Review

The Role of Overweight and Obesity in the Cardiorenal Syndrome

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Key Words

Adiposity • Cardiorenal metabolic syndrome • Chronic kidney disease • Heart failure • Metabolic dyslipidemia • Obesity

Abstract

The presence of a group of interactive maladaptive factors including hypertension, insulin resistance, metabolic dyslipidemia, obesity, microalbuminuria, and/or reduced renal function constitute the cardiorenal metabolic syndrome (CRS). Overweight, obesity, and chronic kidney disease (CKD) have grown to pandemic proportions in industrialized countries during the past decade. The fact that these interactive factors promote heart and renal disease has been documented in large population-based studies. Obesity seems to be the driving force behind the development of heart disease and CKD and therefore the CRS. The relationship between overweight/obesity and kidney disease begins in early childhood and appears to be related to overconsumption of high-fructose corn syrup and insufficient physical activity. Today, 13 million children are obese, and over 70% of these children are likely to become obese adults. Indeed, approximately 30% of male and 34% of female adults in the United States are obese. This lifestyle-related epidemic will be a major societal medical and economic problem that will accentuate the current epidemic of CKD in the United States and other industrialized and emerging industrialized countries. In this article, we will review the potential mechanisms by which obesity and other metabolic abnormalities interact to promote heart and progressive kidney disease.

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Introduction

Overweight and obesity occur in >72 million American adults [1–4]. This epidemic is associated with increased cardiovascular- and renal-disease-related morbidity and mortality [3, 4]. Childhood-adolescent overweight and obesity are emerging major global public health concerns [6–11]. Since 1980 obesity rates in children have tripled. Currently, 13 million children in the United States are obese, including 14% of all 6- to 11-year-old children and 17% of adolescents [6]. The international Obesity Task Force has estimated that 22 million children younger than 5 years are overweight or obese [7]. They have also estimated that 1 in 10 children, approximately 155 million, are overweight. Additionally, about 3% of children aged 5–17 years are now classified as obese (approximately 45 million of the 155 million). This emerging pandemic is largely thought to be triggered by the same sociologic/environmental factors that have resulted in two thirds of adults in this country being overweight or obese [6–15]. These driving forces for overweight and obesity in children, as well as adults, include increasing sedentary lifestyles with physical inactivity and excess compact caloric consumption. Childhood-adolescent overweight is defined as a body mass index (BMI) greater than the 85th percentile but less than the 95th percentile, whereas childhood-adolescent obesity is defined as a BMI greater than the 95th percentile [8]. Childhood obesity is associated with an increased prevalence (up to 50%) of the metabolic (cardiorenal) syndrome; the prevalence is increased on a graded scale based on increasing BMI [9]. Childhood obesity is also the most common cause of insulin resistance (IR), which is associated with dyslipidemia, long-term cardiovascular complications, including hypertension, pre-diabetes (impaired glucose tolerance), fatty liver disease, and overt type 2 diabetes mellitus [10, 11].

Childhood obesity and associated medical problems such as chronic kidney disease (CKD) are more prevalent in minority and socioeconomically deprived children and adults [16–21]. These disparities are also evidenced in the increased prevalence of diabetes and hypertension in these populations [17, 18]. Importantly, childhood obesity is also associated with increased inflammation, with elevated levels of inflammatory biomarkers, including C-reactive protein, interleukin-6, and tumor necrosis factor- α , and decreased levels of adiponectin, a marker of insulin sensitivity synthesized and secreted exclusively by adipocytes [4, 5, 7]. These factors all contribute to the increasingly recognized relationship between obesity and the early development of childhood/adolescent kidney disease and diabetes, and underscore the importance of emerging interventions to prevent the development of these chronic diseases [7, 11–15].

Cardiorenal Metabolic Syndrome and the Epidemic of CKD

As suggested in the preceding information, the presence of a constellation of interactive cardiac and renal risk factors, including overweight/obesity, hypertension, IR/hyperinsulinemia, metabolic dyslipidemia, microalbuminuria and/or reduced renal function, constitute the cardiorenal metabolic syndrome (CRS) in both children and adults (table 1, fig. 1) [22]. For example, in 19,096 non-diabetic persons in the Atherosclerosis Risk in Communities (ARIC) study, the odds ratio for developing CKD in those with CRS compared to those without the syndrome was 1.43 [23]. Likewise, in a cohort of 320,252 adults followed over a 15- to 35-year period, the rate of end-stage renal disease (ESRD) increased in a fashion proportional to BMI [24]. Increasing components of the syndrome progressively enhance the risk for microalbuminuria [25] and proteinuria [26]. In this regard, the association between components of the conventional metabolic syndrome and the risk for both microalbuminuria and CKD was evaluated in the Third National Health and Nutrition Examination Survey (NHANES III) [25]. In multivariate adjusted analysis, the odds ratio for microalbuminuria and CKD was 1.89 and 2.60, respectively. Additionally, the risk for microalbuminuria

Fig. 1. The interrelationship between adiposity and maladaptive changes in the heart and kidney in CRS. GFR = Glomerular filtration rate; IL = interleukin; PAI = plasminogen activator inhibitor; RAAS = renin-angiotensin-aldosterone system; ROS = reactive oxygen species; TNF = tumor necrosis factor; TPA = tissue plasminogen activator.

Table 1. CRS components

1	Central obesity
2	Insulin resistance
3	Hypertension
4	Metabolic dyslipidemia (low HDL, high triglycerides and increased small, dense LDL particles)
5	Albuminuria
6	Reduced glomerular filtration rate (<60 ml/min)

and CKD was proportional to the number of individual components present. In a Japanese population, similar data on the impact of components of the metabolic syndrome and CKD were documented in men younger than 60 years [26, 27]. There are mounting data that support a relationship between dysglycemia and other components of the CRS and CKD independent of the presence of clinical diabetes [28–30].

There is accumulating evidence that overweight/obesity is the driving force for this syndrome [22, 31–37]. To this point, the relationship between BMI and ESRD was observed in a Japanese population of over 100,000 persons followed for 17 years [32]. Indeed, the cumulative incidence of ESRD increased significantly with rising BMI after adjustment for age, systolic blood pressure, and proteinuria. The interaction between obesity and other renal-disease-promoting factors has been partly elucidated by several observational and mechanistic studies [32–49]. One of the potential mechanisms by which obesity promotes CKD is through hyperfiltration-related maladaptive mechanisms [32–49]. Our understanding of the role of obesity and related metabolic factors in promoting renal disease has been advanced by a number of studies conducted recently. In one study [32], investigators phenotyped 1,572 young men (mean age 18.4 years) for metabolic risk factors, and renal function was ascertained by calculated creatinine clearance based on the Cockcroft-Gault equation. These investigators reported that metabolic risk clustering of three or more risk factors was strongly associated with glomerular hyperfiltration. This early renal functional abnormality was especially associated with adiposity (elevated leptin levels and anthropometric determinants) and elevated blood pressure. Based on these data, the authors proposed that increased adiposity, particularly visceral fat production of inflammatory adipokines, was a major driving force of glomerular hyperfiltration.

Glomerular hyperfiltration in humans has been hypothesized to reflect increased glomerular capillary pressure, which is a seminal mediator of glomerular capillary damage in rodent models [22, 37]. In this regard, investigators have recently reported the prevalence of hyperfiltration in 301 non-diabetic adults of African ancestry [36]. The prevalence of glomerular hyperfiltration, defined as an insulin clearance rate >140 ml/min, was threefold higher (27 vs. 7%) among obese participants (BMI >30) compared to lean participants (BMI <25). Obese participants also had higher effective renal plasma blood flow estimated by para-aminohippuric acid clearance. These obesity-related early renal functional changes may be especially detrimental in populations manifesting lower birth weights and lower nephron numbers [16–20, 31–35]. Other factors, such as systemic and renal inflammation and oxidative stress [22], may determine to what extent this hyperfiltration translates into glomerular and tubulointerstitial fibrosis and progressive renal disease.

Obesity, CRS and CKD epidemics in the United States have paralleled the substantially increased consumption of high-fructose corn syrup (HFCS) [50]. Indeed, HFCS consumption has increased dramatically in the past 3 decades. HFCS currently represents 40% of the non-calorie-free sweeteners in food in the United States. Sweetened beverages, such as non-diet soda, account for 70% of the intake of HFCS [50]. Recent investigations have shown that HFCS-sweetened soda consumption is associated with albuminuria [51] and elevated serum creatinine [48]. One of the possible mechanisms by which increased HFCS consumption causes renal disease is through increases in uric acid production. The metabolism of fructose increases the degradation of nucleotides and the associated synthesis of uric acid [43, 52]. In rodent models, fructose-associated hyperuricemia produces CRS with glomerular hyperfiltration, renal hypertrophy, and arteriolopathy of the renal vasculature, and subsequent increases in proteinuria and reductions in creatinine clearance (fig. 1) [43–46].

Hyperinsulinemia can reduce renal excretion of uric acid as insulin can stimulate the urate-anion exchanger and/or the sodium-dependent anion co-transporter in brush border membranes of the renal proximal tubule and increase urate reabsorption [43].

Recently, a relationship between sugar-sweetened soda consumption and hyperuricemia and kidney disease was evidenced from an analysis of data from the ARIC study [50]. Compared to participants who drank less, consumption of more than one soda per day was associated with increased odds of prevalent hyperuricemia and CKD. The odds ratio for CKD significantly increased to 2.59 among participants who drank more than one soda per day and had a serum uric acid >9.0 mg/dl. Indeed, stratified analysis indicated that the association between intake of sweetened beverages and declining renal function was primarily found among participants with elevated serum uric acid levels. As noted by the investigators, these findings are in accordance with prior publications reporting that high-sugar-sweetened soda consumption was associated with prevalent hyperuricemia and renal injury [48–52]. The authors further suggested that this supports other data indicating that increased intake of sugar-sweetened soda may be the driving force for the epidemic of obesity, hypertension, CRS, and diabetes [53–55].

CRS and Heart Disease

Heart failure (HF) is present in >5 million persons in the United States, accounting for nearly 40 billion US dollars in annual health care costs [56]. The most common form of HF is that with preserved ejection fraction, and it is increasing in westernized cultures [57]. Both overweight/obesity and aging are prominent risk factors for this form of HF [56, 57], and they are associated with higher rates of hypertension and diabetes [3, 4], which also contribute to an increase in HF with preserved systolic function. Obesity is associated with a metabolic cardiomyopathy, which is characterized by impaired left ventricular relaxation, usually in association with IR [58–60]. In this metabolic form of heart disease, relaxation abnormalities usually occur before the onset of contractile dysfunction [58–60]. Diastolic dysfunction is characterized by a diminution in the ability of the left ventricle to fill with blood during early diastolic filling [60, 61].

IR appears to play an important role in obesity-related HF. Impaired insulin metabolic signaling, reduced bioavailable nitric oxide (NO), and increased generation of reactive oxygen species, all play a role in maladaptive remodeling, interstitial fibrosis and impaired diastolic relaxation [60, 62–69]. Hyperuricemia may contribute to this maladaptation as it causes increases in reactive oxygen species, reduces bioavailable NO, and promotes endothelial dysfunction [43]. Strategies to prevent and treat metabolic heart disease, especially in the presence of associated kidney disease, include lifestyle changes (weight reduction and exercise) and medical therapies that reduce oxidative stress and improve bioavailable NO and insulin metabolic signaling [60, 70].

Conclusion

The association of overweight/obesity, CKD, and HF with preserved systolic function has spawned an epidemic in industrialized countries. We refer to this constellation of diseases as the *cardiorenal metabolic syndrome*, which is an extension of the prior use of this terminology to refer to coexistent heart and kidney disease. The current use of this terminology considers obesity, especially central obesity, as a pivotal factor in the development of IR, metabolic dyslipidemia, and associated kidney and heart disease. This syndrome is becoming an epidemic, largely because of the high prevalence of overweight/obesity in industrialized countries. We have revised underlying mechanistic and epidemiological factors that promote kidney and heart disease in concert with the development of metabolic components of the syndrome.

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