ORIGINAL ARTICLE

Insight of the Development and Progression of Obesity Related Chronic Kidney Disease

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ABSTRACT

Objective There is a growing appreciation that even in the absence of hypertension and diabetes, obesity itself is a significant risk factor of chronic kidney disease. **Methods** In a cross sectional, observational multi centers study, three hundred seventy two (n=372) chronic kidney disease patients with stage III and IV (eGFR 20-60 ml/min/m^2) have been enrolled in this study. Lean Group I; 153 non diabetic chronic kidney disease patients aged 20-40 years with body mass index between 20-25 kgm/m^2; obese Group II; 130 non diabetic chronic kidney disease patients aged 20-40 years with body mass index >30 kgm/m^2 and old aged Group III; 89 chronic kidney disease patients aged >60 years. Obese Group II showed significant increase of the ALD/PRA ratio when compared with both other groups; lean Group I ($P<0.001$) and old age Group III ($P<0.05$). Obese Group II showed elevated serum levels of AT1 and AT2 than the Lean Group I and old aged Group III ($P<0.001$ and $P<0.01$ respectively in both parameters). Obese Group II also showed significant elevation of serum levels of FGF23, PTH and S.PO4 when compared to the lean Group I values (P values were <0.001, <0.01 and <0.05 respectively). Angiotensin receptors level (AT1 & AT2) both showed significant rise in the obese group than the lean and the old aged groups of patients ($P<0.001$ and $P<0.01$ respectively). **Conclusion** These results support the proposal that obesity per se is an independent risk factor in the development of chronic kidney disease, particularly, in young age patients.

INTRODUCTION

It is well established that excessive caloric intake contributes to organ injury. The associated increased adiposity initiates a cascade of cellular events that leads to progressive obesity-associated diseases such as kidney disease. Recent evidence has indicated that adipose tissue produces bioactive substances that contribute to obesity-related kidney disease [1]. Epidemiological studies showed that the prevalence of CKD has risen at an alarming rate, with suggesting estimates that approximately 17% of the US adult population has CKD [2].

Over the last three decades, the prevalence of obesity has more than doubled among US adults. National Health and Nutrition Examination Survey (NHANES), reported that 32.2% of US adults met the clinical criteria for obesity with a body mass index (BMI) of >30 kgm/m^2 [3].

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Obesity and obesity-associated kidney injuries have played an important role in the rising prevalence of chronic kidney disease (CKD). The link between obesity and kidney disease has always begun with its link with diabetes and hypertension. However, a number of recent clinical and epidemiological studies suggest that obesity itself, independent of its ties to diabetes and hypertension can play an important role in the development of CKD. A cross-sectional analysis of NHANES data found a close association between higher BMI and reduced kidney function [4].

A number of mechanisms have been proposed as explanations for obesity related CKD, including chronic inflammation, abnormal vascular remodeling, and renal lipo-toxicity [5]. These routes of injury can occur in the absence of diabetes and hypertension. Perhaps the best described mechanism of obesity-induced kidney injury involves the adverse effects of increased body mass and subsequent increased glomerular filtration rate (GFR) per intact nephron, i.e. functional stress [6]. Another proposed mechanism involves adiponectin, a hormone produced by adipocytes that regulates glucose and lipid metabolism, this adipocytokine is decreased in obesity, with levels of adiponectin shown to be inversely related to the degree of albuminuria in obese patients [7].

However, a growing body of evidence suggests that elevated aldosterone levels and expanded extracellular

volume are key components of obesity-induced renal disease via aldosterone's non-epithelial effects on the kidney [8]. The kidney contains all the elements of the RAAS, and intrarenal formation of Ang II independent of the circulating RAAS [9]. The demonstration of locaI (Ang II) synthesis in numerous tissues and organs has led to the concept of local or tissue-based RAASs that are independent of but can interact with the traditional circulating RAAS [10]. These local RAASs appear to act in a paracrine/autocrine manner to regulate kidney function and are involved in pathologic events associated with end-stage kidney damage [11]. Adipocytes also contain all the components of the renin-angiotensin-aldosterone system, plasminogen activator inhibitor, as well as adipocyte specific metabolites such as free fatty acids, leptin, and adiponectin which affect renal function and structure. In addition, fat is infiltrated by macrophages that can alter their phenotype and foster a proinflammatory milieu which advances pathophysiologic changes in the kidney associated with obesity [12]. However, a full understanding of the mechanisms involved in progressive renal disease is still absent.

This study was designed to highlight the cross talk between pathogenesis of CKD mechanisms in obese patients independent of hypertension and diabetes. While the current therapies aimed at slowing progressive renal damage include reduction in weight and rely on inhibition of the renin-angiotensin system, the approach will likely be supplemented by interventions aimed at obesity-specific targets including adipocyte-driven cytokines and inflammatory factors.

PATIENTS AND METHODS

In a cross sectional randomized multi centers study, three hundreds and ninety chronic kidney disease (CKD) patients stage III and IV their eGFR between 20-60 mL/nin/m^2. Data have been collected between September first till the end of October 2012, from the regular outpatient's clinics of five general hospitals in Egypt. The participants have been categorized into three groups. Group I : one hundred fifty three non diabetic CKD patients aged 20-40 years with body mass index (BMI) between 20-25 kgm/m^2; Group II : one hundred forty eight non diabetic CKD patients aged 20-40 years with (BMI) >30 kgm/m^2 and Group III : eighty nine CKD patients aged >60 years.

- BMI was computed as weight (in kilograms) divided by the square of the height (in meters).

- Calculated eGFR values were categorized as less than 60 mL/min/1.73 m^2 based on the Kidney Disease Outcomes Quality Initiative (KDOQI) classification of kidney function; eGFR values less than 60 mL/min/1.73 m^2 were considered abnormal and indicative of moderately reduced kidney function and referred to as prevalent CKD Estimation of glomerular filtration rate, biochemical assessments were performed by auto-analyzer in a single laboratory [13].

- Blood samples were collected in three 10-mL liquid EDTA blood tubes, placed on ice packs, stored in polystyrene foam containers, and returned to the HPFS blood storage facility via overnight courier. More than 95% of the samples arrived within 24 hours of collection.

- Measurement of plasma leptin was performed by Linco Research, Inc., St. Louis, Mo, USA. The assay was a radioimmunoassay (RIA) with a polyclonal antibody raised in rabbits against highly purified recombinant human leptin [14, 15].

- Plasma FGF23 levels were measured using a second-generation C-terminal human enzyme-linked-immuno-sorbent assay (Immutopics, San Clemente, CA). Plasma levels were measured twice in each participant averaged. The coefficient of variation was 9.8%.

- 1,25 vitD were determined using a RIA (Diasorin, Stillwater, MN and IDS, Tyne and Wear, United Kingdom, respectively). Serum calcium and phosphorus were measured using standard methods.

- Intact PTH was measured by electro-chemi-luminescence-immunoassay on the 2010 Elecsys-autoanalyzer (Roche Diagnostics, Indianapolis, IN).

- PRA and Ald levels were determined by radioimmunoassay. Plasma Ang I and Ang II levels were measured by double-antibody radioimmunoassay; the details of these methods have been described elsewhere [16, 17].

STATISTICAL ANALYSIS

Variables are reported as the mean and standard deviation (SD) if normally distributed or the median and inter-quartile range (IQR) if not. A t-test was used to compare groups where variables were normally distributed and a Mann-Whitney test used if not. SPSS version 16.0 was used for analysis and $P<0.05$ was considered statistically significant.

RESULTS

No significance difference between the mean age of lean Group I (29.7±4.88) and the obese Group II (31.7±2.41), P=0.362. The mean age of the old age Group III (65.1±4.66) which showed significant difference with both other groups (P<0.001) for both groups. The percentage of hypertensive patients in the lean group I (43%) was higher than that of the obese Group II (35%) though the difference was not significant (P=267) but the percentage of the old age Group III was highly significant when compared with both lean Group (P<0.001) or obese group (P<0.001), **(Table 1)**.

Estimated GFR (eGFR) was significantly high in the lean Group I (49.3±7.51mL/min/m^2) than both Group II (37.71±13.6 mL/min/m^2 & P< 0.01) and Group III (41±13.47mL/min/m^2 & P<0.05).

Plasma rennin activity (PRA) was significantly lower in the obese Group II (2.62±1.45 ng/mL/hr) than both the lean Group I (3.39±2.07ng/ml/hr) P<0.05 and the old age Group III (3.46±2.82 ng/mL/hr) P<0.05. No significant difference between the lean and the old age groups (P=346).

Table 1. Patient's clinical data.

	G I/lean 20-40 y	G II/obese 20-40 y	G III/old Age>60 y
Number	153	130	89
Gender male %	47.70%	46.60%	42.70%
Age year	29.7± 4.9	31.7±4.21	65.1±4.66
BMI kgm/m^2	22.73±3.2	37.3±8.2	29.2±6.4
SBP mmHg	133±25.8	138±36.8	146±41.5
DBP mmHg	80±16.9	82±24.7	81±11.4
Hypertension %	23%	35%	72%

The Aldosterone levels showed significant elevation in obese Group II (89.91±22.6 pg/mL) when compared with lean Group I (47.55±21.8 pg/mL) P < 0.001. No significant difference was observed when it is compared with the old age Group III (86.18±16.8 pg/mL) P=0.34. Assessment of the RAAS activity using the ALD/PRA ratio, the ratio was markedly elevated in the obese Group II (37.8±14.9) than both the lean Group I (14.0±4.1) P<0.001 or the old age Group III (24.91±12.1) P<0.01.

Angiotensin receptors (AT1) and (AT2) were both significantly higher in the obese Group II (AT1=653.28±352.6 pg/ml, AT2=48.1±9.8 pg/mL) than the lean Group I (AT1=290.29±210.6 pg/mL, AT2=25.46±11.4 pg/mL) P<0.001 and P=0.001 respectively. While when those of the obese compared with those of the old age Group III (AT1=407.91±370.4 pg/m, AT2=33.68±7.63 pg/mL) P<0.01 and P<0.01 respectively.

Hyperphosphatemia was significantly noticed in obese Group II (4.74±1.61 mg/dL) which showed significant difference compared with that of lean Group I (3.85±0.92 mg/dl) P<0.05 while in old age Group III (4.09±0.42 mg/dL) and was not significant compared with both groups.

Serum calcium levels were almost of normal range in all groups.

Parathormone levels were elevated in both obese Group II (77.63±32.4 pg/mL) and in old age Group III (70.94±15.26 pg/mL) compared to each other P=0.336 while both were significantly elevated than lean Group I (59.18±24.7 pg/mL) and P<0.1 with Group II and P<0.o5 with Group III.

Serum levels of 1.25D were significantly low in the obese Group II (19.85±3.6 ng/mL) compared to lean Group I (24.42±5.41 ng/mL) or old age Group III (25.0±5.81 ng/mL) P<0.05 for both groups.

Serum leptin levels were markedly and significantly elevated in the obese Group II (24.13±7.81fg/l) when compared with lean Group I (1.92±1.61 fg/L) P<0.001 or old age Group III (5.51±3.21 fg/L) P<0.01.

Plasma insulin levels were also significantly elevated in the obese Group II (13.73±2.38 uU/mL) when compared with lean Group I (5.59±2.31 uU/mL) and P<0.01 or when compared with old age Group III (10.7±1.68 uU/mL) P<0.05.

Serum levels of FGF-23 were significantly elevated in the obese Group II (259.55±138.6 u/ml) when compared with lean Group I (132.81±126.1 u/mL) P<0.001 or with the old age Group III (179.33±237.4 u/mL) P<0.01 **(Table 2)**.

DISCUSSION

The aim of this study was designed as a trial to answer the mysterious question; does obesity per se, apart from its tie to hypertension and diabetes, induce chronic kidney injury?

In an observational study, we assessed the extra-renal RAAS activation parameters, AT1, AT2, PRA and Aldosterone, in non-diabetic obese group of patients (Group II) compared to a group of non-diabetic lean (non-obese) patients (Group I) to evaluate the impact of obesity in these parameters. To exclude the impact of hypertension atherosclerotic changes, we compared the obese Group II to another old aged group of patients (Group III). Plasma insulin and serum leptin have been used to access the early obesity associated diabetes. Serum calcium, serum phosphorous, plasma intact parathormone (iPTH), blood level of 1,25-dihydroxyvitamin D3 (active vitamin D3), fibroblast growth factor 23 (FGF23), serum calcium and serum phosphorus have been used to assess the degree of chronicity of renal involvement among those groups.

Obese patients showed high plasma Aldosterone levels and low PRA than the lean patients due to the negative feed-back loop interaction, the level of each parameter at any given time point was unreliable marker of the activity of the RAAS axis. Plasma aldosterone concentration (PAC)/plasma renin activity (PRA) ratio (ARR) is the most reliable method of screening for primary aldosteronism. This test became widely used in hypertensive clinics. PAC and the PRA measurements must be performed in patients in washout from all hypertensive drugs to avoid false-positive and false-negative results [18]. Significant elevation of ALD/PRA ratio in the obese group of patients than both the lean group and the old patient group can be attributed, at least in part, to increased activity of adipose tissue. Although the old age group showed slight elevation in ALD/PRA ratio, as patients of the old aged group were overweight (BMI<29.9 kgm/m^2), but most of them (73%) were defined as obese using the waist to hip ratio (WHR), anthropometric measure, (Group III WHR > 0.99%). This elevation is still far less than that of the obese supporting this proposal. Injurious effects of aldosterone can be also explained as non-epithelial high sodium intake with expanded extracellular volume [19]. Since our CKD patients have both hypernatremia as well as extracellular volume expansion. The harmful interaction between aldosterone and expanded extracellular volume may be a key component of the pathogenesis of obesity induced kidney injury.

Aniotensinogen receptors (AT1 & AT2) show significant increase in the obese group patients than lean group patients. Angiotensinogen (AGT) is highly expressed in adipose tissue and is constitutively secreted by mature

Table 2. Results.

	Group I lean 20-40 y N=87	Group II Obese 20-40 y N=130	Group III Old Age>60 y N=89	P value Group I Vs Group II	P value Group II Vs Group III	P value Group I Vs Group III
eGFR mL/min/m²	49.3±7.51	37.71±13.6	41.0±13.47	P<0.01	P<0.05	P<0.05
Diabetes %	Nil	Nil	36%	---	---	---
PRA ng/mL/hr.	4.21±2.07	2.08±1.45	3.46±1.36	P<0.05	P<0.05	P=346
ALD pg/mL	47.55±21.8	89.91±22.6	86.18±16.8	P<0.001	P=0.34	P<0.05
ALD/PRA ratio	11.29±4.1	43.23±14.9	24.91±12.1	P<0.001	P<0.01	P<0.01
AT1 pg/mL	290.3±210.6	653.3±352.6	407.1±370.4	P<0.001	P<0.01	P<0.05
AT2 pg/mL	25.46±11.4	48.1±4.8	33.68±7.63	P<0.001	P<0.01	P<0.05
PWV m/sec.	9.48±0.8	9.31±0.9	10.21±0.68	P=0.334	P<0.05	P<0.05
S Ca mg/dL	9.19±0.64	9.27±0.88	9.24±0.49	NS	NS	NS
S PO4 mg/dL	3.85±0.92	4.74±1.61	4.09±0.42	P<0.05	NS	NS
PTH pg/mL	59.18±24.7	77.63±32.4	70.9±15.3	P<0.01	P=336	P<0.05
1,25 D ng/mL	24.4±4.51	19.85±3.6	25.0±5.81	P<0.05	P<0.05	NS
S Leptin fg/L	1.92±1.61	24.13±7.81	5.51±3.21	P<0.001	NS	P<0.01
FGF23 R u/mL	132.8±126.1	259.6±138.6	179.3±237.4	P<0.001	P<0.01	P<0.05
P insulin uU/mL	5.59±2.31	13.73±2.38	10.7±1.68	P<0.01	P<0.05	P<0.01
S albumin gm/L	37.53±4.5	39.1±3.81	37.48±4.2	NS	NS	NS

Mean±SD; NS non-significant; eGFR estimated glomerular filtration rate; PRA plasma renin activity; ALD aldosterone; AT1 & AT2 angiotensin receptor1&2; PWV pulse wave velocity; S. Ca serum calcium; S.PO4 serum phosphate; PTH parathormone; 1,25D3, 1,25 dihydrocholicalciferol; S.Leptin serum leptin; FGF23 fibroblast growth factor 23; plasma insulin; serum albumin

adipocytes in animal models and humans [20]. Adipose tissue is an endocrine organ and adipose AGT has an autocrine/paracrine effect [21]. The RAAS is a major regulator of vasomotor tone and cellular proliferation that affect renal function and structure. Adipocytes and adipose-infiltrating macrophages comprise an important source of RAAS and increased circulating RAAS ligands provide a powerful combination for increasing efferent arteriolar vasoconstriction, glomerular pressure as well as cellular proliferation that culminate in renal damage [22].

Aldosterone blockade lessens renal injury. This beneficial effect is independent of antihypertensive effects [23] and instead, may relate to aldosterone blocking effects on plasminogen activator inhibitor (PAI-1) and transforming growth factor-β [24, 25]. Elevated aldosterone which prevails in obesity may be also injurious to glomeruli through indirect effects to increase GFR as well as through direct podocyte effects [26].

The levels of 1,25 dihydroxyvitamin D (1,25 D3) is significantly reduced in obese than that of the lean or old aged group of patients. Plasma parathormone and serum phosphate were significantly elevated which is a classic finding met with in CKD patients, this pattern was significantly exaggerated in obese patients than the other groups. The first clinical studies suggesting an inverse relationship between calcitriol and renin levels were published two decades age [27] and had been recently confirmed in a large cohort study [28]. Vitamin D deficiency, defined as calcitriol levels below 15 ng/mL, associates with reduced renal plasma flow which responses to infused angiotensin II, suggesting endogenous intra-renal RAAS activation in vitamin D deficient subjects [29].

The FGF-23 levels were significantly elevated in our obese group than the other two groups and this elevation cannot be explained only by the degree of CKD. Whether or not FGF-23 elevation is a cause or a result of decreased GFR and decline in calcitriol level is not elucidated. There is increasing evidences that the interactions between vitamin D, fibroblast growth factor 23 (FGF-23), and klotho form an endocrine axis for calcium and phosphate metabolism, and derangement of this axis contributes to the progression of renal disease [30]. Several recent studies also demonstrate negative regulation of the renin gene by vitamin D. Moreover, chronic kidney disease (CKD), is associated with low levels of calcitriol due to the loss of 1-alpha hydroxylase and increase renal renin production. Activation of the renin-angiotensin-aldosterone system (RAAS), in turn, reduces renal expression of klotho, a crucial factor for proper FGF-23 signaling. The resulting high FGF-23 levels suppress 1-alpha hydroxylase, further lowering calcitriol. This feedback loop results in vitamin D deficiency, RAAS activation, high FGF-23 levels, and renal klotho deficiency, all correlate to the progression of renal damage [31].

Leptin has also been shown to serve as a cofactor of TGF-beta activation, promote renal endothelial cell proliferation, and potentially may play a role in renal glomerulosclerosis [32, 33, 34, 35]. Plasma levels of leptin were significantly elevated in obese than both lean and old aged group patients. Leptin elevation was associated with elevated plasma insulin both of which are byproduct of adipose tissue remodeling. Recent studies have reported that infusion of recombinant leptin into normal rats for 3 weeks fosters the development of focal glomerulosclerosis [33]. Okpechi *et al*. reported that plasma leptin levels were inversely related to eGFR [36]. In another study, common polymorphisms in the *LEP* gene were found to be associated positively with serum creatinine and inversely with eGFR [37].

Together, the associations found in clinical studies and the supporting mechanistic studies make it plausible that vitamin D deficiency could indeed contribute to an inappropriately activated RAAS, as a mechanism for

progression of CKD [38]. Several lines of evidence indicate that persistent RAAS-activity, either by incomplete pharmacologic blockade or related to the reactive rise in renin during therapy, can hamper its therapeutic efficacy [39]. These findings hypothesize that treatment with a vitamin D receptor agonist, on top of conventional RAAS-blockade, would give additional reno-protection through its negative regulation of renin.

In a panoramic viewing of the whole picture of our results we can propose that the obese group behave as if they were old (i.e. early senility). The more we get obese, the more years subtracted from our life. We wonder, how many days or years of our life does one kilogram of overweight cost.

CONCLUSION

Our results gave strong evidence that obesity per se, is an independent risk factor for the development of chronic kidney disease, particularly, in young age patients. Activation of RAAS and FGF23-klotho-1,25D3 axis's via over-expression of adipocytokines and insulin resistance which both start so early in the course of obesity are claimed for the renal injury. Preventing and managing obesity should start early enough to halt, if not prevent, the development and progression of CKD and CVD. While the current therapies aimed at slowing progressive renal damage include reduction in weight and rely on inhibition of the renin-angiotensin system, the approach will likely be supplemented by interventions aimed at obesity-specific targets including adipocyte-driven cytokines and inflammatory factors.

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Conflict of Interest

We, the authors of this review, declare that there is no conflict of interest that could be perceived as prejudicing impartiality of the research. We fully declare that no financial or other potential conflict of interest.

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