sysmex | Lighting the way with diagnostics

SYSMEX EDUCATIONAL ENHANCEMENT AND DEVELOPMENT | May 2020

SEED Urinalysis

Kidney disease, the silent epidemic knocking on our doors

The intended objective of this newsletter is to highlight the importance of early detection of chronic kidney disease (CKD).

The diagnosis of CKD often require the input of many disciplines along side that of the primary health care giver. It is common for patients with CKD to also have other chronic conditions, including but not restricted to hypertension, diabetes and cardiovascular disease.

Kidney function

The primary function of the urinary system is to filter the blood and produce urine as a by-product of waste removal. In the context of describing the urinary system a key objective is to highlight the complexity of the kidneys.
Urea is the breakdown product of proteins where the amount produced is proportional to it's consumption of proteins. Failure of the kidneys to do this would result in the toxic build-up of urea in the blood.

As seen in figure 1 the kidney is comprised of several key areas that aid in the processing of blood to remove waste products. Within the renal cortex lies the nephron. The renal nephron serves as a vital filtration unit with each renal cortex containing thousands of nephrons. The key component of the nephron is the Bowman's capsule and glomerulus, as seen in figure 2.

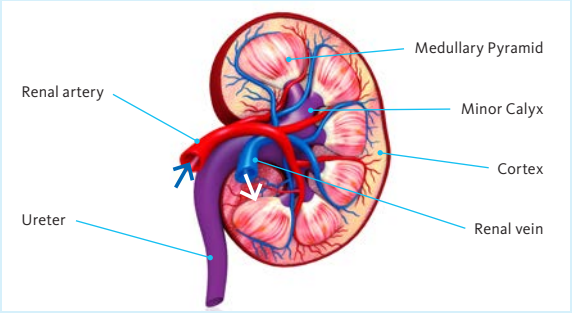

Fig. 1 *Basic view of a cross section of a kidney, indicating the blood flow into and out of the kidney shown by the blue and white arrows respectively.*

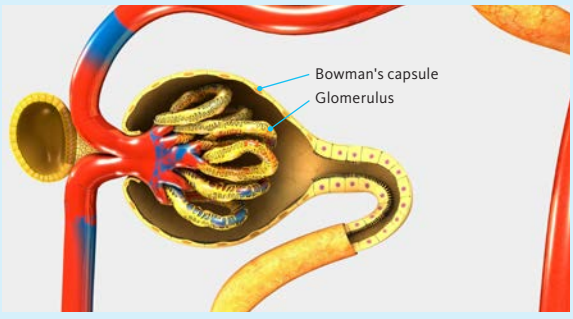

Fig. 2 *The bowman's capsule and glomerulus which is the key component of the nephron to ensure adequate filtration of waste products from the blood*

The glomerulus functions on a pressure system whereby blood entering the capillaries in the glomerulus undergoes filtration. The constriction/dilation of the arterioles entering the glomerulus and a subsequent dilation/constriction of the efferent arterioles exiting the glomerulus determines the glomerular filtration rate (GFR). [1]

Kidney disease explained

The cause of CKD varies from patient to patient. Hypertension and diabetes are two of the leading causes of CKD, of which will be discussed later in this newsletter.

The early stages of CKD are usually asymptomatic, consequently it is important to monitor high risk patients to safeguard against progressive loss of kidney function. High risk patients include those suffering from hypertension, cardiovascular disease and diabetes. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines assist in the classification of CKD. These guidelines recommend that the estimated GFR (eGFR) as well as proteinuria by albumin: creatinine ratio (ACR) are measured. [2]

KDIGO defines CKD as a reduction in kidney function for 3 months or more. An eGFR below 60ml/min/1.73m^2, and a urine ACR of more than 30mg/g have been adopted as the respective thresholds for diagnosis of CKD.

eGFR has its limitations as it has not been validated in the elderly, children, acute kidney injury, extremes of body size and during pregnancy. [3]

The link between diabetes and kidney disease

The prevalence of type 2 diabetes has been increasing worldwide over the past 20 years. It was estimated by the International Diabetes Federation (IDF) that in 2017 there were 451 million people living with diabetes with the expectation that this number will increase to 693 million by 2045. It is also estimated that 90 % of these patients have type 2 diabetes and further to this approximately 50 % will progress to CKD. The prevalence of diabetes in the African population is elevated, with African Americans 2 times more likely to develop type 2 diabetes than their Caucasian counterparts. [4]

Diabetic kidney disease (DKD) is the most frequent cause of end stage renal disease (ESRD) in both developed and developing countries. The costs associated with DKD are substantial and put immense pressure on developing countries public health care systems. The diagnosis of CKD is most often delayed at which point treatment and management options are much more costly.

Diabetic patients are at increased risk of complications from invasive procedures such as renal biopsies and experience prolonged healing times. Consequently, diabetic patients should be screened regularly and thoroughly to identify those who are most likely to have secondary kidney disease.

There have been questions raised over the diagnosis of CKD without a biopsy as the pathogenesis is multifactorial. However, a balance between diabetic patient care and diagnosis needs to be struck. Conventionally the functioning of the glomerulus is the central focus. The hemodynamic changes with high intraglomerular pressure and an increase in filtration are dominating factors in the progression of DKD. Although the filtration of glucose for diabetic patients is increased, it still takes approximately 3 years before the damage to the glomerulus occurs. Subsequent changes in the microvascular permeability and damage to the glomerular filtration barrier cause hallmarks of DKD which include micro-albuminuria or albuminuria. [5]

The link between hypertension and kidney disease

Hypertension is directly linked to CKD, hence blood pressure control is vital. Measurement of blood pressure should form part of the general examination of every patient, irrespective of the reason for medical consultation. Any patient confirmed to be hypertensive, should be routinely screened for evidence of CKD.

Blood pressure is the force of blood pushing against the arterial blood vessel walls. Systolic pressure refers to the pressure in the arteries as the heart beats thereby pushing blood through these vessels. Diastolic pressure refers to the pressure within the blood vessels as the heart relaxes between heart beats. The link between blood pressure and CKD is a cyclic problem. As the high blood pressure causes damage to the blood vessels in the kidneys, this reduces the filtration rate and therefore reduces the removal of excess fluid in the vessels, which in turn causes an increase in high blood pressure.

Many people are unaware that they have high blood pressure as they are asymptomatic, however many experience headaches as a result of elevated blood pressure and thus may serve as a symptom in the early stages. As both CKD and hypertension tend to be asymptomatic in the early stages, early identification of hypertension is of paramount importance. [6]

Ethnicity also plays a role in hypertension, with a higher incidence occurring in the African population. This combined with an increased risk of diabetes further compounds the likelihood of CKD.

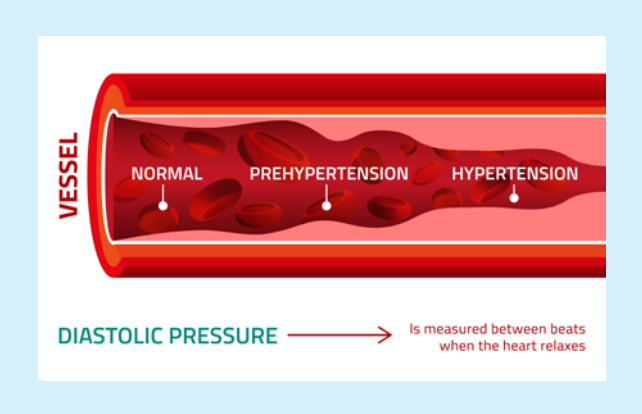

Fig. 3 *Diagrammatic representation of vascular pressure cause by hypertension*

The value of early detection

CKD is an underdiagnosed public health concern globally. As CKD is generally asymptomatic, this delays diagnosis and prevents early treatment. It is important to point out that CKD is treatable and reversable if diagnosed early enough. The later the diagnosis, the higher the costs associated with the disease and progression through to renal failure requiring dialysis and ultimately kidney transplant, if available.

The value of early detection is amplified in low income countries as many people rely on public health for treatment. The risk of hypertension, diabetes, and subsequently CKD has also been shown to be higher in people living in low income countries. To lower the public health burden, early detection is seen as a must. Early detection is reliant on the healthcare professional knowing and understanding the risk factors associated with CKD. Patients with hypertension or diabetes should always be screened for CKD. Albumin and creatinine levels in the urine should be determined followed by the eGFR.

Diagnostics for renal disease

The first step in the diagnosis of CKD is simple urine chemistry analysis to determine if albumin and creatinine are present. These two parameters are used to calculate the albumin: creatinine ratio to determine if proteinuria is present and if so is indicative of CKD. The GFR then needs to be determined. KDIGO endorses the use of CKD epidemiology (CKD-EPI) equation to calculate eGFR.

There are defined cut-offs to determine the severity of CKD in a patient. KDIGO defines CKD as an eGFR below 60ml/min/1.73m^2 in addition to an ACR higher than 30mg/g.

Kidney damage may also manifest by the presence of haematuria. The gold standard for diagnosis of CKD is biopsy, however this is invasive, costly and a high risk for certain patients.

Urinary dipsticks are a common easy urine chemistry test that can show the presence of haemoglobin, red blood cells as well as presence of protein. Some diagnostic dipsticks are more advanced and require the use of an instrument such as the Sysmex UC-1000. This analyser utilises photometric analysis to differentiate between haematuria and RBCs. An added value to the UC-1000, is the measurement of both albumin and creatinine, and automatic ratio calculation. GFR can be calculated with the patient age and sex using the value measured for creatinine.

In combination these calculated values can drastically alter patient care, whereby only the patients who are in need are referred for biopsy.

A diagnosis is made with a combination of the patient profile and chemistry values. The less invasive the procedure to make diagnosis, the better for both patient and healthcare system. [7]

Treatment options

Early detection treatment options are available in hypertensive patients where they are showing early signs of kidney disease, the control of the blood pressure is vital. Whilst there are many hypertensive drugs, the value of each kind can vary. Angiotensin-coverting enzyme inhibitors and angiotensin II receptor blockers have the added benefit of protection to the kidneys while non-dihydropyridine calcium channel blockers have the added benefit of being anti-proteinuric. Loop diuretics are also used to aid in the reduction of high blood pressure.

Glucose control in diabetics is important for managing CKD. The reduction in blood sugar levels often ties in with obesity and the need to lose weight while maintaining a healthy lifestyle.

Most treatments for kidney disease involve preventative treatment and treating the original cause. Once past the point of reversal, treatment revolves around maintaining a healthy lifestyle to slow disease progression without which could lead to dialysis and kidney transplant. It is thus vital to detect kidney disease as early as possible. [7, 8]

Summary

Overall chronic kidney disease is manageable and reversible if detected early. Patients who are at high risk for CKD, such as diabetics and patients with hypertension, should undergo screening with a urine chemistry test to determine the ACR and eGFR. Reduction of high blood pressure and glucose control are needed to limit damage to kidneys.

The late detection of CKD may increase the need for dialysis and possible transplant, thereby drastically increasing the financial burden.

References

[1] ***Roxe, D. M. Urinalysis. in Clinical Methods:*** *The History, Physical, and Laboratory Examinations (eds. Walker, H. K., Hall, W. D. & Hurst, J. W.) (Butterworths, 1990).*

[2] ***CKD Evaluation and Management – KDIGO.*** *https://kdigo.org/guidelines/ckd-evaluation-and-management/*

[3] ***Muse, E. D. & Topol, E. J.*** *A brighter future for kidney disease? The Lancet 395, 179 (2020).*

[4] ***Bancks, M. P. et al.*** *Association of Modifiable Risk Factors in Young Adulthood With Racial Disparity in Incident Type 2 Diabetes During Middle Adulthood. JAMA 318, 2457–2465 (2017).*

[5] ***Selby, N. M. & Taal, M. W.*** *An updated overview of diabetic nephropathy: Diagnosis, prognosis, treatment goals and latest guidelines. Diabetes Obes. Metab. 22, 3–15 (2020).*

[6] ***Mennuni, S. et al.*** *Hypertension and kidneys: unraveling complex molecular mechanisms underlying hypertensive renal damage. J. Hum. Hypertens. 28, 74–79 (2014).*

[7] ***Wouters, O. J., O'Donoghue, D. J., Ritchie, J., Kanavos, P. G. & Narva, A. S.*** *Early chronic kidney disease: diagnosis, management and models of care. Nat. Rev. Nephrol. 11, 491–502 (2015).*

[8] ***Pozzoli, S., Simonini, M. & Manunta, P.*** *Predicting acute kidney injury: current status and future challenges. J. Nephrol. 31, 209–223 (2018).*

Compiled by Dr Angela Harrison