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Clinical Illustration

Beyond the belt; does weight reduction stabilize kidney function in chronic kidney disease?

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Abstract

Background: Obesity is an established risk factor for chronic kidney disease (CKD). Several mechanisms have been found out linking obesity to CKD and these include diabetes mellitus, hypertension, metabolic syndrome, hyperfiltration and inflammation. Obesity may lead to CKD or the worsening of existing CKD. Interventions leading to weight loss in obese patients have been shown to improve renal function and reduce proteinuria. This case illustrates stabilization of renal function in an obese patients with CKD following weight loss.

Aim: Our aim is to remind physicians of the role of conservative management of CKD by weight reduction in improving outcomes of management of CKD.

Index case: The index patient is a 40 year old man with type 2 diabetes mellitus and hypertension who was referred to the nephrology clinic for management of CKD. He was found to have a body mass index of 40.5kg/m^2 and waist:hip ratio of 1.2. He embarked on other measures in conservative management of CKD without much success. With introduction of weight loss program and reduction of body mass index from 40.5kg/m^2 to 29.1mg/kg^2, there was a stabilization in renal function.

Conclusion: Weight loss led to stabilization of renal function and reduction of proteinuria resulting in good outcome of conservative management of CKD in the patient

Keywords: obesity, chronic kidney disease, weight reduction, diabetic nephropathy

Running title: Okwuonu et al. Weight reduction and stable kidney function in CKD

Introduction

There is a growing body of evidence that obesity is a risk factor for CKD.[1-5] Whether that risk is independent of diabetes, hypertension, or other risk factors is not yet clear.[2]. The development of metabolic risk factors- diabetes,[6] hypertension,[7] dyslipidaemia and coronary artery disease[8]- as well as adipocyte-derived factors, in response to obesity may lead to kidney damage, albuminuria, and reduction in glomerular filtration rate (GFR).[5] This case was reported to remind clinicians of the role of obesity in renal function impairment and to highlight the need to emphasize on attainment of normal BMI in overweight and obese patients.

Case report

The index patient is a 40 year old male, civil servant by profession, who was referred from the general practice clinic of University of Benin Teaching Hospital to the renal unit of the same hospital for management of progressive chronic kidney disease (CKD). He was diagnosed of type 2 diabetes and hypertension two years prior to presentation in the hospital and was found to have dyslipidaemia after laboratory evaluation at the referring unit. All these were well controlled prior to referral. On referral to the renal unit, history and physical examination were carried out. There was history suggestive of peripheral neuropathy of both lower limbs. The blood pressure was mildly elevated to 146/90 mmHg. Ophthalmic examination showed retinal changes in keeping with mild non proliferative diabetic retinopathy. His body mass index (BMI) was 40.5 kg/m^2, waist hip ratio was 1.2, estimated glomerular filtration rate (GFR) using the chronic kidney disease epidemiology collaboration (CKD-EPI) equation was 17 ml/min/1.73m^2 (CKD stage 4). His medications were Metformin, Lisinopril, Hydrochlorothizide, Amlodipine and Artovastatin. At the date of referral his laboratory investigation results were as shown in table 1

Table 1: Laboratory parameters of index patient at nephrology consultation

Parameter	Result	Reference value
Serum creatinine (mg/dl)	4.6	0.6-1.3
Serum urea (mg/dl)	93	15-40
Calcium (mg/dl)	8.1	8.6-10.2
Phosphate (mg/dl)	5.3	2.5-4.8
Serum Albumin (g/dl)	4.9	3.2-5.5
Urine Protein/Creatinine ratio (mg/g)	102	20-200
Haemoglobin (mg/dl)	11.6	11-14

Total Cholesterol (mg/dl)	186	<200
Triglyceride (mg/dl)	111	<150
Low density lipoprotein (mg/dl)	93	<100
High density lipoprotein (mg/dl)	55	>60

Result of serum electrolytes, fasting blood sugar, haemoglobin A1c, lipid profile and uric acid were all normal. Renal ultrasound scan showed normal kidney sizes (left kidney was 10cm x 5.5cm while right kidney was 11cm x 5.2cm). There was increased echogenicity and minimal distortion in corticomedullary differentiation. All these were in keeping with a diabetic nephropathy.

Metformin and Hydrochlorothiazide were discontinued due to the reduced GFR. The patient was placed on Gliclazide for glycaemic control and continued on Lisinopril and Artovastatin. He was counseled about the course and prognosis of his kidney disease and advised on diet and exercise for weight loss. The blood pressure changes were unremarkable as average daily reading was 142/74 mmHg. He was referred for arterial-venous fistula placement for providing renal replacement therapy in future. His meal plan was to reduce intake of refined sugar, stop snacking in between meals, avoid heavy meals at night and to eat food rich in vegetables. He was advised to embark on exercise (jogging) at least 30-45 minutes every morning. The patient adhered to the lifestyle modification. Over the course of 25months the patient lost 35kg body weight- his BMI reduced from 40.5kg/m^2 to 29.3kg/m^2, eight consecutive serum creatinine recorded 2.4mg/dl, 2.1mg/dl, 2.3mg/dl, 2.0mg/dl,1.9mg/dl, 2.1mg/dl, 2.45mg/dl, 2.3mg/dl, 2.4mg/dl, 2.1mg/dl, 2.5mg/dl, 9.1mg/dl. Other clinical parameters remained essentially normal and he continued with the prescribed oral medications.

Discussion

Obesity is an established risk factor for chronic kidney disease (CKD). Several mechanisms have been found out linking obesity to CKD and these include diabetes mellitus, hypertension, metabolic syndrome, hyperfiltration and inflammation. Obesity may lead to CKD or the worsening of existing CKD. Agnani *et al* [9] had earlier reported a 43 years old morbidly obese Caucasian male with poorly controlled hypertension and diabetes mellitus, who was referred to the nephrology clinic for management of his chronic kidney disease. The patient was educated about the course and prognosis of his kidney disease and advised diet and exercise for weight loss. Over the course of 6 months the patient failed all conservative methods of weight loss including the use of orlistat. He underwent bariatric surgery.

Obesity is a risk factor diabetes and hypertension, two common risk factors for CKD. Thus, the global obesity epidemic translates into substantially heightened CKD risk factors worldwide.[10] Obesity, especially central obesity, not only increases the risk of hypertension but also makes hypertension more resistant to treatment and hence can lead to accelerated loss of kidney function over time. Also central adiposity is frequently

accompanied not only by hypertension but also hypertriglyceridemia, low HDL cholesterol, inflammation, and a prothrombotic state. These metabolic changes reflect a state of insulin resistance and its interaction with obesity. The clustering of these traits defines the metabolic syndrome.[10]

Increased metabolic demands on the kidney may also mediate increased CKD risk in overweight and obesity.[11] Given that nephron number is fixed at birth, weight gain increases the work of each individual nephron resulting in adaptive glomerular hypertrophy. The glomerular hypertrophy itself may also predispose the glomerular capillary wall to hemodynamic injury because capillary wall tension is a direct function of its diameter, which could potentially increase with glomerular hypertrophy. Because podocytes do not undergo adaptive replication in the setting of glomerular hypertrophy, the density of podocytes for a given glomerular surface area decreases. These podocytes then enlarge to compensate for the reduced density potentially leading to structural changes and detachment of the foot processes from the basement membrane.[12] Thus, in the setting of obesity, there are multiple stimulants of TGF-1, including increased insulin and angiotensin II levels and heightened glomerular volume and capillary pressures. These factors and other proposed factors all interact and promote structural changes and glomerular damage (Box 1).

In the index patient, a reduction in the metabolic demands on the kidneys consequent upon significant weight loss could possibly account for stabilization of the renal function. Though the natural history of CKD implies a relentless progression to ESRD, weight loss is definitely a measure in retarding this progression. Hence, we present this case to remind clinicians of the role of obesity in renal function impairment and to highlight the need to emphasize on attainment of normal BMI in overweight and obese patients.

Figure 1. Proposed Mechanism for Association Between Obesity and CKD[10-11]

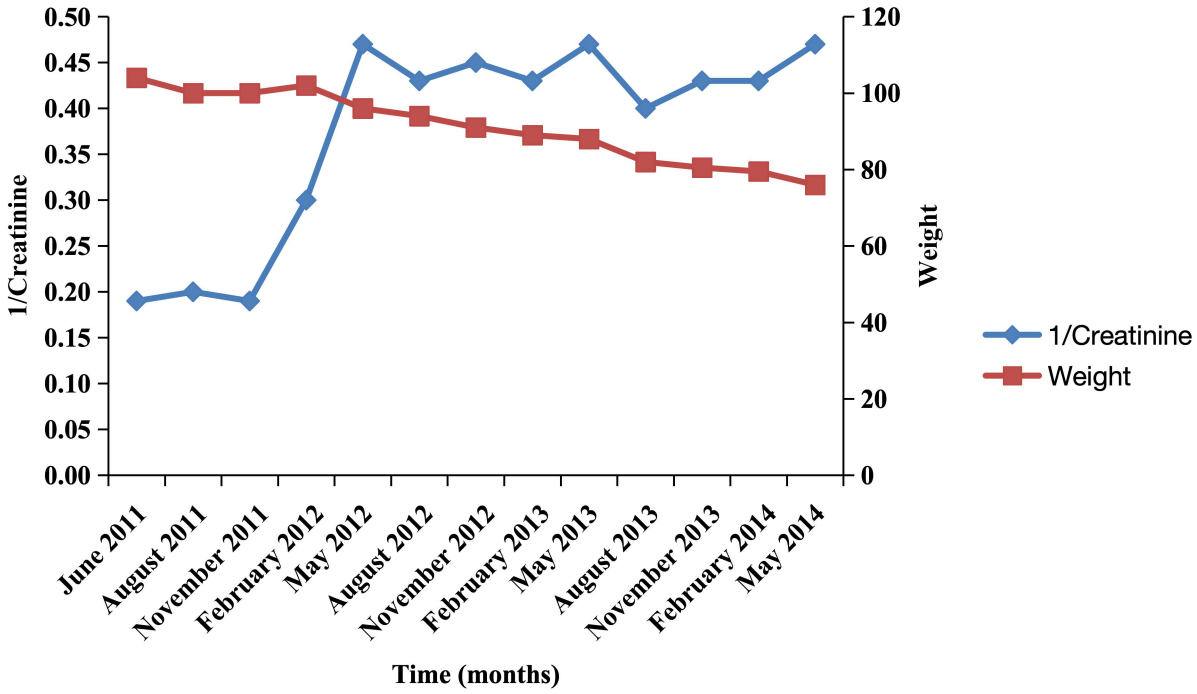
1. Physical compression of the kidneys by visceral obesity
2. Renin-Angiotensin system activation
3. Hyperinsulinemia
4. Sympathetic activation
5. Overnutrition
6. Glomerular hyperfiltration
7. Protein-associated kidney damage
8. Blood pressure elevation

Few studies have examined whether obesity increases risk of end stage renal disease (ESRD) due to the large sample size needed to study this uncommon outcome. A study by Hsu et al. showed a very strong biologic gradient whereby increasing levels of BMI were associated with increasing risk of ESRD. The study cohort consisted of 320,252 adults who volunteered for a screening health checkup

between 1964 and 1985 and were followed until death, ESRD or December 31, 2000. Compared to patients with an ideal BMI of (18.5–24.9 kg/m2), relative risk of ESRD was 3.57 (95% CI: 3.05, 4.18) for those with BMI of 30–34.9 kg/m2, 6.12 (95% CI: 4.97, 7.54) for those with BMI 35–39.9 kg/m2 and 7.07 (95% CI: 5.37, 9.31) for those with BMI ≥ 40 kg/m^2. Controlling for baseline blood pressure and presence of diabetes did attenuate the associations but the strong gradient between increasing body size and ESRD risk remained.

In a population-based cross sectional study of Thai army population and relatives, the prevalence of overweight and abdominal obesity in the participants with CKD were found to be higher than in those without CKD (overweight, 77.6% vs. 61.6%, $P < 0.001$; abdominal obesity, 35.7% vs. 25.3%, $P < 0.001$).[6]

The result of a recent community-based study in Osun state, Nigeria indicate that the prevalence of eGFR <60 ml/min (using MDRD) among participants with central obesity was significantly higher compared to those with no central obesity.[12] Also the prevalence of GFR less than 60 ml/ min was significantly higher among participants with abnormal waist hip ratio(WHR) compared to those with normal WHR have varying results.



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