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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) ≥25 kg/m²] 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 & Stämpfer 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 glomerulonegaly (Tsouli 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 hyperinsulinaemia and increased production of insulin-like growth factor 1 may exert stimulating effects on
<table>
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<tr>
<td>Prevention of Renal and Vascular End-Stage Disease (PREVEND) Study, Pinto-Sietsma et al. (2003)</td>
<td>7,676 Dutch individuals without diabetes</td>
<td>Elevated BMI (overweight and obese*), and central fat distribution (waist-hip ratio)</td>
<td>Presence of urine albumin 30–300 mg/24 h -Elevated and diminished GFR</td>
<td>-Obese + central fat: higher risk of albuminuria -Obese ± central fat: higher risk of elevated GFR -Central fat ± obesity associated with diminished filtration</td>
<td>Cross sectional analysis</td>
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<td>Multinational study of hypertensive outpatients, Thoenes et al. (2009)</td>
<td>20,828 patients from 26 countries</td>
<td>BMI and waist circumference</td>
<td>Prevalence of albuminuria by dip stick</td>
<td>Higher waist circumference associated with albuminuria independent of BMI</td>
<td>Cross sectional analysis</td>
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<tr>
<td>Framingham Multi-Detector Computed Tomography (MDCT) cohort, Foster et al. (2011b)</td>
<td>3,099 individuals</td>
<td>Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT)</td>
<td>Prevalence of UACR &gt;25 mg/g in women and &gt;17 mg/g in men</td>
<td>VAT associated with albuminuria in men, but not in women</td>
<td>Cross sectional analysis</td>
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<td>CARDIA (Coronary Artery Risk Development in Young Adults) study, Chang et al. (2013)</td>
<td>2,354 community-dwelling individuals with normal kidney function aged 28–40 years</td>
<td>-Obesity (BMI &gt;30 kg/m²) -Diet and lifestyle-related factors</td>
<td>Incident microalbuminuria</td>
<td>Obesity (OR 1.9) and unhealthy diet (OR 2.0) associated with incident albuminuria</td>
<td>Low number of events</td>
</tr>
<tr>
<td>Hypertension Detection and Follow-Up Program, Kramer et al. (2005)</td>
<td>5,897 hypertensive adults</td>
<td>Overweight and obese BMI* vs. normal BMI</td>
<td>Incident CKD (1+ or greater proteinuria on urinalysis and/or an eGFR &lt;60 ml/min/1.73 m²)</td>
<td>Both overweight (OR 1.21) and obesity (OR 1.40) associated with incident CKD</td>
<td>Results unchanged after excluding diabetics</td>
</tr>
<tr>
<td>Framingham Offspring Study, Foster et al. (2008)</td>
<td>2,676 individuals free of CKD stage 3</td>
<td>High vs. normal BMI</td>
<td>Incident CKD stage 3 -Incident proteinuria</td>
<td>-Higher BMI not associated with CKD3 after adjustments -Higher BMI with increased odds of incident proteinuria</td>
<td>Predominantly white, limited geography</td>
</tr>
<tr>
<td>Physicians’ Health Study, Gelber et al. (2005)</td>
<td>11,104 initially healthy men in US</td>
<td>-BMI quintiles -Increase in BMI over time (vs. stable BMI)</td>
<td>Incident eGFR &lt;60 ml/min/1.73 m²</td>
<td>-Higher baseline BMI and increase in BMI over time both associated with higher risk of incident CKD</td>
<td>Exclusively men</td>
</tr>
<tr>
<td>Nation-wide US Veterans Administration cohort, Lu et al. (2015)</td>
<td>3,376,187 US veterans with baseline eGFR &gt;60 ml/min/1.73 m²</td>
<td>BMI categories from &lt;20 to &gt;50 kg/m²</td>
<td>Rapid decline in kidney function (negative eGFR slope of &gt;5 ml/min/1.73 m²)</td>
<td>BMI &gt;30 kg/m² associated with rapid loss of kidney function</td>
<td>Associations more accentuated in older individuals</td>
</tr>
<tr>
<td>Nation-wide population-based study from Sweden, Ejerblad et al. (2006)</td>
<td>926 Swedes with moderate/advanced CKD compared to 998 controls</td>
<td>BMI ≥ 25 vs. &lt;25 kg/m²</td>
<td>CKD vs. no CKD</td>
<td>Higher BMI associated with 3x higher risk of CKD</td>
<td>-Risk strongest in diabetics, but also significantly higher in non-diabetics -Cross sectional analysis</td>
</tr>
<tr>
<td>Nation-wide population-based study in Israel, Vivante et al. (2012)</td>
<td>1,194,704 adolescent males and females examined for</td>
<td>Elevated BMI (overweight and obesity) vs. normal BMI*</td>
<td>Incident ESRD</td>
<td>Overweight (HR 3.0) and obesity (HR 6.89) associated with higher risk of ESRD</td>
<td>Associations strongest for diabetic ESRD, but also significantly higher for non-diabetic ESRD</td>
</tr>
</tbody>
</table>
More recently, the endocrine functions of adipose tissue have been shown to be complex, with effects on cancers (Grivennikov et al. 2002), and the generation of an inflammatory milieu with possible effects on immunity (Lamas et al. 2006). It is also 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).

**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

**TABLE 1 (Continued)**

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<tr>
<td>The Nord-Trøndelag Health Study (HUNT-1), Munkhaugen et al. (2009)</td>
<td>74,986 Norwegian adults</td>
<td>BMI categories¹</td>
<td>Incidence of ESRD or renal death</td>
<td>BMI &gt;30 kg/m² associated with worse outcomes</td>
<td>Associations not present in individuals with BL &lt;120/80 mmHg</td>
</tr>
<tr>
<td>Community-based screening in Okinawa, Japan, Iseki et al. (2004)</td>
<td>100,753 individuals &gt;20 years old</td>
<td>BMI quartiles</td>
<td>Incidence of ESRD</td>
<td>Higher BMI associated with increased risk of ESRD in men, but not in women</td>
<td>Average BMI lower in Japan compared to Western countries</td>
</tr>
<tr>
<td>Nation-wide US Veterans Administration cohort, Lu et al. (2014)</td>
<td>453,946 US veterans with baseline eGFR &lt;60 ml/min per 1.73 m²</td>
<td>BMI categories from &lt;20 to &gt;50 kg/m²</td>
<td>-Incidence of ESRD -Doubling of serum creatinine -Slopes of eGFR</td>
<td>Moderate and severe obesity associated with worse renal outcomes</td>
<td>Associations present but weaker in patients with more advanced CKD</td>
</tr>
<tr>
<td>Kaiser Permanente Northern California, Hsu et al. (2006)</td>
<td>320,252 adults with and without baseline CKD</td>
<td>Elevated waist circumference or BMI</td>
<td>Incidence of ESRD</td>
<td>Linearly higher risk of ESRD with higher BMI categories</td>
<td>Associations remained present after adjustment for DM, hypertension and baseline CKD</td>
</tr>
<tr>
<td>REGARDS (Reasons for Geographic and Racial Differences in Stroke) Study, Kramer et al. (2016)</td>
<td>30,239 individuals</td>
<td>Elevated waist circumference or BMI</td>
<td>Incidence of ESRD</td>
<td>BMI above normal not associated with ESRD after adjustment for waist circumference -Higher waist circumference associated with ESRD</td>
<td>Association of waist circumference with ESRD became on-significant after adjustment for comorbidities and baseline eGFR and proteinuria</td>
</tr>
</tbody>
</table>

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.

²Normal weight, BMI 18.5–24.9 kg/m²; overweight, BMI 25.0–29.9 kg/m²; class I obesity, BMI 30.0–34.9 kg/m²; class II obesity, BMI 35.0–39.9 kg/m²; class III obesity, BMI ≥40 kg/m².
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.

REFERENCES
Bastard J.P., Maachi M., Lagathu C., et al. (2006). Recent advances in the relationship between obesity, inflammation, and insulin resistance. European Cytokine Network 17, 4–12.


