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OBESITY AND KIDNEY DISEASE: HIDDEN CONSEQUENCES OF THE EPIDEMIC

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SUMMARY

Obesity has become a worldwide epidemic, and its prevalence has been projected to grow by 40% in the next decade. This increasing prevalence has implications for the risks of diabetes, cardiovascular disease and also for Chronic Kidney Disease. A high body mass index is one of the strongest risk factors for new-onset Chronic Kidney Disease. In individuals affected by obesity, a series of complex pathophysiologic changes occur that lead to the development of Chronic Kidney Disease. These include on the one hand effects mediated by the downstream consequences of obesity (such as diabetes mellitus and hypertension), but also direct effects of adipose tissue, via humoral factors such as leptin, adiponectin, resistin and visfatin). In obese individuals a compensatory hyperfiltration occurs to meet the heightened metabolic demands of the increased body weight, leading to glomerulomegaly and accompanied by deposition of adipose tissue in the glomerulus and the gradual development of focal segmental glomerulosclerosis. The incidence of obesity-related glomerulopathy has increased ten-fold in recent years. In addition to the development of Chronic Kidney Disease, obesity has also been shown to be a risk factor for nephrolithiasis, and for a number of malignancies including kidney cancer. Interventions to stem the tide of obesity are thus extremely important for preventing the development and progression of Chronic Kidney Disease and other disorders of the kidneys. This year the World Kidney Day promotes education on the harmful consequences of obesity and its association with kidney disease, advocating healthy lifestyle and health policy measures that makes preventive behaviors an affordable option.

KEY WORDS **Chronic kidney disease • Obesity • Prevention**

BIODATA

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INTRODUCTION

In 2014, over 600 million adults worldwide were obese. Obesity increases the risk of developing major risk factors for Chronic Kidney Disease (CKD), like diabetes and hypertension, and it has a direct impact on the development of CKD and end-stage renal disease (ESRD). The good news is that obesity is largely preventable. Education and awareness of the risks of obesity and a healthy lifestyle, including proper nutrition and exercise, can dramatically help in preventing obesity and kidney disease. This paper reviews the association of obesity with kidney disease on the occasion of the 2017 World Kidney Day.

EPIDEMIOLOGY OF OBESITY

Over the last three decades, the worldwide prevalence of overweight and obesity [body mass index (BMI) $\geq$25 kg/m^2] has increased substantially (Forouzanfar *et al*. 2015), and it is projected to grow by 40% in the next decade. This increasing worldwide prevalence of obesity has implications for CKD, as obesity is one of the strongest risk factors for new-onset CKD (Elsayed *et al*. 2008; Tsujimoto *et al*. 2014).

Definitions of obesity are typically based on BMI. Although BMI is easy to calculate, it is a poor estimate of fat mass distribution. Alternative parameters to more accurately capture visceral fat include waist circumference (WC) and a waist hip ratio (WHR) of $>$102 cm and 0.9, respectively, for men and $>$88 cm and $>$0.8, respectively, for women. WHR has been shown to be superior to BMI for the correct classification of obesity in CKD.

ASSOCIATION OF OBESITY WITH CKD AND OTHER RENAL COMPLICATIONS

Numerous studies have shown an association between measures of obesity and both the development and the progression of CKD (Table 1). In general, the associations between obesity and poorer renal outcomes persist even after adjustments for possible mediators of obesity's cardiovascular and metabolic effects, such as high blood pressure and diabetes mellitus, suggesting that obesity may affect kidney function through mechanisms in part unrelated to these complications (*vide infra*). The deleterious effect of obesity on the kidneys extends to other complications such as nephrolithiasis (Curhan *et al*. 1998; Taylor & Stampfer 2005; Scales *et al*. 2012) and kidney malignancies (Renehan *et al*. 2008; Bhaskaran & Douglas 2014; Arnold *et al*. 2015).

MECHANISMS OF ACTION UNDERLYING THE RENAL EFFECTS OF OBESITY

The exact mechanisms whereby obesity may worsen or cause CKD remain unclear. Some of the deleterious renal consequences of obesity may be mediated by downstream comorbid conditions such as diabetes mellitus or hypertension, but there are also effects of adiposity which could impact the kidneys directly, induced by the endocrine activity of the adipose tissue via production of (among others) adiponectin (Sharma 2009), leptin (Wolf & Ziyadeh 2006) and resistin (Ellington *et al*. 2007) (Figure 1). These include the development of inflammation (Bastard *et al*. 2006), oxidative stress (Furukawa *et al*. 2004), abnormal lipid metabolism, (Ruan *et al*. 2009) activation of the renin-angiotensin-aldosterone system (Ruster & Wolf 2013), and increased production of insulin and insulin resistance (Reaven 1988; Oterdoom *et al*. 2007).

These various effects result in specific pathologic changes in the kidneys (Kambham *et al*. 2001) including ectopic lipid accumulation (de Vries *et al*. 2014) and increased deposition of renal sinus fat (Henegar *et al*. 2001; Foster *et al*. 2011a), the development of glomerular hypertension and increased glomerular permeability caused by hyperfiltration-related glomerular filtration barrier injury (Knight *et al*. 2008), and ultimately the development of glomerulomegaly (Tsuboi *et al*. 2012), and focal or segmental glomerulosclerosis (Kambham *et al*. 2001) (Figure 2). The incidence of the so-called obesity-related glomerulopathy has increased 10-fold between 1986 and 2000 (Kambham *et al*. 2001).

Obesity is associated with a number of risk factors contributing to the higher incidence and prevalence of nephrolithiasis, such as lower urine pH (Maalouf *et al*. 2004) and increased urinary oxalate (Lemann *et al*. 1996), uric acid, sodium and phosphate excretion (Siener *et al*. 2004). The insulin resistance characteristic of obesity may also predispose to nephrolithiasis (Taylor *et al*. 2005) through its impact on tubular Na-H exchanger (Klisic *et al*. 2002) and ammoniagenesis (Chobanian & Hammerman 1987), and the promotion of an acidic milieu (Daudon *et al*. 2006).

The mechanisms behind the increased risk of kidney cancers observed in obese individuals are less well characterised. Insulin resistance, chronic hyperinsulinemia and increased production of insulin-like growth factor 1 may exert stimulating effects on

Study	Patients	Exposure	Outcomes	Results	Comments
Prevention of Renal and Vascular End-Stage Disease (PREVEND) Study, Pinto-Sietsma *et al*. (2003)	7,676 Dutch individuals without diabetes	Elevated BMI (overweight and obese*), and central fat distribution (waist-hip ratio)	-Presence of urine albumin 30–300 mg/24 h -Elevated and diminished GFR	−Obese + central fat: higher risk of albuminuria −Obese ± central fat: higher risk of elevated GFR −Central fat ± obesity associated with diminished filtration	Cross sectional analysis
Multinational study of hypertensive outpatients, Thoenes *et al*. (2009)	20,828 patients from 26 countries	BMI and waist circumference	Prevalence of albuminuria by dip stick	Higher waist circumference associated with albuminuria independent of BMI	Cross sectional analysis
Framingham Multi-Detector Computed Tomography (MDCT) cohort, Foster *et al*. (2011b)	3,099 individuals	Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT)	Prevalence of UACR >25 mg/g in women and >17 mg/g in men	VAT associated with albuminuria in men, but not in women	Cross sectional analysis
CARDIA (Coronary Artery Risk Development in Young Adults) study, Chang *et al*. (2013)	2,354 community-dwelling individuals with normal kidney function aged 28–40 years	-Obesity (BMI >30 kg/m^2) -Diet and lifestyle-related factors	Incident microalbuminuria	Obesity (OR 1.9) and unhealthy diet (OR 2.0) associated with incident albuminuria	Low number of events
Hypertension Detection and Follow-Up Program, Kramer *et al*. (2005)	5,897 hypertensive adults	Overweight and obese BMI* vs. normal BMI	Incident CKD (1+ or greater proteinuria on urinalysis and/or an eGFR <60 ml/min/1.73 m^2)	Both overweight (OR 1.21) and obesity (OR 1.40) associated with incident CKD	Results unchanged after excluding diabetics
Framingham Offspring Study, Foster *et al*. (2008)	2,676 individuals free of CKD stage 3	High vs. normal BMI*	-Incident CKD stage 3 -Incident proteinuria	-Higher BMI not associated with CKD3 after adjustments -Higher BMI associated with increased odds of incident proteinuria	Predominantly white, limited geography
Physicians' Health Study, Gelber *et al*. (2005)	11,104 initially healthy men in US	-BMI quintiles -Increase in BMI over time (vs. stable BMI)	Incident eGFR <60 ml/min/1.73 m^2	-Higher baseline BMI and increase in BMI over time both associated with higher risk of incident CKD	Exclusively men
Nation-wide US Veterans Administration cohort, Lu *et al*. (2015)	3,376,187 US veterans with baseline eGFR ≥60 ml/min/1.73 m^2	BMI categories from <20 to >50 kg/m^2	Rapid decline in kidney function (negative eGFR slope of >5 ml/min/1.73 m^2)	BMI >30 kg/m^2 associated with rapid loss of kidney function	Associations more accentuated in older individuals
Nation-wide population-based study from Sweden, Ejerblad *et al*. (2006)	926 Swedes with moderate/advanced CKD compared to 998 controls	BMI ≥ 25 vs. <25 kg/m^2	CKD vs. no CKD	Higher BMI associated with 3x higher risk of CKD	-Risk strongest in diabetics, but also significantly higher in non-diabetics -Cross sectional analysis
Nation-wide population based study in Israel, Vivante *et al*. (2012)	1,194,704 adolescent males and females examined for	Elevated BMI (overweight and obesity) vs. normal BMI*	Incident ESRD	Overweight (HR 3.0) and obesity (HR 6.89) associated with higher risk of ESRD	Associations strongest for diabetic ESRD, but also significantly higher for non-diabetic ESRD

TABLE 1 (Continued)

Study	Patients	Exposure	Outcomes	Results	Comments
	military service				
The Nord-Trøndelag Health Study (HUNT-1), Munkhaugen *et al*. (2009)	74,986 Norwegian adults	BMI categories*	Incidence of ESRD or renal death	BMI >30 kg/m^2 associated with worse outcomes	Associations not present in individuals with BL <120/80 mmHg
Community-based screening in Okinawa, Japan, Iseki *et al*. (2004)	100,753 individuals >20 years old	BMI quartiles	Incidence of ESRD	Higher BMI associated with increased risk of ESRD in men, but not in women	Average BMI lower in Japan compared to Western countries
Nation-wide US Veterans Administration cohort, Lu *et al*. (2014)	453,946 US veterans with baseline eGFR <60 ml/min per 1.73 m^2	BMI categories from <20 to >50 kg/m^2	-Incidence of ESRD -Doubling of serum creatinine -Slopes of eGFR	Moderate and severe obesity associated with worse renal outcomes	Associations present but weaker in patients with more advanced CKD
Kaiser Permanente Northern California, Hsu *et al*. (2006)	320,252 adults with and without baseline CKD	Overweight, class I, II and extreme obesity; vs. normal BMI*	Incidence of ESRD	Linearly higher risk of ESRD with higher BMI categories	Associations remained present after adjustment for DM, hypertension and baseline CKD
REGARDS (Reasons for Geographic and Racial Differences in Stroke) Study, Kramer *et al*. (2016)	30,239 individuals	Elevated waist circumference or BMI	Incidence of ESRD	BMI above normal not associated with ESRD after adjustment for waist circumference -Higher waist circumference associated with ESRD	Association of waist circumference with ESRD became on-significant after adjustment for comorbidities and baseline eGFR and proteinuria

Table 1: Studies examining the association of obesity with various measures of CKD.

BMI, body mass index; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; HR, hazard ratio; OR, odds ratio; UACR, urine albumin-creatinine ratio.
*Normal weight, BMI 18.5–24.9 kg/m^2; overweight, BMI 25.0–29.9 kg/m^2; class I obesity, BMI 30.0–34.9 kg/m^2; class II obesity, BMI 35.0–39.9 kg/m^2; class III obesity, BMI ≥40 kg/m^2.

the growth of various types of tumor cells (Calle & Kaaks 2004). More recently, the endocrine functions of adipose tissue (Dalamaga *et al*. 2012), its effects on immunity (Lamas *et al*. 2002), and the generation of an inflammatory milieu with complex effects on cancers (Grivennikov *et al*. 2010; Lim & Savan 2014) have emerged as additional explanations.

OBESITY IN PATIENTS WITH ADVANCED KIDNEY DISEASE: THE NEED FOR A NUANCED APPROACH

In a seemingly counterintuitive manner obesity has been consistently associated with lower mortality rates in patients with advanced CKD (Kovesdy *et al*. 2007; Lu *et al*. 2014) and ESRD (Beddhu *et al*. 2003; Kalantar-Zadeh *et al*. 2006). It is possible that the seemingly protective effect of a high BMI is the result of the imperfection of BMI as a measure of obesity. However, there is also evidence to suggest that higher adiposity, especially subcutaneous (non-visceral) fat, may also be associated with better outcomes in ESRD patients (Kalantar-Zadeh *et al*. 2006). Such benefits may be present in patients who have very low short term life expectancy, such as most ESRD patients; (Dekker *et al*. 2008) including benefits from better nutritional status, higher muscle mass, (Beddhu *et al*. 2003) a more stable haemodynamic status with mitigation of stress responses and heightened sympathetic and renin-angiotensin activity (Horwich *et al*. 2001); increased production of adiponectines (Stenvinkel *et al*. 2004) and soluble tumor necrosis factor alfa receptors (Mohamed-Ali *et al*. 1999; Rauchhaus *et al*. 2000) and sequestration of uraemic toxins by adipose tissue (Jandacek *et al*. 2005).

POTENTIAL INTERVENTIONS FOR MANAGEMENT OF OBESITY

Strategies for controlling the obesity-related CKD epidemic at population level and for countering the evolution of CKD towards kidney failure in obese patients represent the most tantalizing task that today's health planners, health managers and nephrologists face.

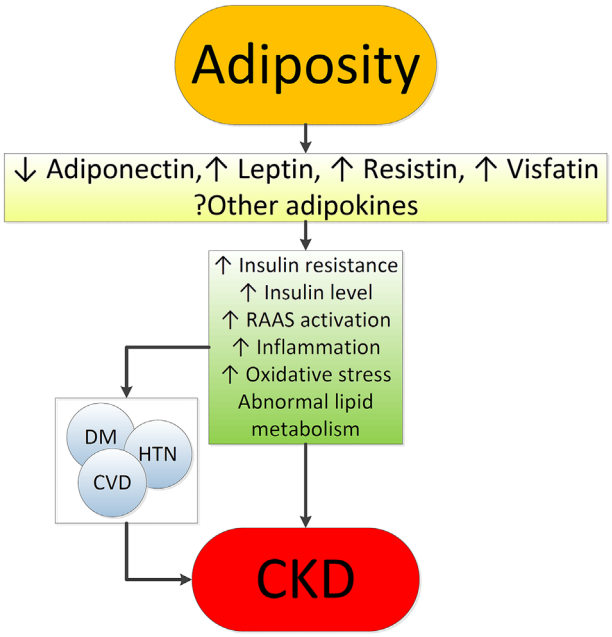

Figure 1: Putative mechanisms of action whereby obesity causes chronic kidney disease.

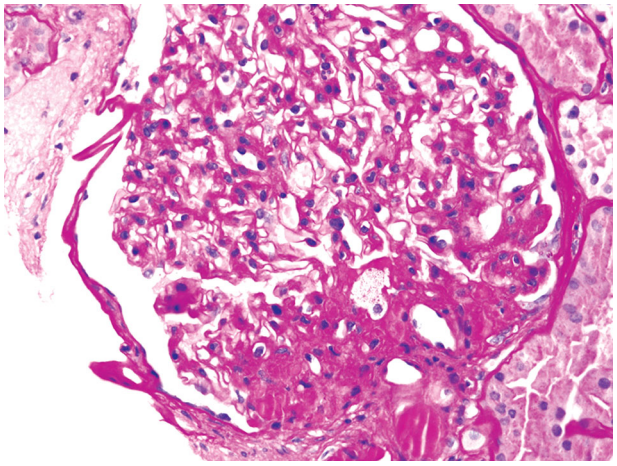

Figure 2: Obesity-related perihilar focal segmental glomerulosclerosis on a background of glomerulomegaly. Periodic Acid–Schiff stain, original magnification 400x. Courtesy of Dr. Patrick D. Walker, MD; Arkana Laboratories, Little Rock, AR.

COUNTERING CKD AT POPULATION LEVEL

Calls for public health interventions in the community to prevent and treat CKD at an early stage have been made by major renal associations. In the United States, Healthy People 2020, a program that sets 10-year health targets for health promotion and prevention goals, focuses both on CKD and obesity. A successful surveillance system for CKD has already been implemented in some places such as the United Kingdom (O'Donoghue & Stevens 2012), which may serve as a platform to improve the prevention of obesity-related CKD. Campaigns aiming at reducing the obesity burden are now at centre stage worldwide and are strongly recommended by the WHO and it is expected that these campaigns will reduce the incidence of obesity-related complications, including CKD.

PREVENTION OF CKD PROGRESSION IN OBESE PEOPLE WITH CKD

Obesity-related goals in obese CKD patients remain vaguely formulated, largely because of the paucity of high-level evidence intervention studies to modify obesity in CKD patients (Bolignano & Zoccali 2013). In overweight or obese diabetic patients, a lifestyle intervention including caloric restriction and increased physical activity compared with a standard follow up reduced the risk for incident CKD by 30% (Wing *et al*. 2013). In a recent meta-analysis collating experimental studies in obese CKD patients, interventions aimed at reducing body weight showed coherent reductions in blood pressure, glomerular hyperfiltration and proteinuria (Bolignano & Zoccali 2013). A *post hoc* analysis of the REIN study showed that the nephron-protective effect of ACE inhibition in proteinuric CKD patients was maximal in obese CKD patients, but minimal in CKD patients with normal or low BMI (Mallamaci *et al*. 2011). Bariatric surgical intervention have been suggested for selected CKD and ESRD patients (Jamal *et al*. 2015; Chang *et al*. 2016; Friedman & Wolfe 2016).

Globally, these experimental findings provide a proof of concept for the usefulness of weight reduction and ACE inhibition interventions in the treatment of CKD in the obese. Studies showing a survival benefit of increased BMI in CKD patients, however, remain to be explained (Ahmadi *et al*. 2015). These findings limit our ability to make strong recommendations about the usefulness and the safety of weight reduction among individuals with more advanced stages of CKD. Lifestyle recommendations to reduce body weight in obese people at risk for CKD and in those with early CKD appear justified, particularly recommendations for the control of diabetes and hypertension.

CONCLUSIONS

The worldwide epidemic of obesity affects the Earth's population in many ways. Diseases of the kidneys, including CKD, nephrolithiasis and kidney cancers are among the more insidious effects of obesity, but which nonetheless have wide ranging deleterious consequences, ultimately leading to significant excess morbidity and mortality and excess costs to individuals and the entire society. Population-wide interventions to control obesity could have beneficial effects in preventing the development, or delaying the progression of CKD. It is incumbent upon the entire healthcare community to devise long-ranging strategies towards improving the understanding of the links between obesity and kidney diseases, and to determine optimal strategies to stem the tide. The 2017 World Kidney Day is an important opportunity to increase education and awareness to that end.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

CPK, SLF, CZ: Drafted the manuscript and approved the final version. Members of the World Kidney Day Steering Committee critically reviewed the manuscript and approved the final version.

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