Sudan Journal of Medical Sciences
Volume 14, Issue no. 3, DOI 10.18502/sjms.v14i3.5214
Production and Hosting by Knowledge E

Research Article

Obese Family Members of Chronic Renal Failure Patients are at Higher Risk for Developing Kidney Diseases: In a Cross-sectional Study

Abozaid M Elemam[1], Amar M Ismail[2], and Maha I Mohammed[3]

[1]Department of Clinical Chemistry, Faculty of Medical Laboratory Science, Omdurman Islamic University, Khartoum, Sudan
[2]Department of Biochemistry and Molecular Biology, Faculty of Science and Technology, Al-Neelain University, Khartoum, Sudan
[3]Department of Medical Biochemistry, Faculty of Medicine and Public Health, Al-Neelain University, Khartoum, Sudan

Abstract

Background: Previously it has been demonstrated that, the obesity is one of the strongest risk factors for incident chronic kidney diseases (CKDs). Currently we examine the association between Body mass index (BMI) and CKD in first degree relatives (FDRs) of renal failure patients on hemodialysis.

Materials and methods: In a cross-sectional study 135 FDRs of end stage renal disease (ESRD) patients on hemodialysis were included. Serum creatinine, urine creatinine and microalbumin were measured. Estimated glomerular filtration rate (e-GFR) and albumin to creatinine ratio (ACR) were calculated. The height in Cm, weight in Kg was measured, and the BMI was calculated.

Results: Females 64% were found to have higher frequency than males 36%. The frequency of BMI categories was found to be 26.7% obese, 26.7% overweight and 46.6% normal weight. The mean BMI was (26.0 ± 6.62). The prevalence of CKDs is 19.3% among relatives. CKDs were more frequent 42.3% in obese, followed by 30.8% in overweight and 26.9% in normal weight relatives. Obese and overweight relatives have significantly higher ACR than normal weight (P= 0.012). GFR found to be significantly lower in obese and overweight relatives than normal weight (P = 0.000). GFR was negatively correlated with BMI (R = - 0.430, P = 0.000).

Conclusion: Obese and overweight renal failure relatives had higher ACR and lower eGFR. Therefore, obese and overweight members are at higher risk for developing CKDs.

Keywords: CKDs, Family members, BMI, Obesity, ACR, eGFR.

Corresponding Author:
Abozaid Mohammed Hamid Elemam;
email: elemam69@hotmail.com
Amar Mohamed Ismail;
email: amarqqqu@yahoo.com

Received 21 February 2019
Accepted 12 May 2019
Published 28 June 2019

Production and Hosting by Knowledge E

Editor-in-Chief:
Prof. Mohammad A. M. Ibnouf

1. Introduction

Chronic kidney disease (CKD) is a global public health problem (1,2), that increasing rapidly worldwide and is gaining much attention in both the developed as well as

developing countries (3, 4). It is found in 10% of the global population (5,6), and it affects 10-16% of the adult population in China, Asia, Australia, Europe and the United States (7). In Sudan, as it was reported by Hassan Abu Aisha in his pilot study at 2009, the prevalence range was 7.7 - 11% (8). CKD is considering as a health issue associated with increased morbidity, mortality and health care costs (5, 7).

Beside CKD, Obesity is another worldwide pandemic problem; it is associated with various metabolic disorders such as CKD and results in a shortened life span related to adverse health consequences (9). In Sudan, the high prevalence of obesity was observed, and it was found that; it is associated with diabetes and hypertension (10). Epidemiological studies have demonstrated that obesity, a family history of ESRD and high body mass index (BMI) are an essential risk factors for incident CKD and increased risk of ESRD (11, 12), and associated with an increased risk of CKD development among adult individuals in the general population (13).

Several studies showed that; the FDRs of ESRD patients with a family history are at risk to develop CKD (14, 15). Furthermore, increased stocktickerBMI and obesity were found to be having direct impact on the development of CKD and ESRD (12), through a compensatory mechanism of hyperfiltration occurs to meet the heightened metabolic demands of the increased body weight and the increase in intraglomerular pressure which can damage the kidney structure and raise the risk of developing CKD in long term (12,16). Recently, screening and early detection of CKDs researches have performed to decrease the prevalence of CKD, minimize the incidence of ESRD and to reduce their different health, social and economic effect (17, 18). Therefore, in this study we investigated whether the study variables (Age and BMI) associated with CKDs, indeed, early detection and management of CKDs in relatives at high risk.

2. Materials and Methods

In a cross-sectional hospital based study during May 2017 – May 2018, 135 randomly selected family members (first degree relatives) of chronic end stage renal failure patients on hemodialysis attending different centers in Khartoum State were included. Ages ranged between 17- 60 years old. After informed consent blood samples were collected, under aseptic condition from relatives. Subject with diabetes mellitus, hypertension, cancer, thyroid dysfunction, glucocorticoids therapy, HIV, pregnancy and hepatitis were excluded. The selection based on clinical history records. The demographic data were gathered using instructed questionnaire. The height in Cm and weight in Kg were

estimated, and then BMI was calculated. ACR and e-GFR were measured. Elevated ACR (>30 mg/g) and/or reduced e-GFR (< 60 ml/min/1.73m^2) considered as CKDs.

2.1. Ethical approval

The study was approval by the local ethical committee of Al-Neelain University and Ministry of Health. Written informed consent was obtained from all participants.

2.2. Calculation of urine albumin to creatinine ratio (U. ACR)

Brief according to manufacturer, mid-stream single spot urine sample was collected. Urine albumin was measured by immunoturbidmetric assay method, which based on reaction of anti-albumin antibodies with antigen in the sample to form antigen/antibody complexes. The assay was performed using Cobas auto analyzer instrument at central laboratory of East Nile Hospital. The concentration of albumin was calculated automatically by Cobas c system turbidimetry assay. Urine creatinine was estimated by kinetic Jaffe reaction without deproteinization method, using Cobas auto analyzer instrument. The creatinine concentration was calculated automatically by Cobas c system and expressed in mg/dl. Albumin - creatinine ratio (ACR) was calculated by Medical, Scy-med calculator, and expressed in mg/g. ACR > 30 mg/gm was considered as albuminuria (19).

2.3. Calculation of estimated glomerular filtration rate (eGFR)

Estimated GFR was calculated by modification of diet in renal disease (MDRD) equation, using a 4-variable version (MDRD-4) that included age, sex, ethnicity, and serum creatinine, this 4-variable version was expressed using serum creatinine values that were standardized to reference methods (20 , 21). (Reduced GFR was detected when eGFR < 60 ml/min/1.73m^2).

GFR = 175 x Serum creatinine (mg/dl) $^{-1.154}$ x age (years) $^{-0.203}$ x 1.212 (if patient is black) x 0.742 (if female)

The serum creatinine was measured by photometric modified Jaffe kinetic method (22), in which the concentration of creatinine was calculated automatically by Mind ray BS200 auto analyzer.

2.4. Statistical analysis

The Statistical Package for Social Sciences (SPSS), version 21.0 (SPSS Inc., Chicago, USA) was used for data analyses. Results are presented as frequencies, percentage, Mean ± SD and regression coefficient. The student's *t*-test was used to compare mean levels between groups. Chi-esquire was used for qualitative data. Person's correlation was employed to determine the association between continuous variables. *P*-value ≤ 0.05 was considered as the statistical significance.

3. Results

In this study 135 family members were participated.Table1 show the demographic and characteristics data, table2 show the frequency and distribution of CKD and table3 show the mean levels of ACR and e-GFR according to BMI categories, while figure1 show association of BMI with ACR and e-GFR. 64% were Females and 36% males. Their mean age was (32.3 ± 14.1). The frequency of BMI categories was found to be 26.7% obese, 26.7% overweight, 39.2% normal weight and 7.4% underweight. The mean BMI was (26.0 ± 6.62). The prevalence of CKDs is 19.3% among relatives. CKDs were more frequent 42.3 % in obese, followed by 30.8 % in overweight and 26.9% in normal weight relatives. Obese and overweight relatives have significantly higher ACR than normal weight (*P*= 0.012). GFR found to be significantly lower in obese and overweight relatives than normal weight (*P* = 0.000). GFR was negatively correlated with BMI (R = -0.430, *P* = 0.000).

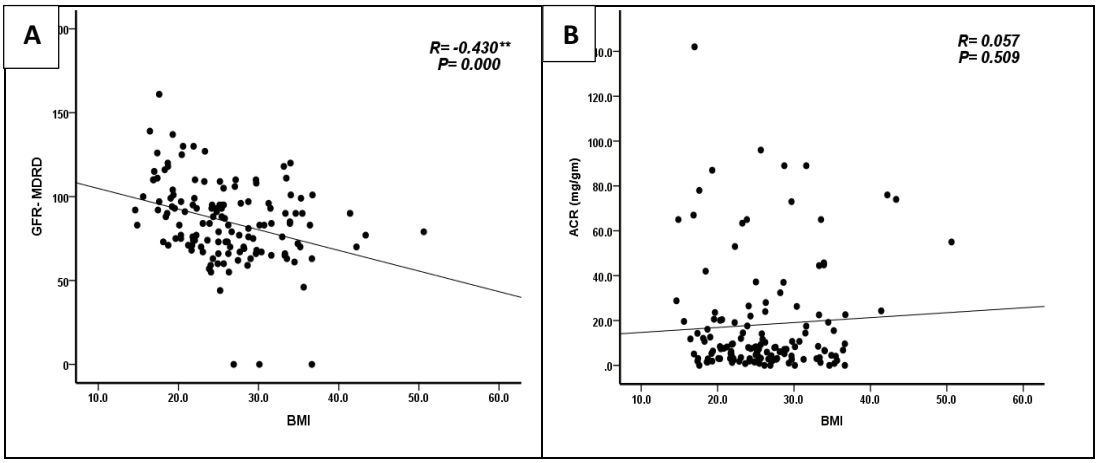

Figure 1: A: Correlation between BMI and estimated -GFR, B: Correlation between BMI and ACR.

Table 1: Demographic and characteristics data of CKD relatives (N = 135).

Characteristics	Frequency (%) or Mean ± SD	Variable	Frequency (%) or Mean ± SD
Gender: N (%)		**Age Groups: N (%)**	
Male	49 (36 %)	**≤ 20 years**	32 (23.7 %)
Female	86 (64 %)	**21 - 40 Years**	65 (48.1 %)
Age: (Mean ± SD)	(32.3 ± 14.1)	**> 40 Years**	38 (28.1 %)
BMI: (Mean ± SD)	(26.0 ± 6.62)	**ACR: N (%)**	
BMI Classification : N (%)		**>30 mg/gm.**	23 (17.0 %)
Normal weight	63 (46.6 %)	**≤ 30 mg/gm.**	112 (83.0 %)
Overweight	36 (26.7 %)	**GFR – MDRD: N (%)**	
Obese	36 (26.7 %)	**< 60 ml/min/1.73m^2**	9 (6.70 %)
		> 60 ml/min/1.73m^2	126 (93.3)

Table 2: Frequency of chronic kidney disease and its distribution based on BMI and age categories among first degree relatives of hemodialysis patients (N = 135).

Characteristics	Frequency (%)
Chronic kidney disease	26 (19.3 %)
BMI Categories	
Normal weight	7 (26.9 %)
Overweight	8 (30.8 %)
Obese	11 (42.3 %)
Total	26 (100 %)
Age group	
≤ 20 years	5 (19.2 %)
21 - 40 Years	9 (34.6 %)
> 40 Years	12 (46.2 %)
Total	26 (100 %)

4. Discussion

Concurrent with several previous studies that showed increased prevalence of CKDs (23, 24). This study has demonstrated higher prevalence (19.3%) of CKDs among family members of renal failure patients. Moreover, the frequency data showed that, CKDs is more frequent in adults followed by adolescence and youngest. Meanwhile, in 135

Table 3: The mean levels of ACR and e-GFR based on BMI categories in total first-degree relatives.

Parameters	BMI categories	Mean ± SD	P- value
ACR (mg /gm.)	Normal weight	12.0 ± 6.60	0.012
	Overweight	16.5 ± 9.80	
	Obese	21.6 ± 8.90	
GFR - MDRD	Normal weight	90.7 ± 20.2	0.000
	Overweight	77.4 ± 21.6	
	Obese	77.7 ± 25.8	

of first-degree relatives, higher frequency of obesity was noted, followed by overweight and normal weight. Several previous studies have reported similar findings, that increased BMI was independent risk factor for CKDs in general population, diabetes and hypertension (25, 26, 27, 28, 29). Indeed, obesity is known to affect hemodynamic, insulin resistance, adipokines changes, low grade inflammation, oxidative stress and endothelial dysfunction, therefore has been suggested to be a risk factor of CKDs. Previous studies have shown that, obesity lead to intraglomerular pressure, which damage the kidneys structure and raise the risk of developing CKD in long term (30, 31). Whereas adiponectins from adipocyte are postulated to be involved in the pathogenesis and progression of CKD (32).

In contrast few studies demonstrated an insignificant association between increased stocktickerBMI and CKD (33, 34). This contradiction attributed to obesity paradox, which suggested to have a protective effect against CKD progression and mortality (35).

Comparison analysis revealed that, obese and overweight relatives had significantly higher stocktickerACR and lower e-stocktickerGFR levels than normal weight, therefore, have been suggested as potential risk factors of CKDs among family members. These findings similar from those reported that, albumin excretion rate is increased in obese subjects, also obese non diabetic subjects had a greater risk for mircoalbuminuria (36, 37, 38). Since the obesity increased renal plasma flow, hyperfiltration and promote renal injury, consequently proteinuria (39, 40, 41, 42). On the other hand the reduced level of e-stocktickerGFR among individuals with increased stocktickerBMI, in addition some data in support of this finding that, the stocktickerBMI of 30 kg/m^2 or more is associated with rapid loss of kidney function in patients with eGFR of at least 60 mL/min /1·73 m^2 (43, 44).

In the present study, the comparison analysis was further reinforced by person's correlation of eGFR and BMI that, eGFR positively associated with BMI. In fact, the association of obesity with an increased ACR-based CKD risk was previously reported (45). In contrast our results differ from those demonstrated that, the BMI is independent factor of CKD (46).

5. Conclusion

In conclusion, the prevalence of CKDs is 19.3% among relatives. Obese and overweight relatives had higher ACR and Lower eGFR. Meanwhile, BMI inversely associated with eGFR. Therefore, obese and overweight chronic renal failure relatives are at increased risk for developing CKDs.

6. Limitation of the Study

Limited number of relatives, the diagnosis of albuminuria based on single laboratory measurement.

Acknowledgments

The authors acknowledge this work to the family members. Mr. Ismail Mohamed Ismail, BSc, MSc and Marwan Nori BSc, MSc, for their help in statistical analyses.

Funding

Nil.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Contribution

All authors contribute equally

References

[1] Kumar J. Screening for Chronic Kidney Disease in Family Members of Dialysis Patients. Journal of Rawalpindi Medical College. 2017 Sep 30; 21(3):262-4.

[2] Chukwuonye II, Ogah OS, Anyabolu EN, Ohagwu KA, Nwabuko OC, Onwuchekwa U, Chukwuonye ME, Obi EC, Oviasu E. Prevalence of chronic kidney disease in Nigeria: systematic review of population-based studies. International journal of nephrology and renovascular disease. 2018; 11:165.

[3] Sayanthooran S, Magana-Arachchi DN, Gunerathne L, Abeysekera T. Potential diagnostic biomarkers for chronic kidney disease of unknown etiology (CKDu) in Sri Lanka: a pilot study. BMC nephrology. 2017 Dec;18(1):31.

[4] Chukwuonye II, Ohagwu KA, Adelowo OO, Chuku A, Obi EC, Onwuchekwa U, Anyabolu EN, Oviasu E. Prevalence and Predictors of Chronic Kidney Disease in a Semiurban Community in Lagos. International journal of nephrology. 2019; 2019.

[5] Meyers AM. Significance, definition, classification and risk factors of chronic kidney disease in South Africa. SAMJ, S. Afr. med. j. vol.105 n.3 Cape Town Mar. 2015 http://dx.doi.org/10.7196/SAMJ.9412)

[6] Kumela Goro K, Desalegn Wolide A, Kerga Dibaba F, Gashe Fufa F, Wakjira Garedow A, Edilu Tufa B, Mulisa Bobasa E. Patient Awareness, Prevalence, and Risk Factors of Chronic Kidney Disease among Diabetes Mellitus and Hypertensive Patients at Jimma University Medical Center, Ethiopia. BioMed Research International. 2019;2019.

[7] Kong X, Liu L, Zuo L, Yuan P, Li Z, Li W, Cai M, Chen X, Jiang A, Long G, Xu J. Association between family members of dialysis patients and chronic kidney disease: a multicenter study in China. BMC nephrology. 2013 Dec;14(1):19.

[8] Abu-Aisha H, Elhassan A, Khamis A, Abu-Elmaali A. Chronic kidney disease in police forces households in Khartoum, Sudan: pilot report. Arab Journal of Nephrology and Transplantation. 2009;2(2):21-6.

[9] Evangelista LS, Cho WK, Kim Y. Obesity and chronic kidney disease: A population-based study among South Koreans. PloS one. 2018 Feb 28; 13(2):e0193559.

[10] Ahmed MH, Ali YA, Awadalla H, Elmadhoun WM, Noor SK, Almobarak AO. Prevalence and trends of obesity among adult Sudanese individuals: Population based study. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2017 Dec 1; 11:S963-7.

[11] Chang TJ, Zheng CM, Wu MY, Chen TT, Wu YC, Wu YL, Lin HT, Zheng JQ, Chu NF, Lin YM, Su SL. Relationship between body mass index and renal function deterioration

among the Taiwanese chronic kidney disease population. Scientific reports. 2018 May 2; 8(1):6908.

[12] Kovesdy CP, Furth SL, Zoccali C, World Kidney Day Steering Committee. Obesity and kidney disease: hidden consequences of the epidemic. Blood purification. 2017;43(4):346-54.

[13] Garland JS. Elevated body mass index as a risk factor for chronic kidney disease: current perspectives. Diabetes, metabolic syndrome and obesity: targets and therapy. 2014; 7:347.

[14] Swartz JE, Perry E, Joy Sand Swartz RD. Using Peer Mentors to screen for CKD at dialysis units: Targeting high–risk family members. Dialysis & Transplantation. 2011 Jun; 40(6):246-51.

[15] Satko SG, Freedman BI, Moossavi S. Genetic factors in end-stage renal disease. Kidney international. 2005 Apr 1; 67: S46-9.

[16] Bellini MI, Paoletti F, Herbert PE. Obesity and bariatric intervention in patients with chronic renal disease. Journal of International Medical Research. 2019 Jun; 47(6):2326-41.

[17] ElHafeez SA, Bolignano D, D'Arrigo G, Dounousi E, Tripepi G, Zoccali C. Prevalence and burden of chronic kidney disease among the general population and high-risk groups in Africa: a systematic review. BMJ open. 2018 Jan 1; 8(1):e015069.

[18] Jaar BG, Khatib R, Plantinga L, Boulware LE, Powe NR. Principles of screening for chronic kidney disease. Clinical Journal of the American Society of Nephrology. 2008 Mar 1; 3(2):601-9.

[19] Burtis CA, Ashwood ER, Bruns DE (eds.). Tietz Textbook of Clinical Chemistry and Molecular Diagnostics, 4th ed Philadelphia,Pa: WB Saunders, 2006:549

[20] Bevc S, Hojs R, Ekart R, Završnik M, Gorenjak M, Puklavec L. Simple cystatin C formula for estimation of glomerular filtration rate in overweight patients with diabetes mellitus type 2 and chronic kidney disease. Experimental diabetes research. 2012 Sep 12; 2012.

[21] Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Annals of internal medicine. 2006 Aug 15; 145(4):247-54.

[22] Tietz N W. Clinical Guide to Laboratory Tests, 3rd edition. Philadelphia; W.B. Saunders Company 1995: 186- 188.

[23] Chan S, Cameron A, Wang Z, Venuthurupalli SK, Tan KS, Healy HG, Hoy WE. Body mass index in an Australian population with chronic kidney disease. BMC nephrology. 2018 Dec;19(1):209.

[24] Temgoua M, Ashuntantang G, Essi MJ, Tochie JN, Oumarou M, Abongwa A, Mbonda A, Kingue S. Prevalence and Risk Factors for Chronic Kidney Disease in Family Relatives of a Cameroonian Population of Hemodialysis Patients: A Cross-Sectional Study. Hospital Practices and Research. 2019 Jan 26; 4 (1): 12-7.

[25] Hallan S, de Mutsert R, Carlsen S, Dekker FW, Aasarød K, Holmen J. Obesity, smoking, and physical inactivity as risk factors for CKD: are men more vulnerable. American journal of kidney diseases. 2006 Mar 1;47(3):396-405.

[26] Shankar A, Leng C, Chia KS, Koh D, Tai ES, Saw SM, Lim SC, Wong TY. Association between body mass index and chronic kidney disease in men and women: population-based study of Malay adults in Singapore. Nephrology Dialysis Transplantation. 2007 Dec 21;23(6):1910-8.

[27] Nomura I, Kato J, Kitamura K. Association between body mass index and chronic kidney disease: a population-based, cross-sectional study of a Japanese community. Vascular health and risk management. 2009; 5:315.

[28] Ejerblad E, Fored CM, Lindblad P, Fryzek J, McLaughlin JK, Nyrén O. Obesity and risk for chronic renal failure. Journal of the American society of nephrology. 2006 Jun 1;17(6):1695-702.3

[29] Choi JI, Cho YH, Lee SY, Jeong DW, Lee JG, Yi YH, Tak YJ, Lee SH, Hwang HR, Park EJ. The Association between Obesity Phenotypes and Early Renal Function Decline in Adults without Hypertension, Dyslipidemia, and Diabetes. Korean journal of family medicine. 2019 May; 40(3):176.

[30] He Y, Li F, Wang F, Ma X, Zhao X, Zeng Q. The association of chronic kidney disease and waist circumference and waist-to-height ratio in Chinese urban adults. Medicine. 2016 Jun;95(25).

[31] Kovesdy CP, Furth SL, Zoccali C, World Kidney Day Steering Committee. Obesity and kidney disease: hidden consequences of the epidemic. Nephron. 2017;135(4):243-51.

[32] Garland JS. Elevated body mass index as a risk factor for chronic kidney disease: current perspectives. Diabetes, metabolic syndrome and obesity: targets and therapy. 2014;7: 347.

[33] Caldararu CD, Tarta D, Pop R, Gliga M, Carasca E, Dogaru G. Body Mass Index and the Relationship with Chronic Kidney Disease in a Tertiary Care Hospital in Romania. Acta Medica Marisiensis. 2016 Jun 1;62(2):225-9.

[34] Brown RN, Mohsen A, Green D, Hoefield RA, Summers LK, Middleton RJ, O'donoghue DJ, Kalra PA, New DI. Body mass index has no effect on rate of progression of chronic kidney disease in non-diabetic subjects. Nephrology Dialysis Transplantation. 2012 Mar 22;27(7):2776-80.

[35] Kalantar-Zadeh K, Rhee CM, Chou J, Ahmadi SF, Park J, Chen JL, Amin AN. The obesity paradox in kidney disease: how to reconcile it with obesity management. Kidney international reports. 2017 Mar 1;2(2):271-81. 32.

[36] Mulyadi L, Stevens C, Munro S, Lingard J, Bermingham M. Body fat distribution and total body fat as risk factors for microalbuminuria in the obese. Annals of nutrition and metabolism. 2001;45(2):67-71.

[37] Pinto-Sietsma SJ, Navis G, Janssen WM, de Zeeuw D, Gans RO, de Jong PE, PREVEND Study Group. A central body fat distribution is related to renal function impairment, even in lean subjects. American Journal of Kidney Diseases. 2003 Apr 1;41(4):733-41.

[38] Kramer H, Reboussin D, Bertoni AG, Marcovina S, Lipkin E, Greenway FL, Brancati FL, Look Ahead Research Group. Obesity and albuminuria among adults with type 2 diabetes: the Look AHEAD (Action for Health in Diabetes) Study. Diabetes Care. 2009 May 1;32(5):851-3.

[39] De Jong PE, Verhave JC, Pinto-Sietsma SJ, Hillege HL. Obesity and target organ damage: the kidney. International Journal of Obesity & Related Metabolic Disorders. 2002 Dec 2;26.

[40] Chagnac A, Weinstein T, Korzets A, Ramadan E, Hirsch J, Gafter U. Glomerular hemodynamics in severe obesity. American Journal of Physiology-Renal Physiology. 2000 May 1;278(5):F817-22.

[41] Koshimura J, Fujita H, Narita T, Shimotomai T, Hosoba M, Yoshioka N, Kakei M, Fujishima H, Ito S. Urinary adiponectin excretion is increased in patients with overt diabetic nephropathy. Biochemical and biophysical research communications. 2004 Mar 26;316(1):165-9.

[42] Tang J, Yan H, Zhuang S. Inflammation and oxidative stress in obesity-related glomerulopathy. International journal of nephrology. 2012;2012.

[43] Kawamoto R, Kohara K, Tabara Y, Miki T, Ohtsuka N, Kusunoki T, Yorimitsu N. An association between body mass index and estimated glomerular filtration rate. Hypertension Research. 2008 Aug;31(8):1559.

[44] Lu JL, Molnar MZ, Naseer A, Mikkelsen MK, Kalantar-Zadeh K, Kovesdy CP. Association of age and BMI with kidney function and mortality: a cohort study. The lancet Diabetes & endocrinology. 2015 Sep 1;3(9):704-14.

[45] Kim YJ, Hwang SD, Oh TJ, Kim KM, Jang HC, Kimm H, Kim HC, Jee SH, Lim S. Association Between Obesity and Chronic Kidney Disease, Defined by Both Glomerular Filtration Rate and Albuminuria, in Korean Adults. Metabolic syndrome and related disorders. 2017 Oct 1;15(8):416-22.

[46] Zaman SB, Hossain N, Rahman M. Associations between Body Mass Index and Chronic Kidney Disease in Type 2 Diabetes Mellitus Patients: Findings from the Northeast of Thailand. Diabetes & metabolism journal. 2018 Aug 1;42(4):330-7.