardiovascular disease and cause of death. Therefore, guidelines for the management of hypertension strongly recommend that patients with hypertension have blood pressure well controlled at all times, especially to improve hypertension control at night in CKD patients.

1. Introduction

Chronic kidney disease (CKD) has been recognized as a public health problem throughout the world, as has hypertension. The prevalence of CKD in 2017 is estimated to reach 9.1% of the world population[1], with 9.5% in women and 7.3% in men, while the prevalence of hypertension in 2019, according to the World Health Organization (WHO), is estimated to reach 23% of the world's population, of which women aged 30-79 years are 32% and men are 34%.[2] In Indonesia, the prevalence of hypertension continues to increase from 25.8% in 2013 to 34.1% in 2018.[3] Hypertension and CKD are interrelated diseases because hypertension can cause or result from CKD, so the prevalence of hypertension is definitely higher, and control is more difficult with worse kidney function.

In 2017, CKD resulted in 1.2 million deaths and was the 12th leading cause of death worldwide, and cardiovascular disease due to CKD accounted for 4.6% of all causes of death. Hypertensive kidney disease is the second most common cause of kidney failure with renal replacement therapy, and the decline in kidney function is also accelerated by uncontrolled hypertension. Meanwhile, data Indonesian Renal Registry (IRR) 2020 shows that hypertensive kidney disease is the first cause of end-stage kidney failure. Uncontrolled hypertension can also cause cardiovascular and cerebrovascular diseases such as

acute coronary syndrome, hemorrhagic and ischemic stroke, heart failure, and even death. In CKD accompanied by cardiovascular disease, it is known that there is an increase in arterial stiffness, which plays a role in the occurrence of uncontrolled hypertension.[4] Arterial stiffness is a marker of vasculopathy in CKD patients. This is due to the involvement of several pathogenic factors, including uremic toxins such as uric acid, phosphate, endothelin-1 (ET-1), advanced glycation end-products (AGEs), and asymmetric dimethylarginine (ADMA) so that it has an impact on the artery walls either directly or mediated by chronic inflammation and oxidative stress resulting in a decrease in blood vessel elasticity.[5]

Therefore, to prevent and reduce cardiovascular events, slow kidney failure, and reduce mortality, it is very important to achieve optimal blood pressure in CKD patients.[6] To achieve optimal blood pressure, blood pressure monitoring should be carried out within 24 hours. The aim is to obtain diurnal variations in blood pressure in CKD. Diurnal variations in blood pressure have been shown to predict cardiovascular events in CKD.[7]

Physiology of diurnal variations in daily blood pressure

Diurnal variations in blood pressure (BP) have been known since the beginning of BP measurement and have been published in several studies using both invasive and non-invasive BP recorders. The observed BP variations continuously fluctuate throughout the day and night and follow circadian rhythms. The circadian rhythm of BP was first proposed by Millar-Craig et al.[8] using continuous intra-arterial monitoring. Blood pressure increases in the morning and afternoon but decreases in the evening before bed and during sleep. Usually, the highest blood pressure is in the middle of the morning between 06.00 – 10.00 and then falls progressively in the afternoon and evening, and the lowest blood pressure is at night when sleeping and starts to increase sharply again (spike) in the morning before morning surge. The decrease in BP at night is known as "dipping". That is, there is a decrease in BP at night (nocturnal) of 10-20% of daytime BP. If the decrease in BP at night is >20%, it is called “extreme dipping”. A decrease in night BP < 10% is called “non-dipping" and if the BP at night does not decrease but the BP actually increases higher than the BP during the day, it is called "reverse dipping”. By dipping measured using the following formula "Change in BP at night = (1-(average systolic BP at night/average systolic BP during the day)) x 100".[9-11]

Factors that influence daily blood pressure variability are divided into internal and external factors. However, there are also those who divide it into demographic factors (age, gender, ethnicity, body mass index), physiological factors (baroreflex sensitivity, hormone levels, sympathetic nerve activity), behavioral factors (physical and mental activity, obesity, and exercise), environmental factors (eating habits, sodium intake, smoking, and alcohol intake) and comorbid factors (Figure 1).[9]

Sympathetic nervous factors

Daily BP variations appear to be mediated by circadian rhythms of the sympathetic nervous system associated with changes in the sleep-wake cycle. Increased BP in the morning is associated with increased sympathetic vasoconstrictive activity in the morning. A decrease in BP during sleep is associated with a decrease in sympathetic activity that corresponds to the sleep stage of non–reparity eye movement (NREM). However, during the REM sleep stage (during dreaming), sympathetic activity will increase, and blood pressure will increase.[9] Activity Sympathetic nerves can influence the increase in heart rate performance due to the release of hormones norepinephrine from marrow adrenals, and vasoconstriction occurs, as well as sodium and water retention due to the release of renin.[10]

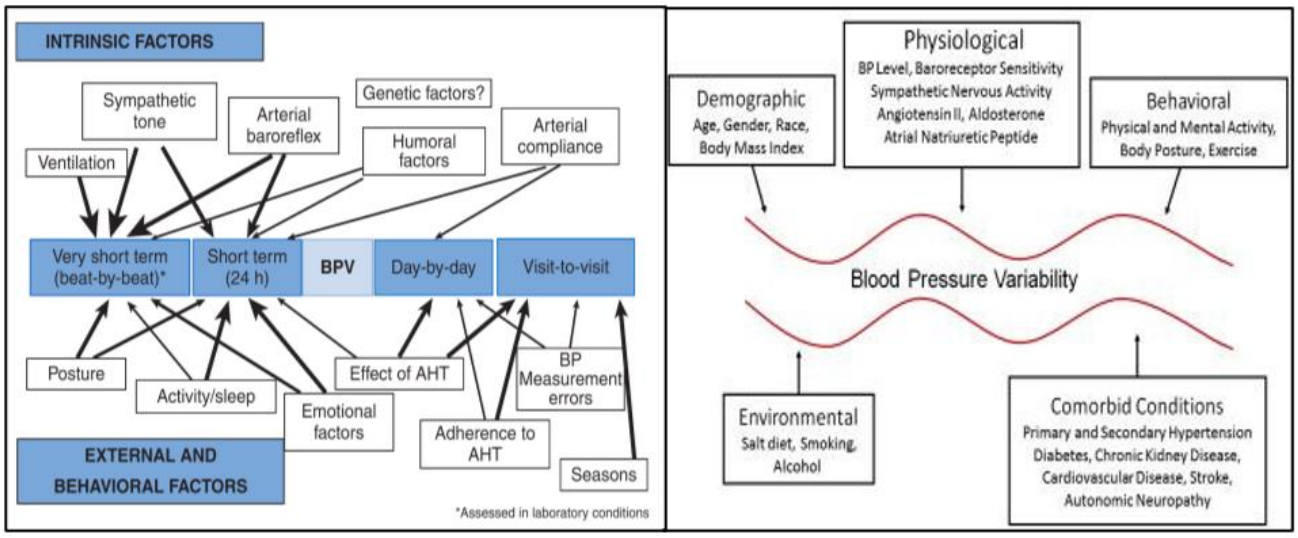

Figure 1. Various factors affect the overall degree of blood pressure variability in a particular individual. A. Internal and external factors, B. Demographic factors of behavior, physiology, environment, and comorbid conditions.[9,10]

Hormonal factors

Cortisol hormone secretion also follows a circadian rhythm, with plasma cortisol levels increasing from early morning until reaching a peak a few minutes before waking up and then decreasing gradually during the day and reaching the lowest levels at the start of sleep at night. Likewise, plasma catecholamine levels increase in the morning before waking up and reach a peak during the day, then decrease and reach their lowest point at night before bed. Increased vascular sensitivity to catecholamines coincides with increased plasma cortisol levels. This shows that cortisol and catecholamines are factors involved in the spike in blood pressure in the morning. However, catecholamine levels can immediately increase if you wake up while dreaming (REM). In contrast to the hormones cortisol and catecholamines, the hormone melatonin decreases when exposed to light, especially when exposed to sunlight, while it increases, especially when it is dark or before bed at night. This hormone is greatly influenced by exposure to light. Even when you go to bed at night but still turn on the lights, the secretion of melatonin will be delayed. Melatonin functions to lower blood pressure by inhibiting sympathetic nerve activity.[12,13]

The diurnal pattern for renin and aldosterone is also involved in the morning spike in blood pressure. It is known that levels of plasma renin activity (PRA) increase from the beginning of the morning and reach its peak before waking up in the morning and gradually decreases during the day until it reaches its lowest point at night, starting at the start of sleep.[14] (Figure 2) Plasma aldosterone levels also follow a diurnal pattern similar to renin, namely with an increase in the early hours of the morning and peaking just before or upon awakening. What's interesting is that PRA levels are closely related to sleep cycle patterns. When the sleep cycle is complete, the decrease in PRA levels coincides with the REM sleep stage, and the increase in levels coincides with the NREM sleep stage. Spontaneous awakening will provoke a rise in PRA levels that normally coincide with the NREM sleep stage. The nocturnal timing of PRA levels closely reflects the distribution pattern of sleep stages and is modified when sleep is disturbed. These observations suggest that regulatory mechanisms in the central nervous system control both the timing of PRA levels and REM-NREM sleep alternation. Apart from the levels of cortisol, catecholamines, PRA, and aldosterone, which have the same circadian timing and play a role in the morning

BP spike, arginine vasopressin (AVP), also called antidiuretic hormone (ADH) has the same role in increasing spikes in the morning. This is because increasing PRA levels will indirectly stimulate ADH secretion via angiotensin II and cause H_2O retention so that there is an increase in the circulation volume in the blood vessels.[9]

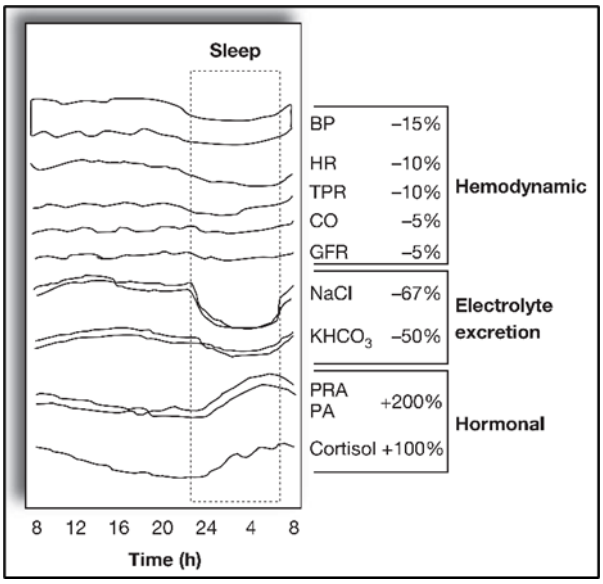

Figure 2. Pattern of decreased and increased hormones on blood pressure patterns.[14] PRA : plasma renin activity, PA: plasma aldosterone, GFR : glomerular filtration rate, CO : cardiac output, TPR: total peripheral resistance, HR : heart rate, BP : blood pressure, $KHCO_3$: potassium bicarbonate, NaCl : sodium chloride.

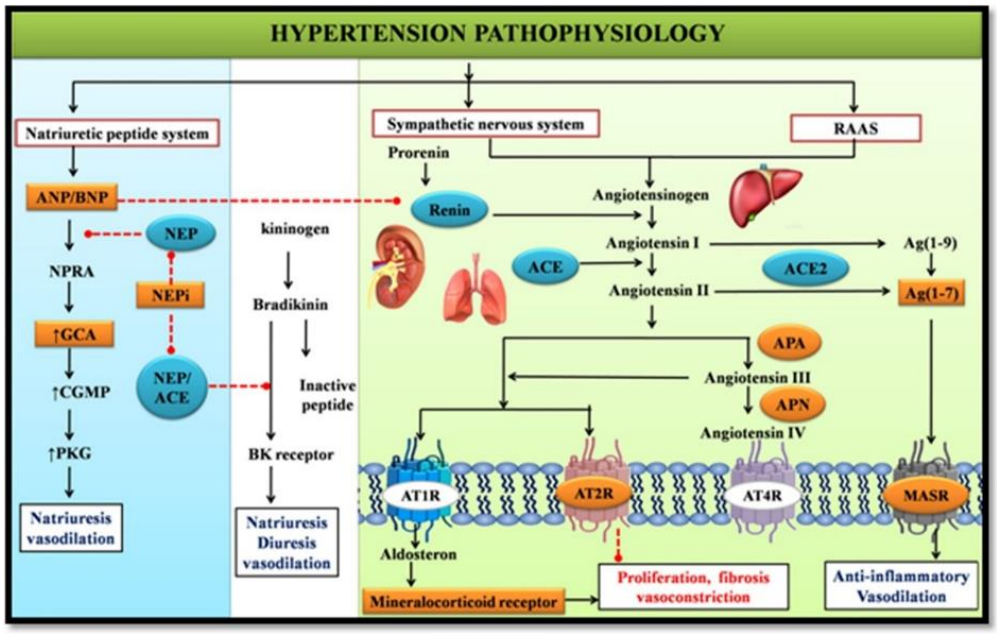

Figure 3. The role of ANP and RAAS in the pathophysiology of hypertension.[17] Renin-angiotensin-aldosterone system (RAAS), angiotensin type 1 receptor (AT1R), angiotensin type 2 receptor (AT2R), angiotensin type 4 receptor (AT4R), angiotensin-converting enzyme (ACE), atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), Natriuretic peptide receptor-A (NPR-A), Guanylyl cyclase A (GCA), Cyclic guanosine monophosphate (cGMP), protein kinase G (PKG), neprilysin (NEP), neprilysin inhibitor (NEPi), aminopeptidase A (APA), aminopeptidase N (APN).

Atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) also exhibit a circadian rhythm that provides 24-hour daily control of BP regulation. ANP functions to suppress plasma concentrations of renin, aldosterone, ACTH[15], and catecholamines and increase Na^+ excretion in urine with the aim of maintaining Na^+ balance at lower arterial pressure during night sleep (Figure 3). ANP weakens the total peripheral resistance of blood vessels, resulting in a decrease in blood pressure. Peak levels of ANP are at night before the start of sleep, which coincides with the lowest point of PRA and aldosterone levels.[16]

Endothelial vasodilator hormone nitric oxide (NO) and vasoconstrictor endothelin-1 (ET-1) also play a role in changes in blood pressure through blood vessel muscle tone. In a healthy person, NO levels are lowest when he wakes up in the morning, and the highest levels are 12 hours later, namely in the afternoon and evening.[18] Meanwhile, ET-1 increases when you wake up in the morning and decreases when you go to bed at night.

Behavioral factors

Physical and mental activity/stress

As previously explained, changes in blood pressure variations will increase in the morning when you wake up. It turns out that this is also influenced by physical activity, where waking up while the body is still lying down will slightly increase blood pressure, but if the waking position is in a sitting/upright position leaving the bed, then blood pressure will increase even faster than the previous position. Apart from physical activity, mental conditions & stress related to work conditions are also associated with increased BP. This is proven by monitoring blood pressure for 24 hours (ambulatory blood pressure monitoring (ABPM)), which shows that when someone wakes up on a weekday (Monday), there will be a 10% higher increase in BP than when they wake up on a holiday (Sunday).

Sport

Blood pressure will increase during exercise and decrease again after completing exercise. This factor is influenced by cardiac output (CO) according to the weight and lightness of the sport. There is a decrease in blood pressure after exercise (post exercise hypotension) resulting from a decrease in peripheral resistance for several hours. Based on this, exercise is recommended for non-pharmacological therapy for hypertension sufferers. Several studies have shown that regular exercise can reduce BP in patients with hypertension. Exercise done in the morning will have an impact on reducing BP during the day, while exercise done in the afternoon will have an impact on reducing BP during sleep at night.[20]

Food intake, dietary salt (Na^+), K^+, As^{2+}, Mg^{2+}, alcohol, smoking

Blood pressure slowly increases while eating and falls after eating. This increase is due to physical activity and a decrease in BP due to a decrease in total peripheral resistance due to vasodilation of the visceral organs. Several studies have found that BP decreases are higher in old age compared to young age after eating. Apart from that, the decrease in BP was also higher after consuming carbohydrates than consuming fat. This mechanism is not very clear, but the decrease in BP after eating (postprandial hypotension) is believed to be due to the inability to compensate the sympathetic nervous system due to disruption of the baroreceptor reflex, insulin-induced vasodilation, and the release of substances vasoactive intestinal peptide (VIP) which induces vasodilation so that blood pressure decreases.[20]

Someone who consumes a diet high in salt will clearly increase the risk of high blood pressure, especially at night. This happens because at night, the body contains a lot of Na^+ due to Na^+ excretion. The urine is relatively lower than Na excretion$^+$ and relatively higher urine output during the day. Meanwhile, someone who consumes K^+, As^{2+}, and Mg^{2+} has an inverse relationship with hypertension. In other words, there is a decrease in BP after consuming this mineral. This mineral content is abundant in fruits, vegetables, and dairy products.[20]

Consuming drinks such as tea, coffee, and chocolate is also believed to influence BP and cardiovascular disease. However, the caffeine contained in coffee can increase sympathetic nerve activity, causing an increase in BP. This neutralizes the effect of postprandial hypotension after eating. Meanwhile, the flavonoid content found in tea and chocolate will actually improve endothelial function in blood vessels and have an antihypertensive effect. Alcohol use will also increase BP during the day and part of the morning but will reduce BP at night. Smokers also see an increase in BP and an increase in heart rate due to the activity of the sympathetic nervous system. In smokers, BP will increase during the day and at night, so smoking can cause an increase in BP throughout the day. Smoking is known to cause increases in HR and BP through sympathetic nervous system activity.[20]

Obesity and sleep apnea

The relationship between obesity and increased BP is well known, and guidelines for hypertension also suggest losing excess weight or obesity to control BP. In obesity, there is a higher increase in BP during the day and night. In obesity incidence, sleep apnea often occurs, so the incidence of increased BP at night will be more frequent due to compensation due to circumstances of hypoxia/hypercapnia during the episode apnea.[20]

Effects of bathing

Bathing is also known to affect BP. In healthy people, BP will usually be high before bathing and will decrease when bathing in hot water. BP will decrease much more after bathing, and then gradually, BP will return to normal. This shows that there is a physiological response to bathing at high temperatures. Even post-showering hypotension can continue for up to 1 hour.[20] This is proven based on research by Kawabe et al.[21] In Japan, many people who soak in high-temperature water experience a decrease in BP 30-60 minutes after bathing, and there is no decrease in BP 61-120 minutes after bathing.[20]

Sleep physiology

There are two types of sleep, namely sleep non-rapid eye movement (NREM) and rapid eye movement (BRAKE). NREM sleep stages are divided into stages 1, 2, 3, and 4 according to the depth of sleep. Each sleep stage has unique characteristics, including variations in brain wave patterns, eye movements, and muscle tone. When you first enter sleep, go through stage 1 of NREM sleep (Figure 4) as usual and continue to the next stage. In individuals who experience sleep disorders, narcolepsy (a nervous system disorder that causes excessive sleepiness during the day and falling asleep suddenly without knowing the time and place) when entering sleep directly through the REM stage.[22]

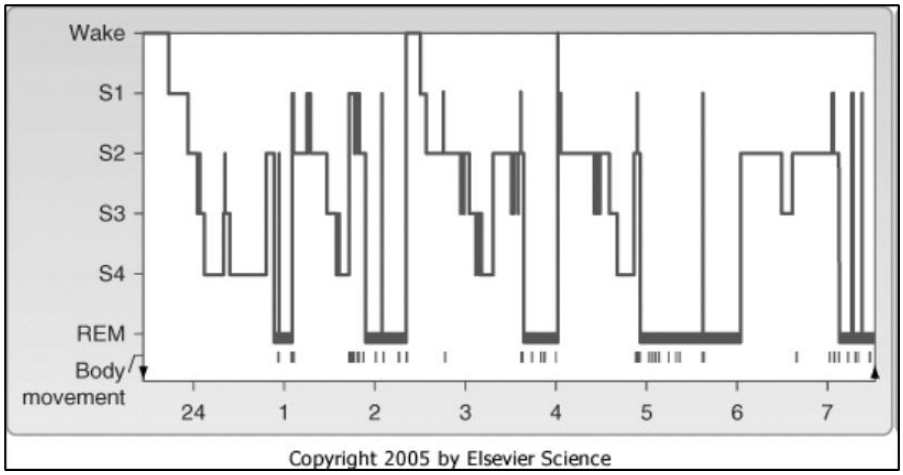

Figure 4. Sleep status processes in one night in young adults.[22]

In stage 1, NREM sleep usually lasts 1 to 7 minutes in the initial cycle, which is 2 - 5 percent of total sleep, and is easily disturbed by noise disturbances. In stage 2, NREM lasts approximately 10 to 25 minutes in the initial cycle and lengthens with each successive cycle and constitutes 45 - 55 percent of the total sleep episode. Stage 2 requires more intense stimulation than stage 1 to wake up. Sleep stages 3 and 4 are collectively referred to as slow-wave sleep (SWS), which mostly occurs in the first third of the night. Each has distinguishing characteristics. Stage 3 only lasts a few minutes and constitutes about 3 - 8 percent sleep. The final NREM stage is stage 4, which lasts about 20 to 40 minutes in the first cycle and makes up about 10 - 15 percent of sleep. In the REM sleep stage, there is desynchronization of brain wave activity, muscle atonia, and rapid eye movements. During the initial cycle, REM periods may only last 1 to 5 minutes and become longer as the sleep episode progresses.[22]

Blood pressure (BP) measurement

BP readings vary greatly based on the measurement method. When diagnosing hypertension, adjustments should be made based on the measurement method (Table 1). There are several methods for measuring BP, including measuring BP in clinics using manual or automatic BP measurements (Automated Office Blood Pressure Monitoring = AOBPM) and BP measurements outside the clinic such as BP measurements at home (home blood pressure monitoring = HBPM) and ambulatory blood pressure monitoring (ABPM 24 hour) (Figure 5).

We often find that blood pressure becomes high when the patient comes to the clinic, whereas at home, the BP becomes normal without antihypertensive medication. This is referred to as white-coat hypertension. High BP can be caused by excessive activity before coming to the clinic or stress due to fear of going to the doctor. However on the other hand, blood BP can also be normal when you come to the clinic, but when you go home, your BP becomes high. This is referred to as masked hypertension. This condition actually has a higher risk of cardiovascular disease because you do not receive antihypertensive medication.

Table 1. Diagnosis of hypertension based on blood pressure measurement methods:[23]

Measurement method	SBP (mmHg)		DBP (mmHg)
BP clinic	≥ 140	and/or	≥ 90
ABPM (ambulatory blood pressure monitoring)			
Average morning-afternoon (or waking up)	≥ 135	and/or	≥ 85
Average nighttime (or sleep)	≥ 120	and/or	≥ 70
24-hour average	≥ 130	and/or	≥ 80
Average HBPM (home blood pressure monitoring)	≥ 135	and/or	≥ 85

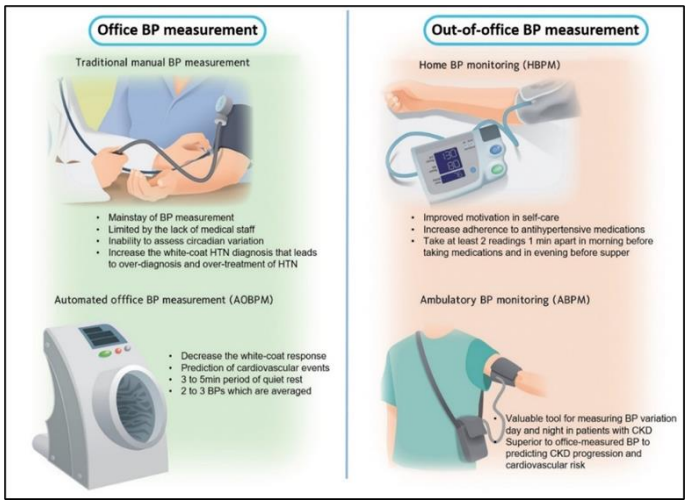

Figure 5. BP measurement methods in the clinic and outside the clinic.[24]

Measurements with AOBPM that are widely available in clinics or hospitals have been shown to reduce the risk of white-coat hypertension on self-measured BP compared with manual BP measurement. Meanwhile, measurement with HBPM is known to increase motivation in self-care and increase compliance with antihypertensive medication so the BP target is expected to be achieved. All measurements at home must be measured with 2 BP measurements with a distance of 1 minute each day and night BP measurements and BP taken at the same time every day and after 2-4 weeks, the BP measurements must be averaged to assess the effect of antihypertensive treatment. Patients should also ensure that there are no significant differences between the left and right arms. If the difference is significant, the doctor should instruct the patient to measure the blood pressure in the arm with a higher reading. In addition, BP should be checked in the morning before taking medication and in the evening before dinner. Of all the measurements mentioned above, there are still shortcomings, especially in assessing them masked hypertension and nocturnal hypertension.

The most recommended measurement method is to use 24-hour ABPM (Figure 6), because apart from being more precise in diagnosing hypertension, it can also be used as a parameter to state whether blood pressure is under control or not. Around 10%-30% of known patients who come to the clinic have white coat hypertension, while 10-15% have masked hypertension. Therefore, a measurement method using 24-hour ABPM is very necessary, especially for the identification of white coat hypertension, masked hypertension, and nocturnal hypertension.[23]

Apart from that, the benefit of measuring the ABPM method is that it can minimize the increased risk of cardiovascular disease by detecting the highest BP in the morning-afternoon and the morning BP spike before morning surge. Because the morning BP spike before waking up contributes to an increased incidence of sudden death, non-fatal myocardial infarction, unstable angina, and stroke in the morning. The BP measurement method with ABPM is more practical because there is no special preparation for the examination, in contrast to measuring BP in the clinic which requires preparation (Table 2). Blood pressure measurement with 24-hour ABPM, usually around every 15-30 minutes during the day (09.00-21.00) and 30-60 minutes at night (01.00-06.00).[11] However, measurements can vary depending on the equipment, clinic, and doctor's instructions.

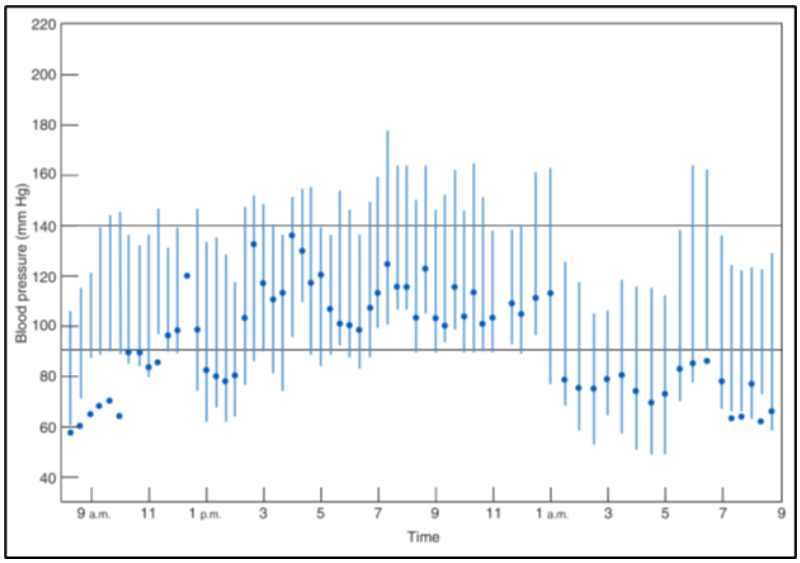

Figure 6. Example of measuring 24-hour ABPM in male patients aged 50 years with hypertension who did not receive antihypertensive therapy.[10]

Table 2. Summary of standard measurements of BP clinic.[25]

Patient preparation	Caffeine, exercise, and smoking should be avoided at least 30 minutes before measuring BP. Make sure the patient empties the bladder before BP measurement. The patient should sit in a chair with the backrest and feet placed on the floor, then relax for more than 5 minutes. The patient or examiner should not talk at rest and during measurements. All clothing covering the location of the cuff placement must be removed.
Selecting BP measurements for diagnosis and therapy in elevated BP	Measure BP from both arms at the first visit and select the arm with higher BP for subsequent measurements.
BP measurements methods	Use a validated BP measuring device, which should be calibrated regularly. The patient should have an arm brace with the cuff positioned on the patient's upper arm at the level of the right atrium (arm sternum point). Use the correct size cuff. The cuff should encircle 80% of the arm to be used.
Record BP measurements	Measure BP ≥ 2 times with an interval of 1-2 minutes and record the average BP measurement. The data recorded should be SBP, BDP, and the last time took medication before measuring BP.

BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Arterial stiffness in CKD

Cardiovascular disease is often associated with causes of death in patients with chronic kidney disease (CKD). This is because there are traditional and non-traditional cardiovascular risk factors in CKD. Non-traditional risk factors include the presence of chronic kidney disease-bone mineral disorders (CKD-GMT), which are characterized by disorders of bone and mineral metabolism, including biochemical abnormalities, hyperphosphatemia and hyperparathyroidism, renal osteodystrophy, and vascular calcification. Increased arterial stiffness in the CKD population may be associated with the development of vascular calcification and contribution to cardiovascular disorders. It is known that the examination in measuring arterial stiffness is by assessing the pulse wave speed (pulse wave velocity (PWV)), which can be measured invasively or non-invasively.

Invasive examinations are carried out using PWV catheterization, while non-invasive ones use tonometry PWV in the carotid-femoral artery segment (cfPWV), Finger-toe photoplethysmogram (PPG), and cuff in the arterial segment brachial-ankle (baPWV) (Figure 7). Until now, cfPWV has been used as "gold standard" to assess arterial stiffness. Based on the research results of Van et al.[26] The normal value of PWV is 6 m/s, and the PWV value> 10 m/s indicates stiffness in the arteries, resulting in a risk of cardiovascular death. In CKD, the risk of arterial stiffness increases even higher. This shows that there is a more rapid increase in arterial PWV in CKD patients than in individuals with normal kidney function. Patients with various stages of CKD and who have undergone dialysis or kidney transplantation are known to have different biological environments that influence changes in arterial stiffness and PWV.[27]

Pathogenesis of arterial stiffness in CKD

In CKD, there are many conditions that influence the occurrence of arterial stiffness, including physiological conditions that are related to age and pathological conditions, namely chronic inflammatory disorders, hypertension, and previous diabetes. Apart from that, other multifactorial factors involved are the atherosclerosis process and the vascular calcification process, which is induced by metabolic disorders (uremia toxins) such as phosphate, calcium, uric acid, advanced glycation end products (AGEs), renin angiotensin aldosterone system (RAAS), ET-1, asymmetric dimethylarginine (ADMA), and endothelial nitric oxide synthase (eNOS).

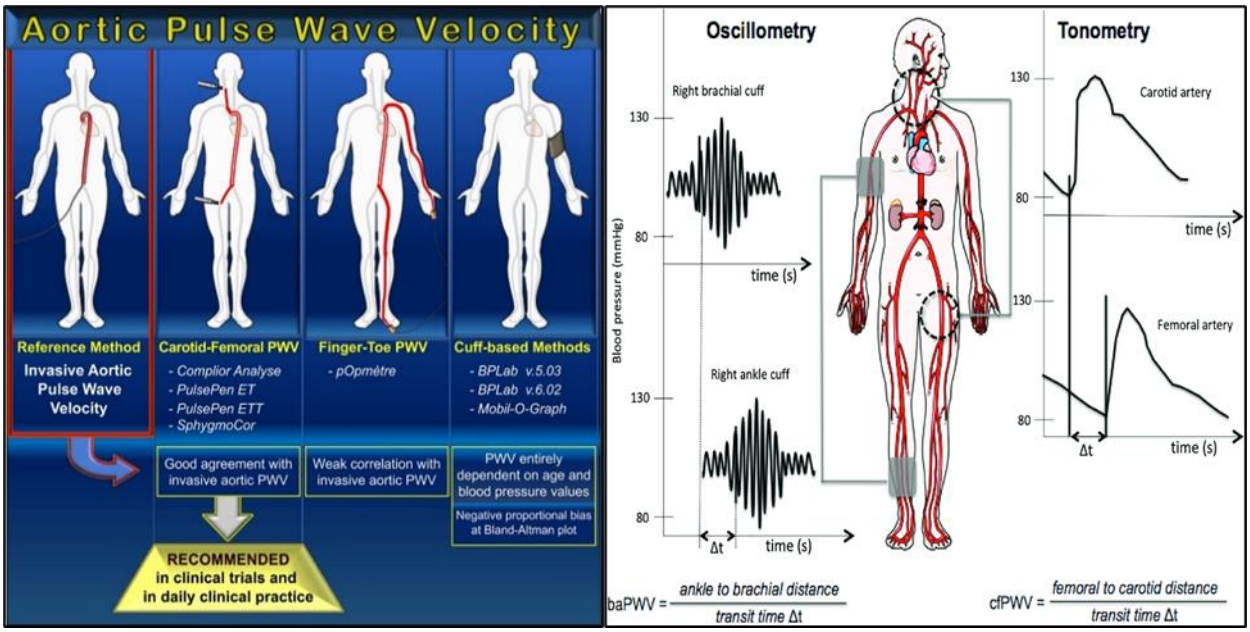

Figure 7. Type of PWV[28] measurement and brachial-ankle PWV (baPWV) calculation by measuring transit time between brachial artery and tibial artery through oscillometric amplitude and carotid-femoral PWV calculation (cfPWV) = 0.833 x baPWV -2.333 (m/s).[29]

Age

Age is often associated with changes in the structure of blood vessels in older people, especially in the elderly. The structure of small or large blood vessels becomes stiff due to the degeneration process, so the elastic function of the blood vessels will be disrupted. Increased arterial stiffness in the elderly is associated with disease processes such as atherosclerosis and vascular calcification.[27] In CKD patients, vascular calcification occurs in the tunica media due to inflammation, thereby speeding up the EVA process. Therefore, the blood vessels in CKD are always older than their actual age.[32] This is proven by the finding of a progressive increase in PWV of 6-8% with increasing age every 10 years in the research of Delima et al.[30]

Inflammation

Patients with CKD are known to experience chronic inflammation, which is characterized by high levels of pro-inflammatory cytokines such as TNF-α and IL-6, especially in patients with chronic inflammation. diabetic nephropathy.[31] The dialysis process can also affect the immune system and cause additional chronic inflammation (IL-1, IL-6, IL-23, and TNF alpha), as well as high sensitivity C-reactive protein and fibrinogen). In addition, short fragment bacterial DNA, endotoxins, and muramyl dipeptide in small amounts can also potentially be found in dialysate fluid, and if it has passed through the membrane, high-flux can induce IL-6 production.[32] Furthermore, catheters used for both hemodialysis and peritoneal dialysis also have the potential to be a source of inflammation. Changes in the microbiota in CKD can also result in increased cytokine production, oxidative stress, and inflammation.[32] In peritoneal dialysis, high levels of glucose and glucose degradation products in conventional dialysis solutions can cause product formation, advanced glycation end-products (AGEs), oxidative stress, and chronic inflammation.[32] Chronic inflammation and oxidative stress will ultimately result in endothelial dysfunction and changes in the phenotype of vascular smooth muscle cells (vascular smooth muscle cell (VSMC)) and lead to the process of premature aging of blood vessels (early vascular aging (EVA)) plus CKD conditions are known to also have a decrease in anti-aging genes such as Klotho and Fetuin-A activity.[33]

Atherosclerosis

Increased cholesterol levels, such as triglycerides and cholesterol low-density lipoprotein (LDL), can be found in CKD patients. This was also confirmed by the discovery of a decrease in cholesterol levels of high-density lipoprotein (HDL) in CKD patients. As a result of this increase in cholesterol levels, LDL will be more easily oxidized by free radicals, namely reactive oxygen species (ROS), which increase due to conditions of oxidative stress and chronic inflammation that occur in CKD. Oxidized LDL cholesterol (oxLDL) will enter the tunica intima layer of arteries that experience endothelial dysfunction, thereby activating inflammatory mediators (macrophages) originating from monocytes that enter the artery walls to phagocytose oxLDL. This process will take shape over time foam cells (foam cells), which then develop into a lipid core that has a fibrous cap, and atherosclerosis occurs.[27] With its formation, a fibrous cap will result in progressive narrowing of the arterial lumen and a decrease in blood vessel elasticity, which results in stiffness of the arterial blood vessel walls.[31] Fibrous caps are very fragile and, when unstable, will easily suffer rupture, which will trigger thrombogenesis as in acute coronary syndrome (ACS) (Figure 8).

Vascular calcification

Under normal conditions, some calcification inhibitors such as pyrophosphate (Ppi), adenosine, matrix Gla Protein (MGP), osteopontin, fetuin-A, osteoprotegerin (OPG), magnesium, bone morphogenetic protein-7 (BMP-7), and Klotho protects against abnormal mineral deposition in the vascular wall, whereas hypercalcemia, increased levels of parathyroid hormone (PTH), inflammatory cytokines, oxidative stress, uremic toxins, AGEs, and most importantly phosphate induce vascular calcification.

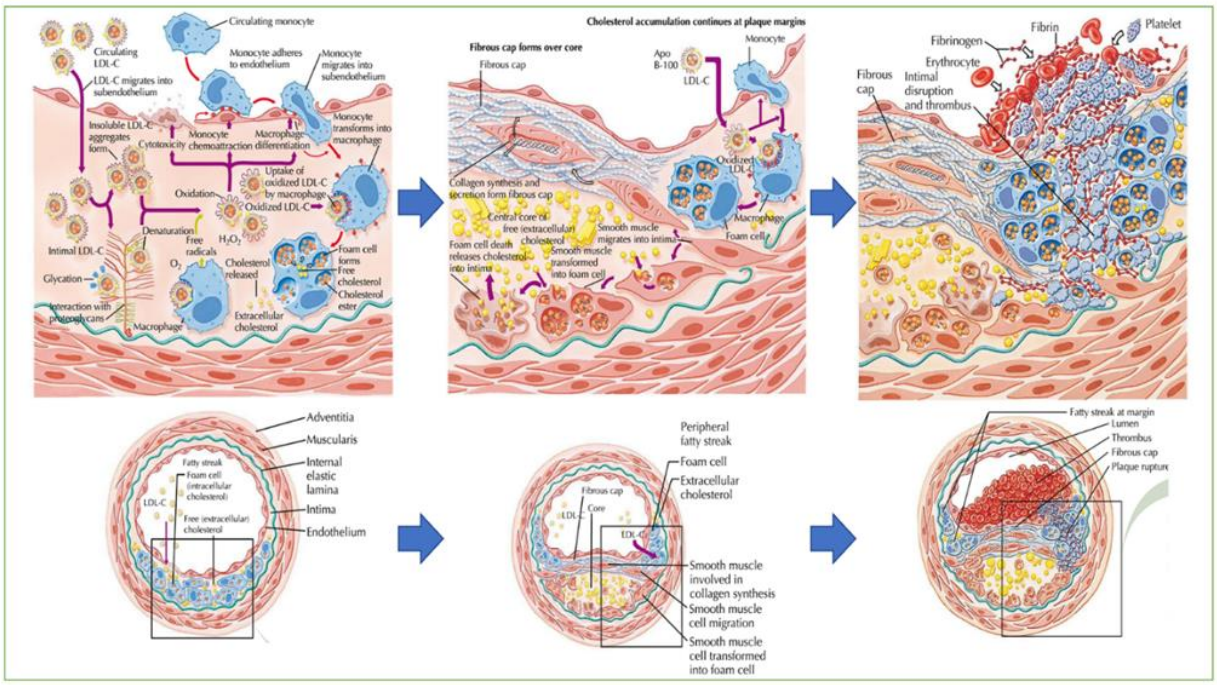

Figure 8. Atherosclerosis pathogenesis.[34]

In CKD, there is an imbalance between inhibitors and inducers of vascular calcification. Worsening kidney function due to CKD causes decreased excretion and accumulation of various uremic toxins including Pi (inorganic phosphate), and impaired Ca^{2+} homeostasis through improving PTH regulation and fibroblast growth factor-23 (FGF-23). Increased calcium and phosphate in the circulation

(extracellular) will increase the activity phosphate transporter (Pit-1), which will stimulate the uptake of phosphate into VSMC. An increase in phosphate in VSMC will activate nuclear factor kappa-B (NF-kB) and change the VSMC phenotype to bone-forming cells (osteoblast-like cells) through an increase in transcription factors such as Muscle Segment Homeobox homolog 2 (Msx2), Runt-Related Transcription Factor 2 (Runx2), Bone morphogenetic protein-2 (BMP-2), OPN and alkaline phosphatase (ALP). Other uremic toxins, such as indoxyl-sulfate (IS), will also stimulate improvement in transforming growth factor beta (TGF-β) and VSMC proliferation to produce reactive oxygen species (ROS), which will then activate NF-kB translocation to the nucleus. Furthermore, NF-κB promotes the expression of several pro-inflammatory, pro-apoptotic genes and extracellular matrix degradation molecules such as elastase and MMP-2 and -9.

VSMC that has differentiated into osteoblast-like cells experienced a decrease in protein expression smooth muscle 22α (SM22α) andα-smooth muscle actin (α- SMA) as contractile smooth muscle cell (SMC)) and produces crystals hydroxyapatite (HA), which consists of a vesicle matrix (diameter 30–300 nm) as a membrane and apoptotic bodies (diameter 50–5000 nm) as crystal nuclei due to high calcium in VSMC. Inside this HA crystal is found a calcium-phosphate product (CaxP), which will later deposit into the walls of the tunica media blood vessels, causing media vascular calcification and arterial stiffness (Figure 9).[35]

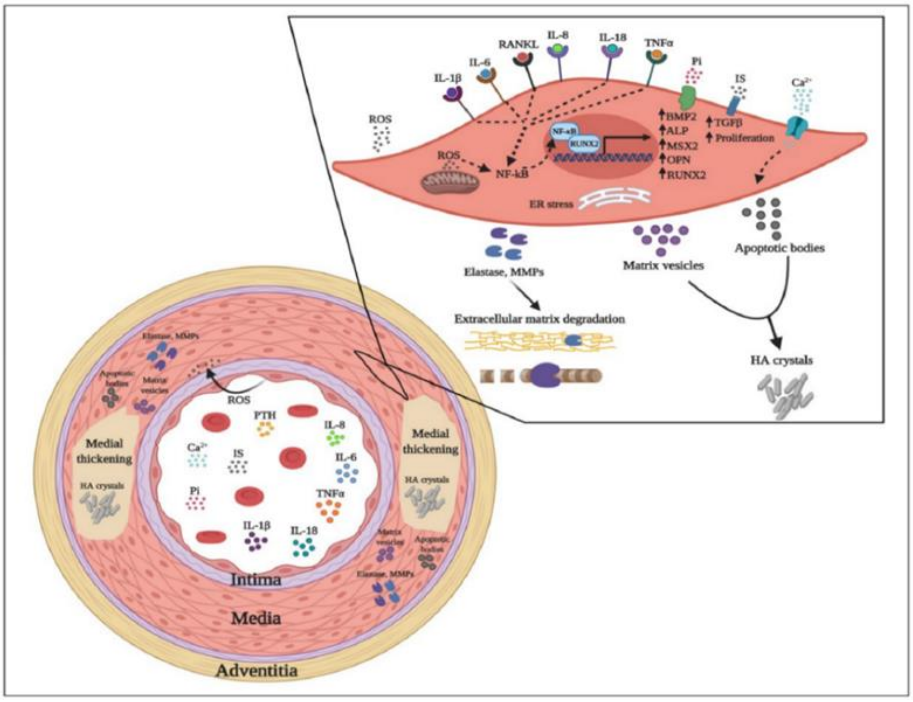

Figure 9. Vascular calcification (media) pathogenesis and VSMC phenotype change to osteoblast-like cells.[35]

Uremic toxin

Uric acid

Another vascular toxin that is increased in CKD patients is uric acid due to failure to excrete it. This increase in uric acid can reduce the activity of endothelial nitric oxide synthase (eNOS), reducing the production of nitric oxide (NO), increasing VSMC proliferation, and increasing angiotensin II production, thereby contributing to increased blood pressure and arterial stiffness.

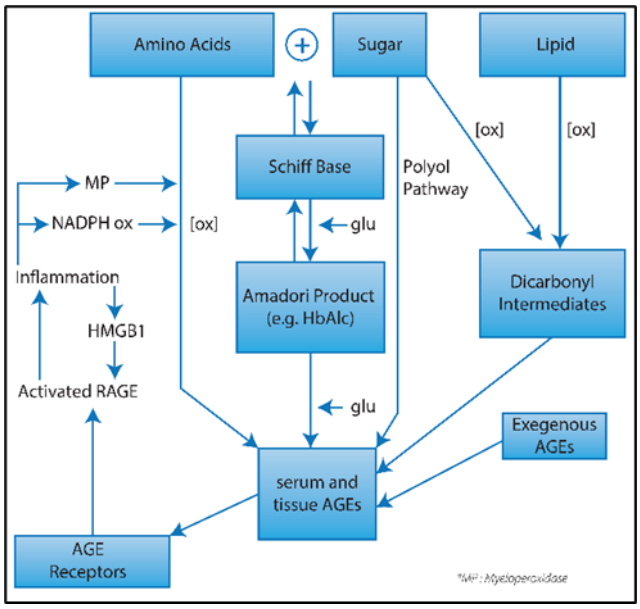

Figure 10. Mechanism of formation of AGEs.[37]

Advanced glycation end-products (AGEs)

AGEs, also known as glycotoxins, are a diverse group of highly oxidized compounds (highly oxidant compounds) which are involved in the incidence of diabetes and a number of other chronic diseases. AGEs are formed through the non-enzymatic process of adding reduced sugars to free amino acids from proteins, fats, and nucleic acids (Figure 10). There are several pathways for the formation of AGEs, including the reaction of glucose and amino acid groups to form reversible intermediate products, namely Schiff base and Amadori product (HbA1c), before finally forming irreversible AGEs. Apart from that, there is a route carbonyl stress" namely the process of oxidizing sugar and/or fat to form intermediate compounds dicarbonyl (group carbonyl which is highly reactive) and binds to amino acids to form AGEs, as well as a pathway that does not involve glucose but involves neutrophils, monocytes and macrophages, which with inflammatory stimulation will produce enzyme myeloperoxidase nicotinamide adenine dinucleotide phosphate (NADPH) oxidase which then induces the formation of AGEs through the oxidation of amino acids. Once bound to AGEs, x (RAGE) will tend to form reactive oxygen species (ROS), which then forms more AGEs through the NADPH oxidase pathway.[36]

In CKD patients who have progressed, AGEs will accumulate as a result of decreased renal clearance and increased production. Thus, significant accumulation may occur even in non-diabetic patients. The accumulation of AGEs influences eNOS activity, which causes endothelial dysfunction and supports changes in VSMC phenotype, which causes structural arterial stiffness through NF-kB activation, which contributes to the development of vascular inflammation.

Asymmetric dimethylarginine (ADMA)

Asymmetric Dimethylarginine (ADMA) is another vascular toxin in CKD associated with arterial stiffness. Increased ADMA levels are associated with decreased excretion in the kidneys and increased AGEs and oxidative stress in CKD, which will damage and disrupt enzyme activity. dimethylarginine dimethylaminohydrolase (DDAH)-1 so it cannot degrade ADMA to L-citrulline and dimethylamine.[38] ADMA can cause endothelial dysfunction through eNOS inhibition, causing vasoconstriction in blood vessels. Increased ADMA also causes sympathetic stimulation, inflammation, blood vessel stiffness, andLeft ventricular hypertrophy (LVH).

Endothelin -1 (ET-1)

Endothelin-1 (ET-1) is a vasoconstrictor secreted by endothelial cells, which acts as a vasodilator antagonist nitric oxide (NO). ET-1 contributes to the vascular tone and regulates cell proliferation through the activation of ETA and ETB receptors. ETA receptors promote endothelial dysfunction, increased vascular tone, vascular inflammation, and vascular calcification through the induction of VSMC differentiation into osteoblast-like cells, whereas ETB receptors contribute to vasodilation, sodium excretion, and inflammation inhibition. In CKD conditions, ET-1 experiences increased production and decreased excretion. Increased synthesis and release of endothelin-1 during CKD is regulated by angiotensin II, vasopressin, IL-1, oxidized LDL, cyclosporine, and decreased extracellular pH.[32]

Baroreflex system

The baroreflex system also regulates constant changes in blood pressure. Baroreceptors located in the carotid bulb and in the aortic arch are very sensitive to changes in the arterial wall. In CKD, there are changes in the vascular components that cause arterial stiffness. As a result, there is impaired baroreflex function and impaired changes in blood pressure. This condition will increase the incidence of cardiovascular diseases such as myocardial infarction, stroke, and LVH (Reno-cardiac dysfunction/failure) (Figure 11).[32]

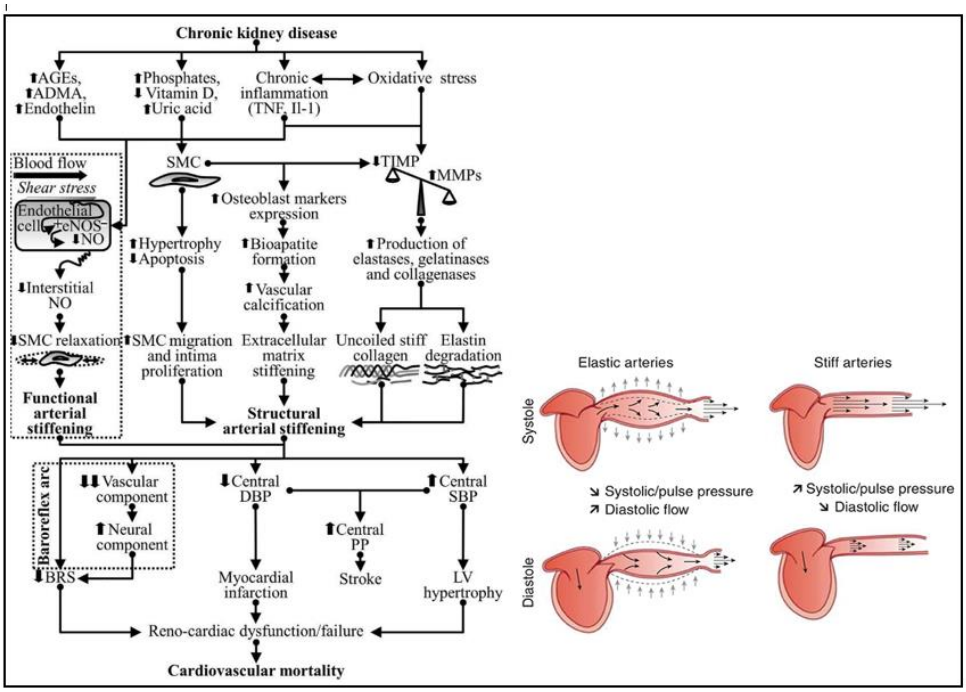

Figure 11. Reno-cardiac dysfunction/failure mechanism and elasticity difference in arterial stiffness.[32,39]

Diurnal variation of BP in CKD patients

In normal, healthy people, there is a pattern of decreasing BP at night when sleeping by 10-20% of daytime BP (dipping). However, it is different in CKD patients who have not received anti-hypertensive treatment, where nighttime BP will remain high or the same (non-dipping) can increase even more than daytime BP (reverse dipping). The prevalence of non-dipping in CKD compared to those without CKD ranged from 60.6%: 43.2%. Nocturnal hypertension can be diagnosed when BP in the clinic is normal during the day but increases at night. This condition is part of masked hypertension and is often missed from the diagnosis of hypertension, so antihypertensive therapy is not given to CKD patients with hypertension. The ratio between CKD patients

with normal BP and masked hypertension based on BP in the clinic is known to be 40%: 70%. In addition, decreased GFR and proteinuria in CKD are associated with nocturnal hypertension and masked hypertension.[40]

The risk of cardiovascular disease and progression of CKD is also higher in patients who experience diurnal variations such as nocturnal hypertension, masked hypertension, by non-dipping during sleep, increased pulse pressure, and excessive morning blood pressure spikes (morning surge).[39] The mechanisms underlying changes in BP variability and diurnal variation in CKD are not completely understood. However, several factors and conditions that occur in CKD, such as increased sodium retention and fluid volume, RAAS activation and endothelin factors, changes in sympathetic nervous system activity, endothelial dysfunction, oxidative stress, inflammation, increased arterial stiffness and impaired baroreceptor sensitivity, have been believed and explain that This is what disrupts the diurnal variation of BP in CKD. Several studies (Table 3) using 24-hour ABPM have also proven that CKD patients have experienced changes in diurnal variations in BP. Thus, this altered BP circadian rhythm causes target organ damage and has detrimental effects on the development of cardiovascular disease and kidney disease. (Figure 12).[9]

Another study on the effect of kidney transplantation on the BP variation profile of end-stage renal disease patients (End Stage Renal Disease = ESRD) has also been demonstrated. Gatzka et al., evaluating the 24-hour circadian profile of ABPM in 45 patients after kidney transplantation, has succeeded in increasing the prevalence of dipping from 27% in the early phase (<7 months) to 73% in the late phase (≥1 year). The longer the time after kidney transplantation, the more pronounced the decrease in blood pressure during sleep at night. Meanwhile, research by Covic et al.[42] who compared ABPM profiles at 1 month before and after 1 month and >1 year after kidney transplantation in 20 transplant recipients, found a significant improvement in circadian BP profiles.

Management of BP in CKD

As mentioned above, hypertensive patients with CKD show a change in BP diurnal variation like pattern non-dipping, nocturnal hypertension, sustained hypertension, morning BP spike (morning surge), and increased pulse pressure. Blood pressure should be taken from morning to evening, regardless of whether in the clinic or outside the clinic. Thus, the use of 24-hour ABPM can help to detect changes in diurnal variations in BP in patients with CKD. A study conducted on the general population in Japan showed that nighttime BP was a better predictor of CKD progression compared to daytime BP. Therefore, BP measurement with ABPM is superior to clinic BP measurement or HBPM in measuring variations between daytime and nighttime BP to evaluate the risk of CKD and cardiovascular complications. Besides that, much evidence supports the use and superiority of ABPM over in-clinic BP measurements in making accurate diagnoses and classification of hypertension, assessing target organ damage, predicting outcomes, and evaluating response to therapy in patients with CKD because the condition of CKD makes optimal BP control often difficult to achieve.[6]

Epidemiological research shows that patients without CKD with pre-hypertension (SBP 130-140 mmHg) alone are associated with a higher risk of developing CKD compared to those with SBP <120 mmHg. Moreover, uncontrolled BP in CKD patients can lead to a poor and serious prognosis, such as cardiovascular disease and the progression of CKD to ESRD. With 24-hour ABPM, the BP profile in CKD can be known so that one of the important strategies in the management of hypertension with CKD is to reduce nocturnal hypertension and restore the diurnal rhythm of BP, be precise, and achieve optimal BP targets. An example is the timely use of diuretic therapy alone or in combination with other antihypertensive agents to treat nocturnal hypertension.[6]

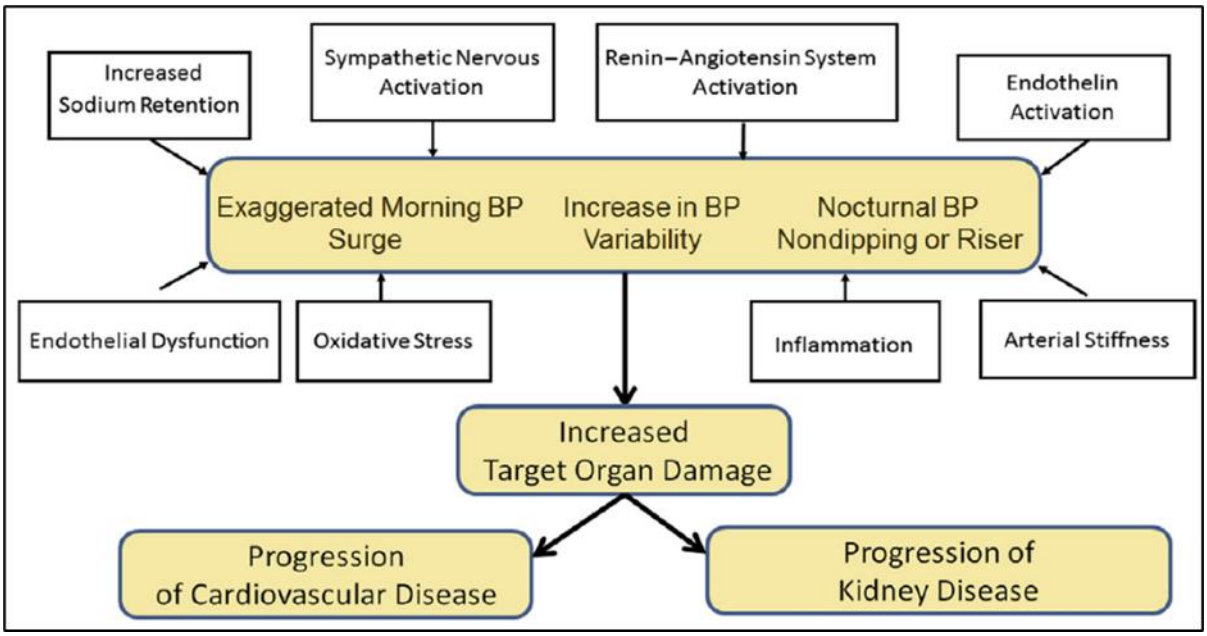

Figure 12. Mechanism of change in diurnal variation of BP in CKD.[9]

Currently, hypertension chronotherapy has been considered in the management of hypertension in CKD. Chronotherapy in hypertension is the timing of antihypertensive drug administration adjusted to the circadian rhythm, where the drug administration schedule is adjusted to the body's physiological needs at different times during the duration of treatment. Known usage doses of 1 or more antihypertensive drugs at bedtime have been shown to improve BP control, reduce nocturnal BP, reduce proteinuria,[9] and reduce the risk of cardiovascular events in some studies compared with taking all medications while awake. However, other research states that it is necessary to be careful in applying antihypertensive chronotherapy to CKD. Excessive reduction in BP also carries a risk of cardiovascular death, such as myocardial infarction and stroke.

Most clinical trials on the effects of various classes of antihypertensive drugs on 24-hour ABPM have been conducted in hypertensive patients without CKD. Generally, calcium channel blocker such as nifedipine is more effective at bedtime than taken in the morning.[9,45] Given that the renin-angiotensin system follows a circadian rhythm and is active during night sleep, research by Hermida et al. has shown that the bedtime dose of angiotensin-converting enzyme inhibitor (Those) or angiotensin receptor blocker (ARB) provides a more pronounced BP lowering effect during sleep than when awake in hypertensive patients. This is proven by research Wang et al.[46], which showed that the use of ARB drugs once a day before bed was significantly more effective than the use of ARB drugs when waking up in reducing nighttime BP, proteinuria, and the risk of LVH in CKD patients with a pattern of non-dipping. However, further research is still needed to determine whether other classes of antihypertensive drugs or interventions are superior in controlling nocturnal hypertension in CKD patients.[6]

Apart from achieving optimal BP, the selection of antihypertensive drugs with renoprotective and cardioprotective effects is very important. In principle, the treatment of hypertension with and without CKD is the same, and the choice of drug consideration is based on the presence or absence of proteinuria (Figure 13). Almostallguideline recommends Renin-angiotensin system blockers (RASB) such as ACEi and ARB are used as the first line,[43,47] in hypertensive patients with CKD[6] (Table 4). Captopril was first used to protect against a decline in renal function in patients with insulin-dependent type 1 diabetes mellitus and studies of CKD with RASB have consistently shown the drug to have renoprotective

effects, including reducing proteinuria and slowing the decline in eGFR. These beneficial effects were proven in patients with and without diabetes. Besides that RASB also prevents the onset of microalbuminuria in patients with type 2 diabetes mellitus and normal urinary albumin excretion.[44]

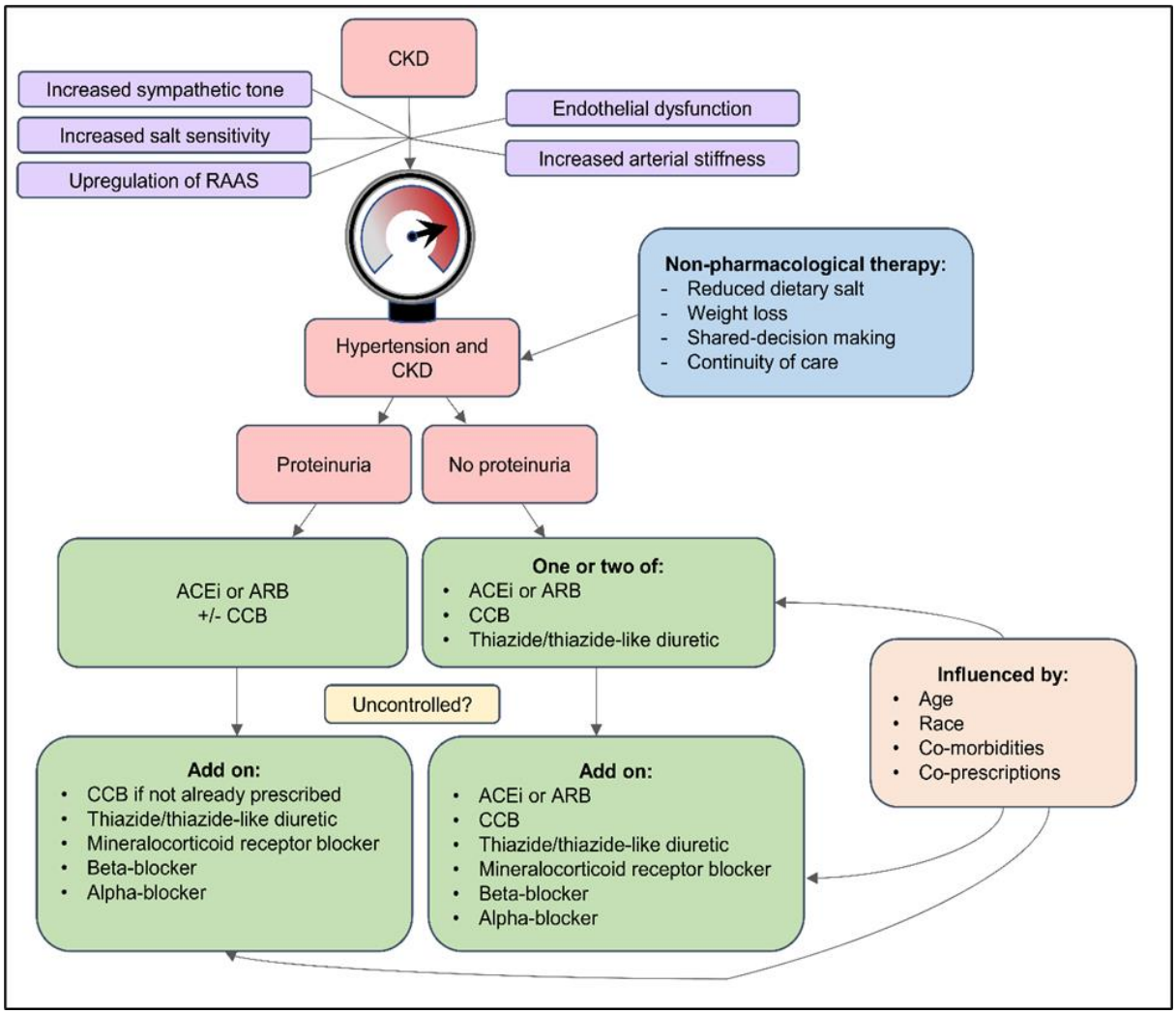

Figure 13. Pathogenesis and management of hypertension in CKD.[47]

Apart from RASB, other renoprotective drugs are new anti-diabetic drugs, such as Sodium-glucose Cotransporter-2 Inhibitors (SGLT2i) and Glucagon-like peptide-1 Receptor Agonists (GLP-1RA). The American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), and KDIGO recommend SGLT2i and GLP1RA as first-line therapy for patients with diabetic kidney disease (Figure 14). Interestingly, this drug has also been reported to reduce deaths from cardiovascular events by 15-20%. In experimental research on Dapagliflozin and prevention of adverse outcomes in chronic kidney disease (DAPA-CKD), dapagliflozin can reduce the risk of kidney failure or death from kidney or cardiovascular disease, even in CKD patients without diabetes, and reduce BP by 5 mmHg.[6]

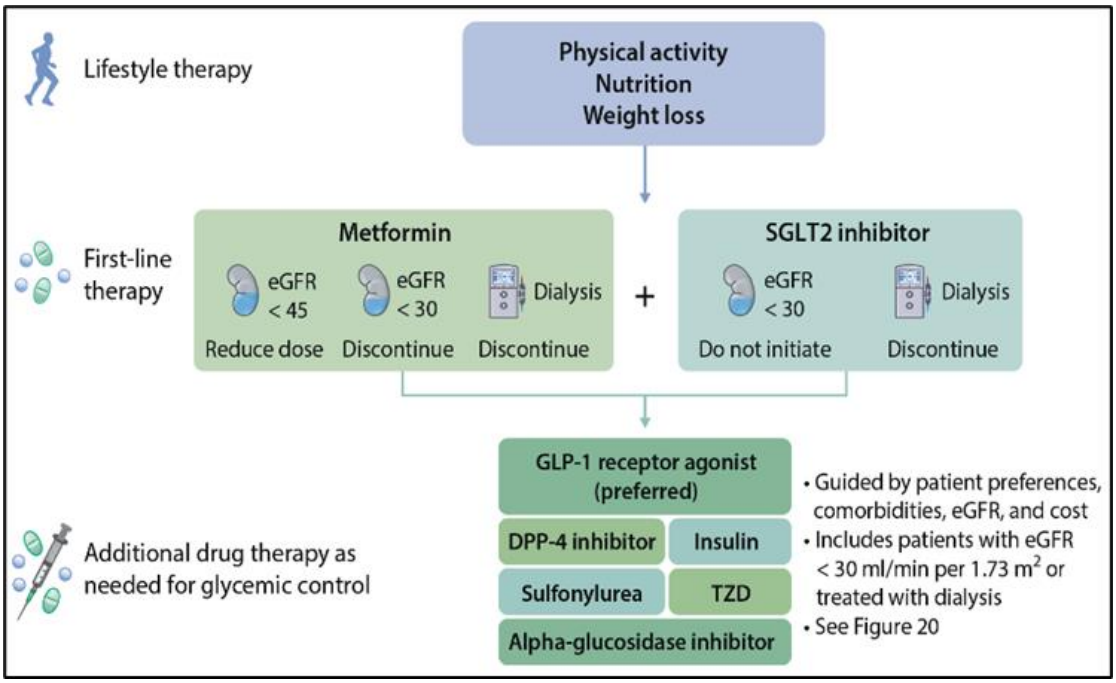

Figure 14. Algorithm of therapy of CKD patients with type 2 diabetes mellitus.[44]

Mineralocorticoid Receptor Antagonist (MRA) also has renoprotective and cardioprotective effects. This drug may also reduce BP in individuals with resistant hypertension. Spironolactone is a first-generation nonselective MRA reported to provide renoprotective effects by reducing proteinuria and maintaining eGFR in CKD patients without diabetes. Recently, the drug finerenone, which is a new-generation selective MRA, has emerged as a potential therapy. On research Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD), finerenone can reduce the risk of CKD progression and cardiovascular disease events in patients with CKD and type 2 diabetes mellitus. This drug is promising and is expected to improve the continuity of kidney function and better outcomes when combined with RASB.[6]

Based on the role of ET-1 in arterial stiffness and diurnal variations in BP in CKD patients, there is also the drug atrasentan, which is an antagonist. Endothelin A Receptor (ETAR) is highly selective, and short-term use has been reported to reduce albuminuria in patients with diabetic nephropathy and can reduce BP. This is proven by research by Dhaun et al which showed that ET-1 levels increased at night, resulting in the disappearance of the nocturnal BP decrease in CKD, and treatment with a selective ETAR antagonist (sitaxentan) for 6 weeks increased the decrease in nocturnal BP and TDD in patients with CKD.[48] Based on sparsentan phase 2 research (combination ETAR and ARB antagonists) also demonstrated a significant reduction in proteinuria in patients with focal segmental glomerulosclerosis (FSGS).

Apart from the medicines mentioned above, it is also necessary to regulate your lifestyle by implementing a healthy lifestyle such as maintaining ideal body weight, implementing dietary approaches to stop hypertension (DASH) diet, regular physical activity for at least 30 minutes/day or with a total time of 150 minutes/week or according to tolerance for cardiovascular disease, low salt diet < 2 grams/day or < 5g NaCl/day in CKD patients with hypertension43 meditation to reduce stress, limiting alcohol intake to 1-2 glasses/day for each woman and man, and stopping smoking. (Table 6) All of the healthy lifestyle patterns above have a role in inhibiting the mechanism of hypertension so that reducing BP will be easier to achieve (Figure 15).

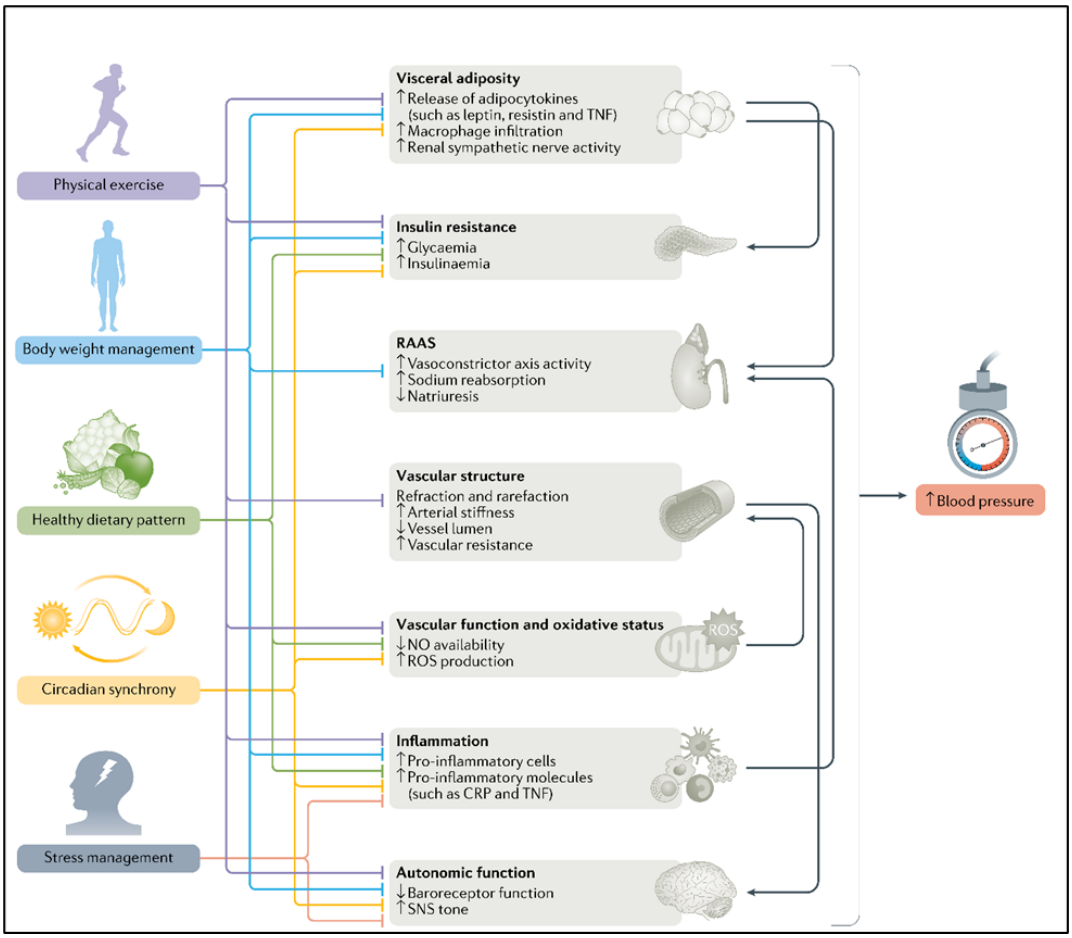

Figure 15. The role of a healthy lifestyle in the mechanism of hypertension.

2. Conclusion

In CKD, many factors cause arterial stiffness, causing a high incidence of hypertension, cardiovascular disease, and death in CKD patients. There is a general picture of diurnal variations in BP in CKD, such as nocturnal hypertension (non-dipping/reverse dipping), masked hypertension, BP surge in the morning (morning surge), increased pulse pressure, and resistant hypertension, which causes cardiovascular complications to increase. The latest guideline recommends optimal BP control with a lower BP target intended to reduce the incidence and death of cardiovascular disease and delay the progression of CKD to ESRD. 24-hour ABPM is the test that best provides important information about BP variability and nocturnal BP, but if it is difficult to access, HBPM is also recommended and can be applied to patients to control BP. So measuring blood pressure outside the clinic, in this case HBPM and ABPM, can improve the overall assessment of BP control in patients with CKD compared to measuring BP in the clinic alone.

To reduce cardiovascular events and control hypertension in CKD, several studies have proposed administering at least one antihypertensive drug at bedtime. Renoprotective drugs are preferred, such as RASB, SGLT2i, GLP-1RA, and MRA. Apart from that, drugs such as ETAR antagonists can also be considered in controlling BP and reducing nocturnal hypertension. A healthy lifestyle, low salt diet, and physical activity in the afternoon are also recommended to prevent nocturnal hypertension.

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