INTRODUCTION

The kidneys manifest the aging process by a steady loss of nephrons, and an equivalent reduction in the GFR that begins at the age of 30 years ***(Glassock et al., 2017).***

Aging is also characterised by a gradual loss of the muscle mass; loss of the muscle mass with aging begins early, and there is a 30% decrease in the muscle mass from, 20 to 80 years of age. ***(Evans, 2010).***

Chronic kidney disease is associated with loss of muscle mass ***(Laviano et al., 2010).***

During the last decades, in most studies and clinical practice, serum creatinine level has become the most broadly used biomarker for renal function and GFR ***(Hojs et al., 2006).***

Creatinine is a metabolic product of creatine and phosphor-creatine arising from the muscles. Thus, the creatinine level is related to the muscle mass directly ***(Garasto et al., 2014).***

So, there are factors including age, race, sex, body size and muscle mass affect the serum creatinine level, which limits the capability of creatinine to assess kidney function accurately amongst subjects with different levels of muscle mass and particularly in the elderly population ***(Froissart et al., 2005).***

This is an important restriction in elderly persons with renal disease because of the high prevalence of sarcopenia, frailty, and cachexia ***(Froissart et al., 2005).***

So, an obvious decrease in GFR can be existing before it is mirrored in a noticeable rise in serum creatinine level, about 50% of kidney function would already be lost before creatinine level changes ***(Odden et al., 2006).***

Creatinine-based equations to calculate GFR have been developed to overcome the limitation of creatinine. The most broadly used in clinical practice are the Modification of Diet in Renal Disease (MDRD) ***(Levey et al., 2000)*** and the Cockcroft-Gault ***(Cockcroft and Gault, 1976)*** equations ***(Kilbride et al., 2013).***

However, many studies revealed that the Cockcroft-Gault equation may underestimate the real GFR, particularly in subjects older than 79 years, and the MDRD equation underestimates the GFR in individuals with a GFR< 60 ml/min/1.73 m^2 ***(Kilbride et al., 2013).***

So, there is great attention currently in defining novel biomarkers that will give us an idea about the kidney function and the GFR in elderly patients with renal impairment, one of these promising markers is serum cystatin C ***(Barr et al., 2017).***

Cystatin C was first pronounced as 'gamma-trace' in 1961 as a trace protein in the cerebrospinal fluid and the urine

of patients with renal failure. Grubb and Löfberg first reported its amino acid sequence and noticed it was increased in patients with renal failure ***(Grubb and Löfberg, 1982).***

Equations to estimate GFR depending on serum cystatin concentration also developed. In 2012, CKD-EPI Cystatin C (Chronic Kidney Disease Epidemiology Collaboration) was developed to estimate GFR from serum cystatin C, age, and sex. The promising advantage of the CKD-EPI Cystatin C 2012 equation has over the creatinine-based equation is that it is less affected by age, sex, and race ***(Inker et al., 2012).***

CKD-EPI Creatinine-Cystatin C was developed in 2012 to estimate GFR from serum creatinine, cystatin C, age, sex, and race ***(Inker et al., 2012).***

Some studies showed an improved precision of the e-GFR using the cystatin C-based equations over creatinine ***(Domingueti et al., 2016).***

However, little is known about whether estimated GFR by serum cystatin C (e-GFRcys) can be an accurate marker of renal function in elderly patients with decreased muscle mass.

AIM OF THE WORK

The aim of the current study was to assess the accuracy of serum cystatin-C and cystatin-C based GFR as a marker of kidney function in the elderly with CKD and low muscle mass.

Chapter 1

CKD AND AGING, A REAL CHALLENGE

Epidemiology of CKD and its national burden:

Chronic kidney disease is an important public health problem, resulting in end-stage renal disease (ESRD) and increases the risk of morbidity and mortality ***(Astor et al., 2011).***

A GFR below 60 ml/min/1.73 m^2 is considered CKD, while individuals with a GFR of 60 to 89 ml/min/1.73 m^2 without kidney damage are classified as "decreased GFR." ***(Garasto et al., 2014)***

The disease pattern shifts from infectious to chronic diseases as the country becomes more developed. However, the main cause of morbidity and mortality in many of the poorest nations is due to Chronic Diseases (CDs), in spite of low overall indicators of development ***(Nugent et al., 2011).***

In 2005, 60% of the deaths were attributed to CDs, with 4 out of 5 deaths in low and middle income countries, by 2030, it is expected that 3 out of the 4 leading causes of death will be due to chronic conditions, indicating an alarming health burden ***(WHO, 2005).***

The rising of global diabetes and hypertension pandemics are the cause of the increase the surge in the incidence of CKD worldwide ***(Ito et al., 2008).***

The worldwide prevalence of CKD is 11-13%; stage 3 is more predominant among the different stages ***(Hill et al., 2016).***

In Egypt, 31.9% of patients with CKD were found to be between 50 and 60 years in both males and females ***(Ghonemy et al., 2016).***

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) report that one in ten American adults have some level of CKD. Kidney disease is the 9th leading cause of death in the United States ***(CDC, 2017).***

In a study by ***Okada et al., 2014 a,*** the prevalence of CKD among the Japanese was not significantly different between males and females; the prevalence was 27.7% and 28.2%, respectively.

In a systematic review of population-based studies, the prevalence of CKD was 7.2% in individuals aged ≥ 30 years, but it ranged from 23.4% to 35.8% in individuals aged ≥ 64 years ***(Abdulkader et al., 2017).***

The highest macro-economic load of CKD and other CDs falls on low and middle-income countries (LMICs), where

the high prevalence and the costs of treating disease create a great burden on the gross domestic product (GDP) ***(Nugent et al., 2011).***

Much of the economic load of CDs can be accredited to direct medical expenditures associated with expensive and long-term treatment costs. In LMICs, public health care systems receive only 0.8–4% of the GDP, as opposed to 10–15% in developed countries ***(Nugent et al., 2011).***

The increase in the prevalence of CKD with age can be attributed to the several age-related changes that occur in the kidneys ***(Hill et al., 2016).***

The Aging kidney:

Aging is both a natural and an inevitable biological process. With increasing age, the kidneys undergo many anatomical and physiological changes ***(Glassock et al., 2017).***

- **Molecular biology of kidney aging:**

Six decades ago, Dr. Harman was the first who suggested the theory that free radical induced accumulation of oxidative stress and damage at a cellular level was the essential cause of aging and a major determinant of life span; this simplified

theory has been one of the most popular explanations of aging ***(Dai et al., 2014).***

Aging leads to GFR decline, changes in the permeability of the capillary wall in the level of glomeruli, increased susceptibility to podocytes injury, increase apoptosis, changes in reabsorption and secretory capacities in the tubules and changes in the urine concentration ***(Wiggins, 2012).***

It is hypothesized that the progressive decrease in the number of viable and functioning podocytes, along with reduced capacity for their regeneration and repair, lead to glomerular obsolescence and also deterioration of the integrity of slit pore membrane in glomeruli, affecting both whole kidney GFR and albumin permeability at the level of the nephrons ***(Zhang et al., 2011).***

- **Structural changes of the aging kidney:**

A) Micro-anatomical changes:

Nephrosclerosis and nephron hypertrophy are the major aging-related changes observed at the microscopic level in the kidneys ***(Denic et al., 2016).***

1. Nephrosclerosis

The age-associated changes in the light microscopic assessment of kidney biopsies can be divided into two groups: (1) nephrosclerosis and its features (glomerulosclerosis, tubular atrophy, interstitial fibrosis, and arteriosclerosis) and (2) morphometric changes of microanatomy (particularly glomerular size) ***(Rule et al., 2010).***

The glomerulosclerosis has an ischemic appearance with tuft collapse and intra-capsular fibrosis, suggesting a vascular origin for the lesions. Also, some functional glomeruli show an ischemic capillary wrinkling of tufts, thickening of the basement membranes, and mild intra-capsular fibrosis, all of them are precursors for glomerulosclerosis ***(Glassock et al., 2017).***

Each kidney has approximately 700,000 to 1.8 million functional nephrons; however, this amount progressively declines due to aging with increased nephrosclerosis ***(Tan et al., 2010).***

2. Nephron Hypertrophy

Nephron hypertrophy seems to associate relatively weakly with age alone, but associates more strongly with some comorbidities which become more common with aging for example obesity and hyperuricemia. Prominently, older age is much more powerfully associated with nephrosclerosis than with nephron hypertrophy ***(Elsherbiny et al., 2014).***

It is reasonable to expect that with the age-related increase in glomerulosclerosis that compensatory hypertrophy may occur in the residual functional nephrons ***(Grantham, 2012).***

B) Macro-anatomical changes

1. Kidney Volume

Renal mass declines between the age of 30 and 80 years, with the greatest reduction after the age of 50, fibrosis and fat may replace parenchymal tissue, primarily in the renal cortex. Even in normal aging kidneys, 30% of the glomeruli are damaged and show diffuse glomerular sclerosis by age 75 ***(Nitta et al., 2013).***

Ultrasound and Computerized Tomography (CT) are the tools that allow a precise evaluation of the kidney size with aging. Two decades ago, Emamian and his colleagues used ultrasound in over 600 adults and revealed that greater kidney

volume correlated with younger age, height, weight and total body surface area ***(Emamian et al., 1993).***

2. Other Structural Changes

Other parenchymal changes that similarly become more common with aging include fibro-muscular dysplasia, parenchymal calcifications, cortical focal scars, and renal artery atherosclerosis without stenosis. Atherosclerosis of the renal arteries is the most noticeable, with a prevalence of 0.4% for age <30 years that rises to 25% of the age of 60-75 years ***(Lorenz et al., 2010).***

C) Functional changes in the aging kidney

- ***Age-related decline in GFR***

As a result of the above mentioned anatomical changes, there is a reduction in the GFR and the effective renal plasma flow; the latter declines disproportionately more than GFR, this decline is 10% per decade from 600ml/min/1.73 m^2 in youth to 300 ml/min/1.73 m^2 by the age of 80 years ***(Musso and Oreopoulos, 2011).***

Measurement of the GFR with 51 Cr-EDTA confirms that healthy elderly subjects have a lower GFR than younger ones, GFR peaks at approximately 140 ml/min/1.73 m^2 at the third decade of life, and from then on, progressively declines to an approximate rate of 8 ml/ min/1.73 m^2 per decade ***(Alvarez et al., 2009).***

D) The clinical significance of the aging kidney

Normal senescence of the kidneys with subsequently decreased function is of clinical significance when treating elderly patients ***(Nitta et al., 2013).***

Dose adjustment of water-soluble drugs that are cleared through the kidneys may be needed and attention with non-steroidal anti-inflammatory drugs and contrast agents is necessary ***(James et al., 2010).***

Age-related nephrosclerosis with the loss of the functional nephron reserve, without doubt, makes elderly patients more liable to acute kidney injury and a more severe initial presentation of CKD ***(Mjøen et al., 2014).***

Predominant comorbidities in the elderly population also aggravate the decline in kidney function as ***Inaguma et al. 2017*** found that high systolic blood pressure and urine albumin creatinine ratio were risk factors that were significantly associated with CKD and CKD progression to ESRD in Japanese patients.

Risk factors for CKD in the elderly:

- **Diabetes mellitus (DM):**

There is agreement that DM prevalence is growing as revealed in one large population study, the number of individuals with diabetes is predicted to rise from 171 million

in the year 2000 to 366 million by 2030. An associated increase in both the aging and diabetic population has resulted in an increasing prevalence of CKD ***(Mallappallil et al., 2014).***

Diabetic kidney disease (DKD) has been surging as the leading cause of ESRD, as revealed by ***Zhang et al., 2016*** as about one-half of CKD patients in Europe, United States, Japan, and Taiwan was due to DKD, while in Egypt 15.5% of patients with ESRD had DM in El-Sharkia as revealed by ***Ghonemy et al., 2016.***

Serious metabolic changes that change kidney hemodynamics and promote inflammation and fibrosis in early diabetes include hyper-aminoacidemia, a promoter of glomerular hyperfiltration and hyperperfusion, and hyperglycemia ***(Grabias and Konstantopoulos, 2013).***

Glomerular hyperfiltration is a well-defined consequence of early diabetes. Overall, it is detected in up to 75% of cases with type 1 DM and up to 40% of cases with type 2 DM ***(Premaratne et al., 2015).***

Mechanisms of glomerular hyperfiltration in DM are incompletely understood; however, one mechanism is increased proximal tubular reabsorption of glucose via sodium–glucose co-transporter 2, which decreases distal delivery of solutes, mainly sodium chloride, to the macula densa ***(Tuttle, 2017).***

The subsequent decrease in tubuloglomerular feedback may dilate the afferent arteriole to increase glomerular perfusion, while simultaneously; high local production of angiotensin II at the efferent arteriole produces vasoconstriction. The overall effect is high intra-glomerular pressure and glomerular hyperfiltration ***(Grabias and Konstantopoulos, 2013).***

The National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend a goal HbA1c of about 7.0% to delay the progression of the micro-vascular complications of DM. However, patients at risk of hypoglycemia, such as those with DM and CKD, should not be treated to an HbA1c target of <7.0% ***(KDOQI, 2012).***

The more recent Cochrane Collaborative meta-analysis revealed that there were similar risks of renal failure, death and major cardiovascular events among those with strict glycemic control (HbA1c <7%) as opposed to those with less strict control ***(Ruospo et al., 2017).***

- **Hypertension**

Hypertension is a major worldwide public health problem, ***Riggen and Agarwal, 2014*** revealed that hypertension is the 2nd leading cause of ESRD in the United States; hypertension also has a main role in the progress of

most types of CKD including diabetic nephropathy ***(Bidani et al., 2013).***

Uncontrolled hypertension is a major risk factor in non-dialysis CKD ***(De Nicola et al., 2013).***

Normally, increases in blood pressure, episodic or sustained, result in proportional auto-regulatory vasoconstriction of the afferent arteriole, so GFR is maintained relatively constant. However, when the pre-glomerular vasculature exposed to the elevated blood pressure develops the slowly progressive vascular pathology of benign nephrosclerosis ***(Bidani et al., 2013).***

In benign nephrosclerosis, the changes occurring are gradual and progressive; however, there can be enough kidney reserve capacity to preserve adequate kidney function for many years ***(Tahir et al., 2010).***

KDIGO guidelines recommend the usage of angiotensin converting enzyme inhibitors (ACEI) or angiotensin enzyme blockers (ARBs) and a target blood pressure <130/80 mmHg in patients with CKD and albuminuria irrespective to diabetes status ***(Tuttle et al., 2014).***

- **Obesity**

Data from the National Health and Nutrition Examination Survey between 2007 and 2010 reported that more than a third