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Obesity, preterm birth and kidney disease: a global epidemic

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Worldwide, chronic kidney disease (CKD) affects over 500 million people, and the majority of these persons with CKD live in low- and middle-income countries [1]. Over the past several decades, middle-income countries have experienced dramatic increases in life expectancy due to improvements in nutrition and prenatal care. Morbidity and mortality from infectious diseases continue to decrease in low- and middle-income countries due to improved access to prevention and treatment, leading to longer lifespan and decreased infant mortality. This epidemiologic transition has been accompanied by a societal movement away from the traditional agrarian lifestyle in many countries. Less time is now spent on obtaining and preparing food, while processed drinks and foods are very easily accessible. This metamorphosis of obtaining, preparing and eating foods can be viewed as the industrialization of dietary practices, and these changes have evolved over just a few decades [2]. This industrialization of population dietary practices has led to higher intake of red meat, animal fat, highly processed foods preserved with phosphate and sodium, and reduced intake of fresh fruits and vegetables [2]. This dietary pattern heightens inflammation [3] and increases risk of both kidney and cardiovascular diseases [2, 4–6]. But the most apparent change in public health as a consequence of dietary industrialization is obesity.

The industrialization of diet has led to higher caloric intake accompanied by lower energy expenditure leading to weight gain [7]. By the year 2025, ∼20% of men and women worldwide will be obese and >6% of men and 9% of women will be severely obese as defined as a body mass index (BMI) ≥35 kg/m^2 [8]. The epidemic of obesity among adults shows no signs of abatement and if anything will worsen over time given the burden of obesity among children [9]. Within a decade, the number of obese children worldwide may exceed the number of those that are undernourished. Around the globe, BMI has increased by 0.32 kg/m^2 among children aged ≥5 years on average per decade, and over 100 million children worldwide are now obese [9]. These societal transformations in nutrition are threatening to outpace existing healthcare budgets and infrastructure, which are often restrained in low- and middle-income countries. Furthermore, the rapidity of this obesity epidemic has impeded public health efforts and fueled a substantial increase in chronic noncommunicable diseases, especially diabetes and hypertension, the most common risk factors for CKD. Lack of attention to CKD within the context of an ongoing epidemic of obesity and diabetes combined with limited economic resources may lead to an explosion of deaths due to kidney disease, as recently shown in the Mexico City Study [10]. An estimated 30% of the excess diabetes-associated mortality in Mexico is attributed to diabetes and kidney failure. In fact, excess mortality risk due to kidney disease in Mexico is approximately 7-fold higher than the excess mortality risk due to cardiovascular disease [10].

If rates of CKD are to be envisaged, then the impact of societal industrialization on fertility and premature births must also be considered. Delaying pregnancy until older age, using fertility treatments and being obese prior to pregnancy all contribute to increasing rates of preterm birth. Since 1990, the percentage of births that are preterm worldwide has increased by 0.8% per year. In 2010, >10% of all livebirths globally were preterm with almost 15 million infants born prior to 37 weeks gestation [11]. The increasing rates of preterm births are not limited to low- and middle-income countries. In fact, the USA has one of the highest rates of preterm births worldwide [11]. Rates of preterm birth are anticipated to increase steeply over the next decade, which is important for forecasting kidney disease [12].

Premature babies face increased lifetime risk of diabetes, hypertension and CKD due to disruption of beta cell and nephron development at crucial time periods [13]. Over 60% of nephrons are formed during the last trimester of pregnancy and a reduced number of nephrons impacts future risk of kidney disease and leads to heightened salt sensitivity and steeper trajectories of blood pressure with aging [14]. In addition, premature births are often preceded by maternal protein malnutrition, which also impacts nephron development and function [15]. While estimates of acute kidney injury in middle- and low-income countries remain poorly quantified, existing data suggest that up to 20% of preterm births are complicated by acute kidney injury, an important risk factor for CKD [16].

Growing up in an obesogenic environment will greatly exacerbate the risk of developing chronic diseases including CKD among adults with a history of preterm birth (Figure 1). Total glomerular filtration rate (GFR) is the product of single-nephron GFR and total nephron number. With weight gain, GFR must increase to match the higher metabolic demands of the individual. Such increases in absolute GFR with obesity are

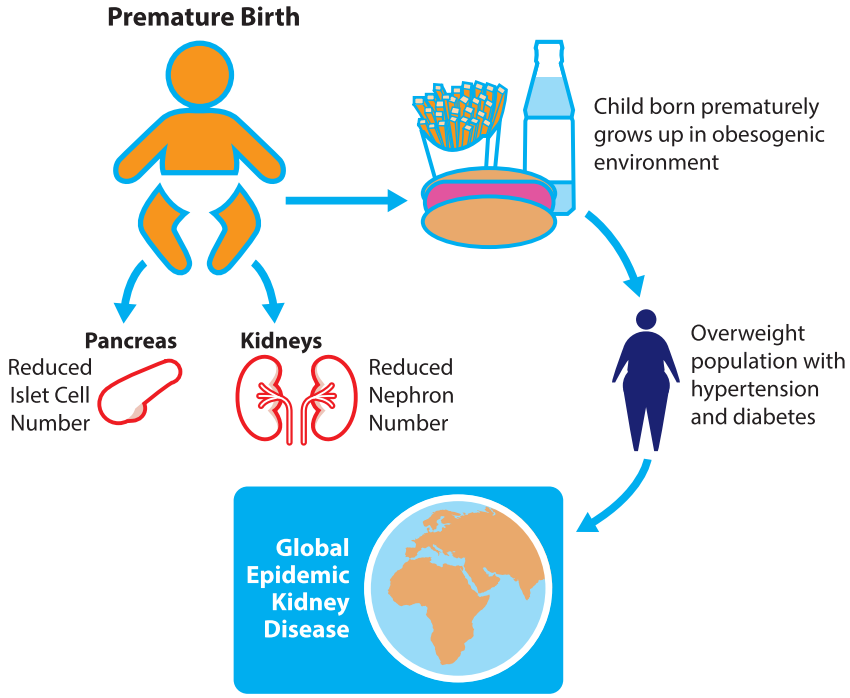

FIGURE 1: Cartoon depicting the interaction between premature birth (birth prior to 37 weeks gestation) and risk of kidney disease. Premature birth is associated with reduced nephron number leading to heightened risk for kidney disease and hypertension. Premature birth is also associated with reduced islet cell number, which heightens diabetes risk. Such risks will be apparent if the person becomes overweight or obese.

quite small compared with changes in single-nephron GFR as a result of the demands of pregnancy or unilateral nephrectomy [17]. Thus, obesity itself is likely not sufficient to induce CKD and requires other factors and insults such as reduced nephron number and elevated blood pressure.

To increase single-nephron GFR in the setting of reduced functioning nephron number, the afferent arteriole vasodilates to some degree, and this vasodilation theoretically may impede autoregulation. Impairment of autoregulation of glomerular blood flow can facilitate transmission of elevated systemic blood pressures to delicate glomerular capillaries. Glomerular capillaries are not supported by muscle, fat or bone, and instead are suspended in urine. In fact, terminally differentiated podocytes may provide the only mechanical support for glomerular capillaries. Without autoregulation, risk of barotrauma in glomerular capillaries remains high because glomerular capillary pressure is not restricted to a narrow range [18]. Transmission of elevated blood pressure and heightened intraglomerular pressure increase the risk of obesity-associated glomerular sclerosis and nephron drop out [19, 20]. With very severe obesity, glomerular enlargement can also lead to increase in glomerular capillary diameter, which equates with increased glomerular capillary wall tension based on the law of LaPlace [18].

$$\text{LaPlace's Law}: \text{Tension} = \text{Pressure} * (\text{Radius}/\text{Wall thickness})$$

Another issue with severe obesity, especially morbid obesity, is the possibility of decreased podocyte density, because podocytes must cover a larger glomerular capillary surface area. This lower podocyte density leads to reduced mechanical support of the glomerular capillaries and heightens susceptibility to barotrauma [21, 22]. Thus, obesity in the setting of low nephron number and elevated systemic blood pressure is a state of heightened CKD risk due to impaired autoregulation, increased capillary wall tension and reduced mechanical support of glomerular capillaries culminating in barotrauma, glomerulosclerosis and nephron drop out. This pathology in glomerular hemodynamics in obesity is then compounded by overconsumption of calorically dense processed foods loaded with salt, which elevates blood pressure and exacerbates weight gain. This cycle of overconsumption of calories and salt creates an environment conducive for progressive loss of kidney function, which can only be curbed with caloric restriction.

Reducing caloric intake by at least 30%, regardless of nutrient intake, reduces metabolic rate in humans, which in theory, will reduce the metabolic demands on the kidney [23]. Few studies have examined the benefits of caloric restriction on kidney function in humans but existing data suggest that caloric restriction retards kidney disease incidence and progression. After bariatric surgery, caloric intake is substantially reduced for the first 6–12 months due to marked decreases in stomach size, and these effects occur immediately after surgery. Within a few weeks after bariatric surgery, changes in GFR and effective renal plasma compared with baseline levels can be detected despite the lack of substantial weight loss at this time point [24]. Such glomerular hemodynamic changes after bariatric surgery may translate to long-term kidney benefits. Chang *et al.* [25] reported a significantly lower risk of a $\geq$30% decline in GFR, doubling of serum creatinine or end-stage renal disease among morbidly obese adults without CKD who underwent bariatric

surgery compared with demographically matched morbidly obese adults who did not undergo surgery. These differences in kidney outcomes were noted within a short period of time (~4 years). Caloric restriction has also been associated with reductions in proteinuria in obese adults with established CKD [26, 27]. These renal benefits of caloric restriction are supported by animal studies from multiple independent groups showing amelioration of kidney injury with caloric restriction in models of glomerular adaptation such as 5/6 nephrectomy or uninephrectomy regardless of protein intake [28, 29].

Implementing a comprehensive prevention and treatment strategy for chronic diseases including CKD should be a public health priority, imperative for all countries [30]. While kidney disease may occur as a result of infectious diseases, the majority of kidney diseases worldwide are now attributed to noncommunicable chronic diseases that are largely preventable [31]. The epidemic of kidney disease as a result of the industrialization of diet and enlarging average body size may just be beginning. Only recently has kidney disease emerged as an increasing cause of mortality, and this trend is likely to continue. In order to reduce chronic diseases including CKD, public health policies must address and optimize maternal and infant health. Interventions are urgently needed in both developed and developing countries to reduce preterm birth, which is an important risk factor for CKD and its associated risk factors hypertension and diabetes. Public health interventions alone are not sufficient to combat the ongoing obesity epidemic affecting all countries, and policy changes that promote healthy eating patterns and exercise are indispensable. Policymakers must create initiatives that lead to reduced portion sizes in prepared and processed foods, lower sodium and phosphate food additives in prepared foods and create incentives for safe physical activity, especially for children. Initiatives must also ensure that treatment for diabetes and hypertension is consistently accessible and affordable for all persons [31]. Because dietary practices strongly influence CKD incidence and progression, medical nutrition therapy should be recommended and accessible for all patients with or at risk for CKD [32, 33]. Without public health interventions and policy changes, the future holds a global increase in CKD and CKD-related deaths.

CONFLICT OF INTEREST STATEMENT

None declared.

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