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A Study of insulin resistance in cases of Chronic kidney disease with or without hemodialysis on comparison with normal individuals.

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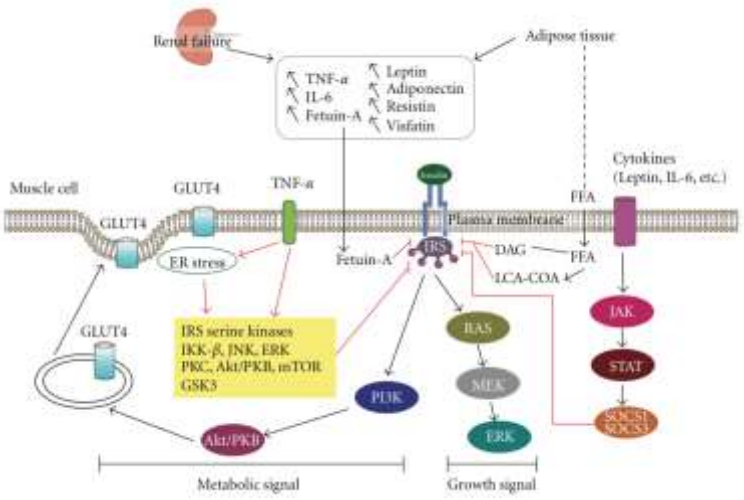
Introduction :

In Diabetes Mellitus & Metabolic Syndrome IR is related to innate immunity & inflammation is related to insulin sensitivity and energy metabolism. [1-2]Recent advances indicate involvement of gut microbiota & Uraemia Retention Molecules (URMs) in CKD.[3-5] In Uraemia , Endogenous production of specific factors are involved in insulin signaling pathways in CKD.[6-7] White adipose tissue is a source of specific molecules in the causation of metabolic disturbances (IR) in CKD [8] which leads to impairment of insulin signalling through inhibitory serine phosphorylation of insulin receptor substrate (IRS).IR leads to impairment of insulin signalling system in the target organs which may be due to pre-receptor or post receptor mechanism defect.

Lipotoxicity initiates activation of novel protein kinase (PKC) followed by impairment of insulin signalling through serine phosphorylation of IRS-I [9].In the absence or deficiency of Insulin ectopic fact in the form of TGL gets deposited at sites such as liver, heart , skeletal muscle and visceral adipose tissue. Accumulation of DAG activates serine kinase such as PKC - O in muscles and PKC - E (eeta) in liver. Ceramide can directly inhibit phosphorylation of PKB / AKt [10] TNF alpha and leptin also cause increase in IR linking inflammation to the development of IR which leads to increase in lipolysis and free fatty acid levels [11]

The alteration in microbiota of gut causes increased lipopolysaccharides (LPS) absorption which are component of outer membrane of gram negative bacteria.LPS initiates inflammatory pathways related to NF-kb and mitogen activated protein kinase (MAPK) which induces release of TNF Alpha & IL-6 [9,12]

IR in CKD



Effects of IR in CKD

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 01, 2024

In Physiological hyperinsulinemia the inhibitory effect of insulin on glucose production seem to be decreased in uremias whereas insulin stimulated glucose transport was reduced to 50% in muscles from uremic patients [13] IR found in patients with uraemia is due to a post receptor defect of insulin pathway.[14] Some reports found a decreased expression of GLUT4 skeletal muscle in uraemic rats compared with control [15] Several components of the insulin signaling path ways (IRS-1, PI3K) remain constant at the m RNA level in WAT of uremic patients [16] On maximal stimulation with supra-physiological dose of insulin Bailey et al found functional abnormalities in the PI3k cascade with subsequent down regulation of PKB /Akt in nephrectomized rats. [17] In CKD mice after insulin stimulation reduced tyrosine phosphorylation of IRS-1 and decreased serine phosphorylation of PKB/AKt is evident [18]

A growing body of evidence reveals that the kidney is an important organ of glucose homeostasis thus it is hypothesised

Staging	Description	GFR
I	Kidney damage with normal or increased GFR (ex: Diabetic nephropathy)	greater than or equal to 90ml/mt
II	Kidney damage with mildly reduced GFR	60-89ml/mt
III	Moderately reduced GFR	30-59ml/mt
IV	Severely reduced GFR	15-29 ml/mt
V	ESRD	<15 ml/mt need for dialysis

that kidney function would lead to complex disturbances of glucose appearance in the circulation resulting in insulin resistance .Metabolic studies in type II DM reveals that renal gluconeogenesis similarly to hepatic gluconeogenesis is not suppressed by insulin to a similar extent as in healthy individuals.This observation points to the preface of insulin resistance on the lead of renal glucose metabolism.A study by Shinohara et al. has reviewed that insulin resistance assessed by HOMA-IR is an independent predictor for cardiovascular mortality in Non-Diabetic patients with end stage renal disease (ESRD) (End Stage CKD)

The study by Xu et al in this issue of CJ ASN [19] is the first to address the important question of whether insulin resistance is an independent factor of cardiovascular mortality in a population with mild to moderate kidney impairment by using the euglycemic clamp technique the study included 446 non diabetic men aged 70-71 years from the upscale longitudinal study of adult new cohort. Among the studied population only 12.5% of patients were identified as insulin sensitive.
As many as 63.5% of patients were insulin resistant according to the glucose infusion rate required to maintain euglycemia to the amount of insulin infusion.The data Xu et al. support the finding that IR can already be observed in early stage of CKD [19] In line with other observation IR was found to be independent of overweight - a major risk factor in the classic metabolic syndrome [20,21]

Becker et al found a significant association of insulin resistance with cardiovascular events in a cohort study of 227 non diabetic patients with mild and moderate CKD during a 7 year follow up [21] and Shinohara et al had similar findings in an investigation of a population of patients with ESRD [20] the latter studies were conducted in younger populations and assessed insulin sensitivity with HOMA-IR [20,21]

NKF-KDOQ 1 : Stages of CKD [22]

All individuals with GFR less than 60ml/mt / 1.73mt^2 is classified as having CKD.
Conversely in individuals with a GFR 60-89 ml / mt / 1.73m^2 is classified as decreased GFR.
"Moderate " or clinically significant CKD refers to CKD stage 3 (GFR 30-59ml/mt) and stage 4 (GFR 15-29ml/mt) With less than 60ml/mt chosen as a cut off because it represents loss of about 50% of normal renal function.A recent meta-analysis of 8 cohorts of 845, 125 general and high risk people confirms the marked and graded increased risk for ESRD in those with GFR less tan 60 ml/min (Stage 3 CKD).DM, HTN and glomerulonephropaties cause approximately 75% of adult cases of CKD.Arterial hypertension can wither be a cause or consequence of CKD and is associated with its progression. [23] Under Normal conditions , renal blood flow (RBF) is auto regulated over a broad range of systemic mean arterial pressure (MAP 80-160 mm Hg) Chronic HTN, DM and High protein intake disturb the auto regulatory

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 01, 2024

mechanisms and increases the pressure load to the renal vasculature regulating in glomerulosclerosis. Proteinuria can further accelerate injury to the tubular interstitial epithelial cells and is an independent promoter of kidney disease.

Insulin resistance is closely coupled with mitochondrial dysfunction , generation of reactive oxygen species , endothelial dysfunction and other cardiovascular risk factors.Insulin resistance may contribute to these processes. Association of IR enhances risk of CV events and deaths [24,25]
Insulin has direct effect on multiple cells in the kidney. Induction of IR in podocytes leads to glomerulosclerosis in animal models and IR leads to albumuniuria and the progression of chronic kidney disease (CKD) in observational human studies [26] DeFronzo et al. colleagues published a series of articles documenting severe IR in hemo dialysis patients , specifically those without overt diabetes.These studies used a technique called the hyperinsulinemic euglycemic clamp to directly measure whole body glucose intake in response to an insulin stimulus. Accordingly these studies by Defronzo ESRD patients are very insulin resistant which is localised to skeletal muscle and the IR partially improves with dialysis [27] Recent studies have identified specific uremic toxins that may mediate this effect, including gut derived molecules such as P-cresyl Sulphate [28] these observations, coupled with the epidemiology of IR and Cardiovascular disease described above suggest that IR may explain impart , the accelerated cardiovascular disease observed in patients with CKD.

However estimates of IR have not been well validated in CKD in health , the kidney catabolises approximately half of insulin in the systemic circulation. Fasting Glucose concentrations are determined largely by hepatic glucose production and may not reflect insulin resistance in skeletal muscle. The site of most important defect is CKD.In this regard , the paper by Jia et. al makes an important contribution to the evaluation of IR in CKD [29] with the hyper insulinemic euglycemic clamp technique (upscale longitudinal study of adult man)

Jia et al . reported that IR based on fasting glucose and insulin performed slightly less well in participants with CKD (-0.67) than in those without CKD (-0.71). (The Negative sign reflects estimation of insulin resistance versus insulin sensitivity.

IR is an integral component and a constellation of metabolic and hemodynamic abnormalities.
Presence of IR and compensatory Hyper insulinemia is strongly associated with the presence of CKD stages 1-4 [30,31,32] and constellates with the other abnormalities such as obesity,hypotension and hyperlipedemia ex : Cardiorenal metabolic syndrome [33,34,35,36] There are number of mechanisms thought to contribute to the impaired responses to insulin.

Most abnormalities are characterised by either as a pre-receptor, receptor or post receptor signalling defects , the bulk of work to date points to impaired signalling at the insulin receptor and post receptor levels therefore altered IRS/IRS-1/PI3K/AKt signalling and reactions in glucose transport or uptake

Dysregulation of this signalling pathway leads to resistance to the metabolic reactions of insulin that results in a compensatory increase in circulating insulin (Hyperinsulinemia).the excess insulin may result in insulin - dependent growth pathway activation in tissues with normal or minimally impaired insulin sensitivity such as in kidney.the compensatory increase in insulin states has a number of maladaptive consequences on cardiovascular and importantly for this review ,kidney tissue.

Materials and methods :

Estimation of Glucose by Trinder's endpoint method

Estimation of Serum Insulin done by Access-2 IMMUNOENZYMATIC ("SANDWICH") ASSAY

Calibration achieved and controls checked by Randox Quality control level 1,2,3.

Creatinine estimation by Jaffe's Method.

Samples are collected with informed consent at Dept. of Nephrology,Dialysis Unit, GGH,Guntur

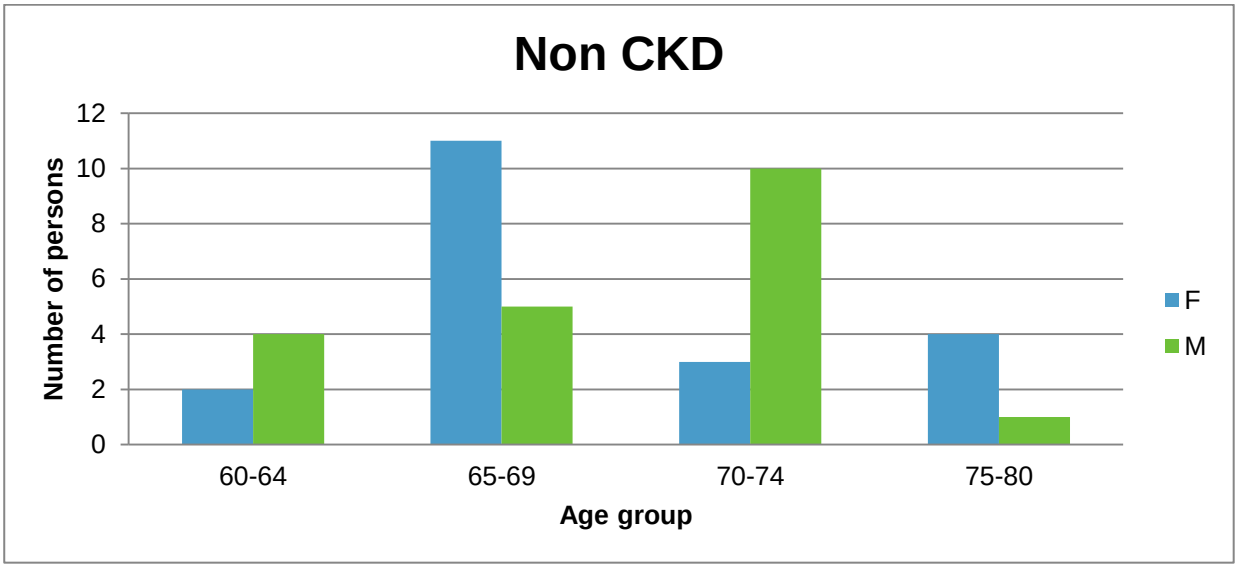
Descriptive Statistics:

Normal

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 01, 2024

Age group wise

Sl.No	Age	F	M	Grand Total
1	60-64	2	4	6
2	65-69	11	5	16
3	70-74	3	10	13
4	75-80	4	1	5
	Grand Total	20	20	40

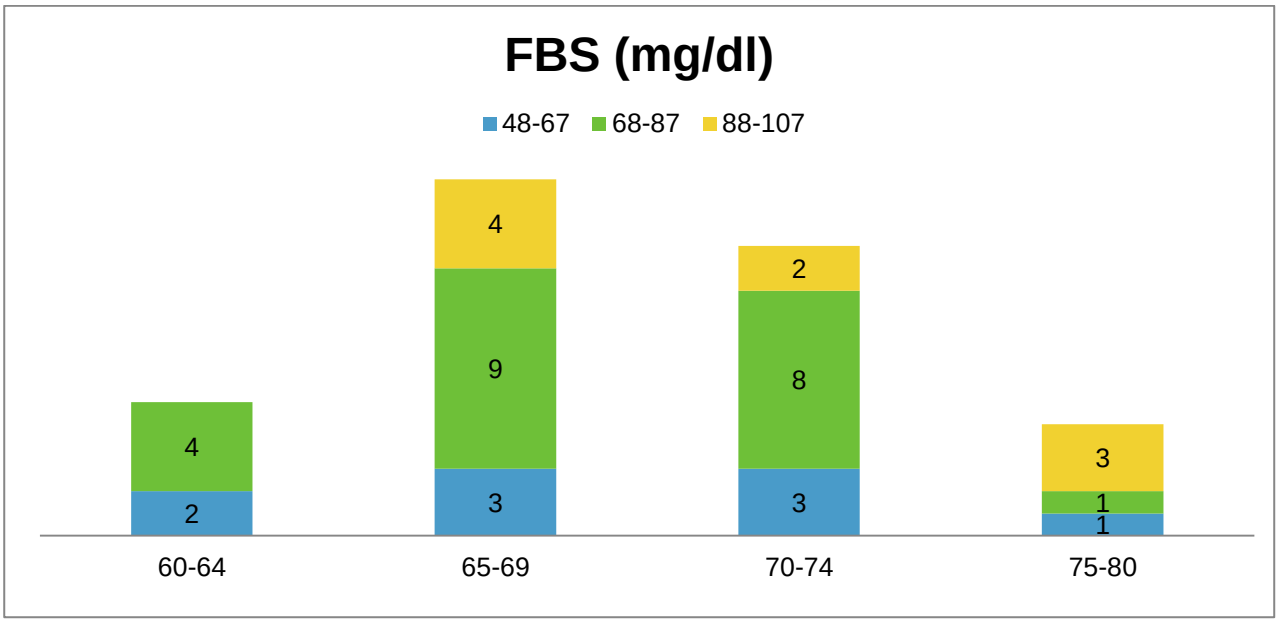


Age group wise- FBS

Sl.No	Age	48-67	68-87	88-107	Grand Total
1	60-64	2	4	0	6
2	65-69	3	9	4	16
3	70-74	3	8	2	13
4	75-80	1	1	3	5
	Grand Total	9	22	9	40

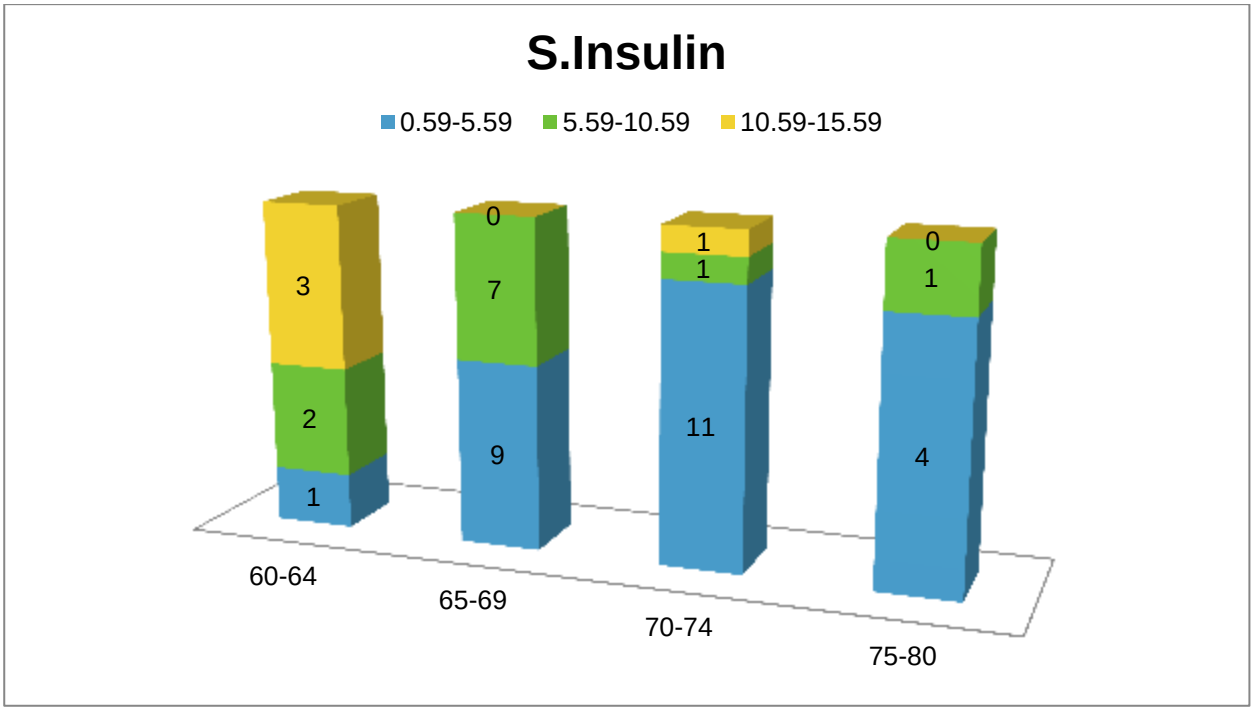
FBS

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 01, 2024



S.Insulin

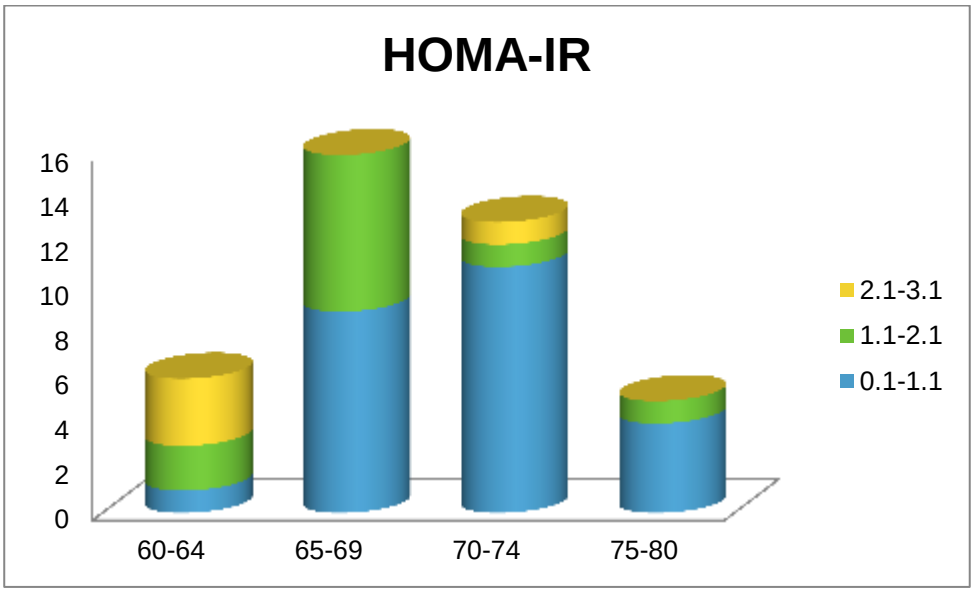
Sl.No	Age group	0.59-5.59	5.59-10.59	10.59-15.59	Grand Total
1	60-64	1	2	3	6
2	65-69	9	7		16
3	70-74	11	1	1	13
4	75-80	4	1		5
	Grand Total	25	11	4	40



ISSN: 0975-3583,0976-2833 VOL15, ISSUE 01, 2024

HOMA -IR

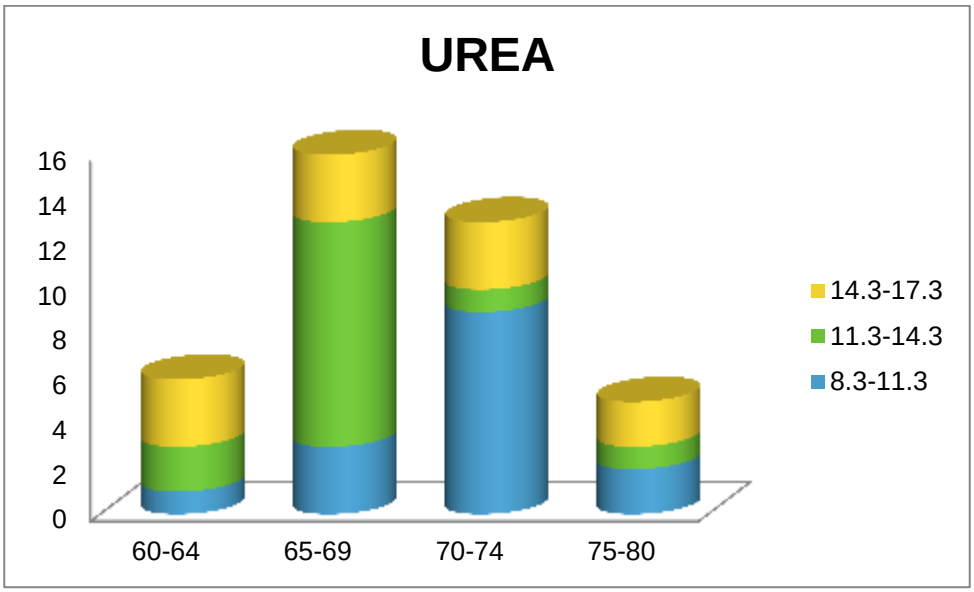
Age	0.1-1.1	1.1-2.1	2.1-3.1	Grand Total
60-64	1	2	3	6
65-69	9	7	0	16
70-74	11	1	1	13
75-80	4	1	0	5
Grand Total	25	11	4	40



UREA

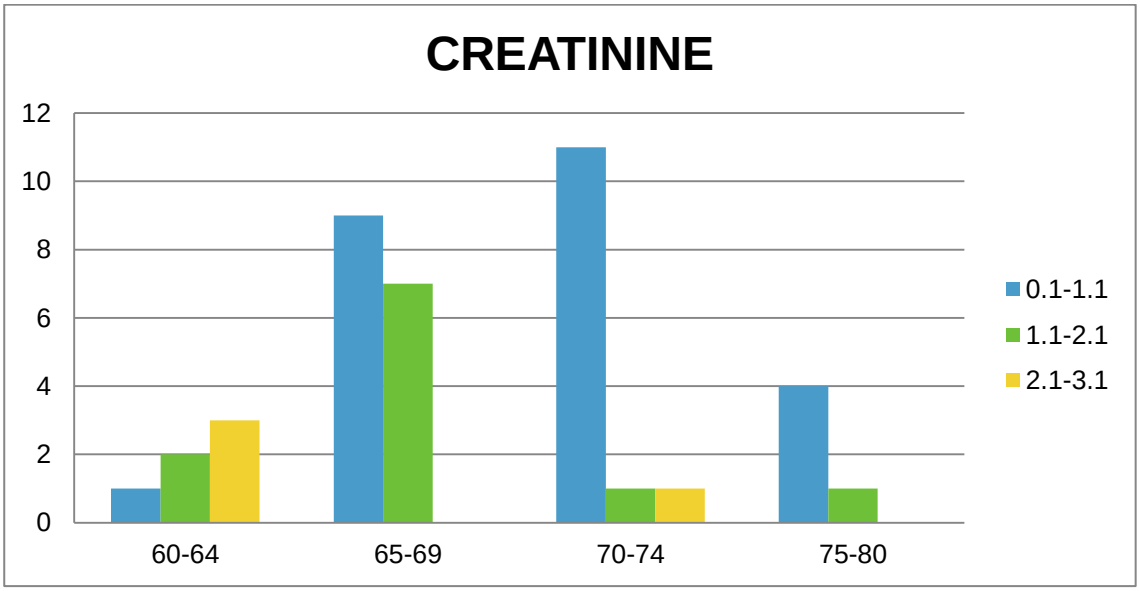
Age	8.3-11.3	11.3-14.3	14.3-17.3	Grand Total
60-64	1	2	3	6
65-69	3	10	3	16
70-74	9	1	3	13
75-80	2	1	2	5
Grand Total	15	14	11	40

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 01, 2024



CREATININE

Sl.No	Age	0.82-1.12	1.12-1.42	1.42-1.72	Grand Total
1	60-64	1	5		6
2	65-69	7	8	1	16
3	70-74	5	8		13
4	75-80	3	2		5
	Grand Total	16	23	1	40



ISSN: 0975-3583,0976-2833 VOL15, ISSUE 01, 2024

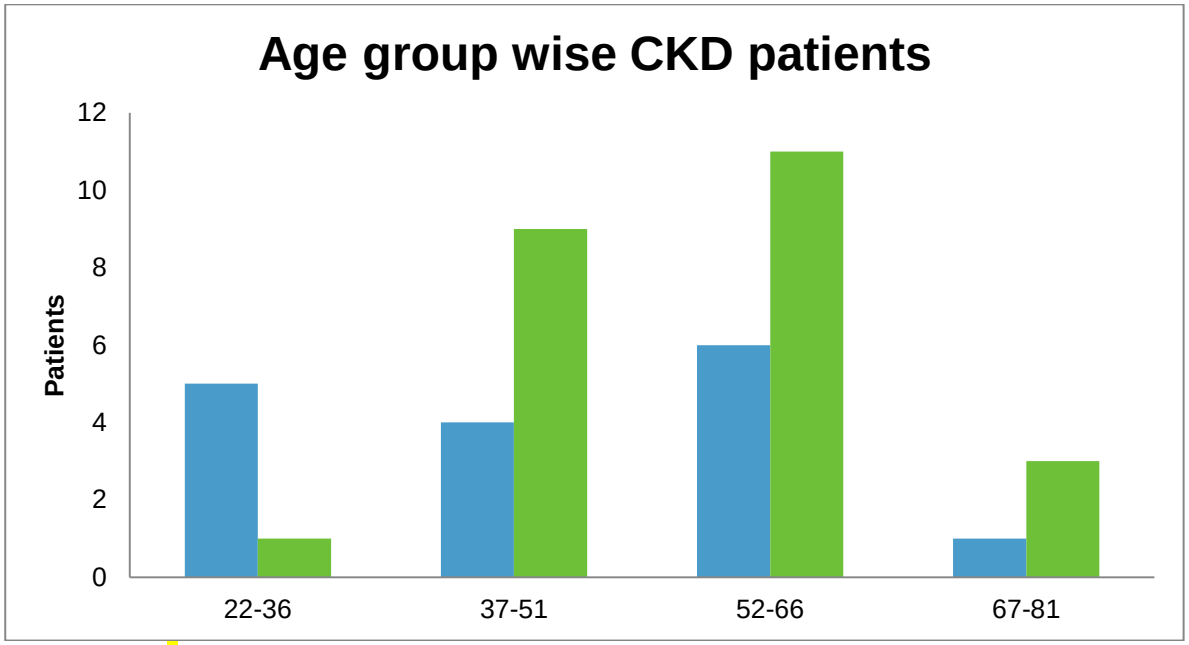
Descriptive Statistics:

CKD PATIENTS

Sl.No	Descriptive statistics	*Age*	*FBS (mg/dl)*	*S.Insulin (IU/ml)*	*HOMA-IR*	*UREA*	*CREATININE*
1	Mean	51.35	105.20	6.09	1.62	132.63	7.67
2	Standard Error	2.21	11.93	0.82	0.29	10.96	0.48
3	Median	52.50	83.00	3.82	0.99	125.00	6.80
4	Mode	54.00	62.00	2.80	0.59	83.00	5.70
5	Standard Deviation	13.95	75.48	5.21	1.81	69.29	3.02
6	Confidence Level(95.0%)	4.46	24.14	1.66	0.58	22.16	0.97

Age group wise

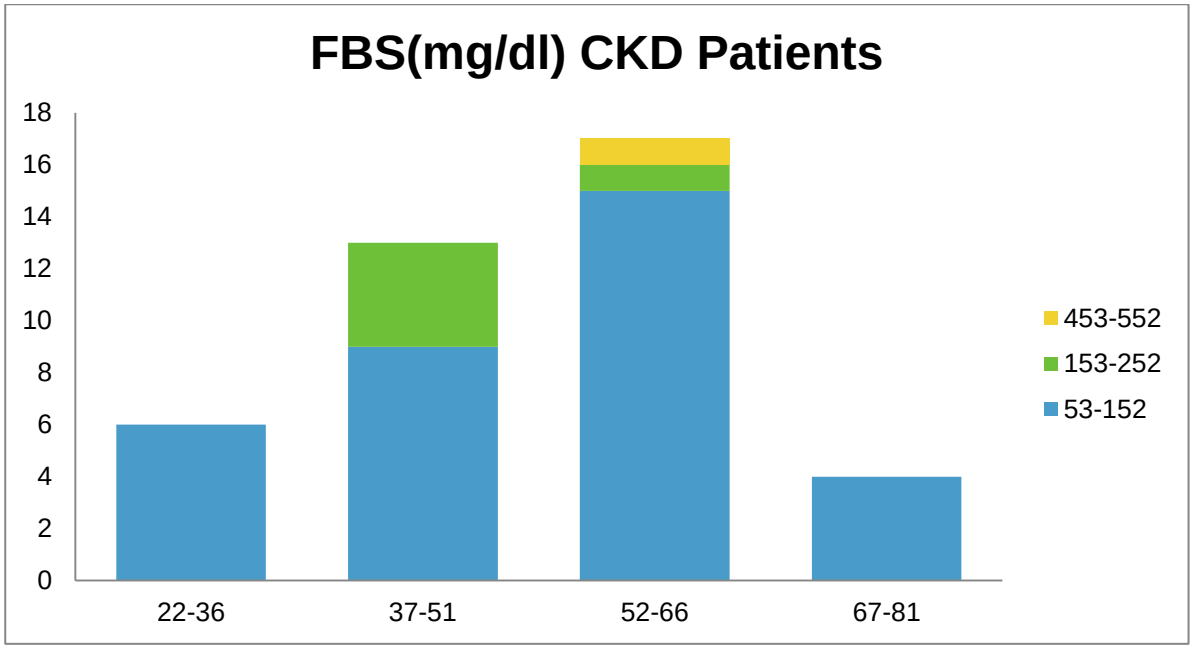
Sl.No	Age group	F	M	Grand Total
1	22-36	5	1	6
2	37-51	4	9	13
3	52-66	6	11	17
4	67-81	1	3	4
	Grand Total	16	24	40



FBS(mg/dl) :

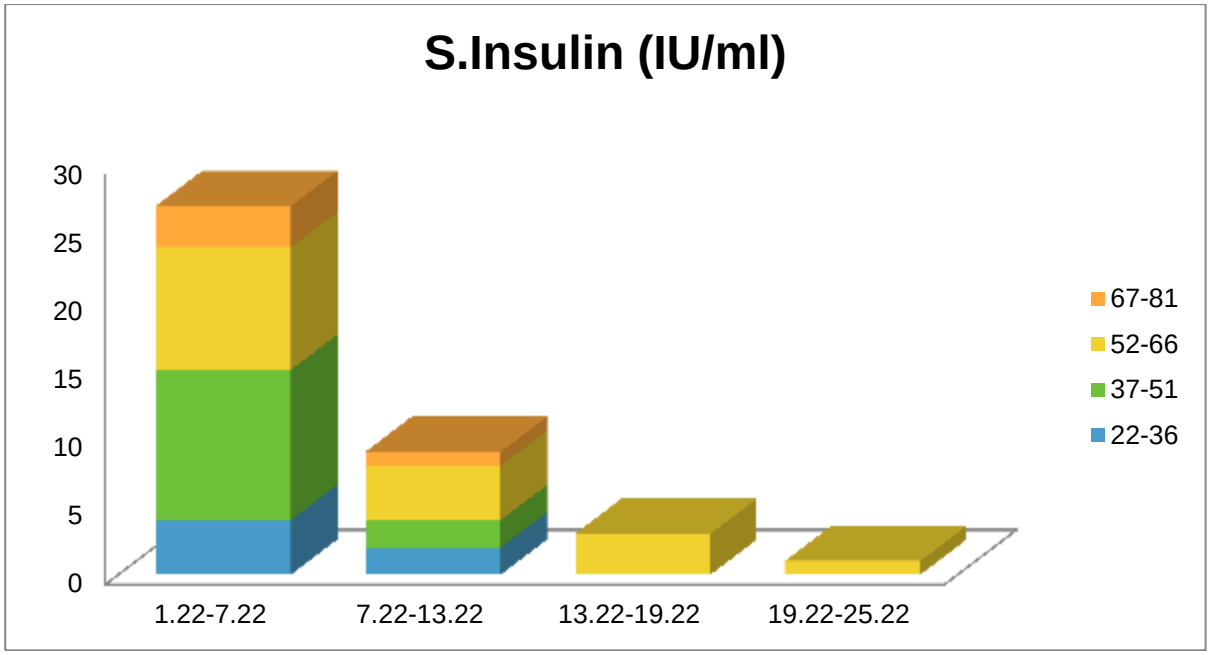
Sl.No	Age group	53-152	153-252	453-552	Grand Total
1	22-36	6	0	0	6
2	37-51	9	4	0	13
3	52-66	15	1	1	17
4	67-81	4	0	0	4
	Grand Total	34	5	1	40

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 01, 2024



S. Insulin (IU/ml):

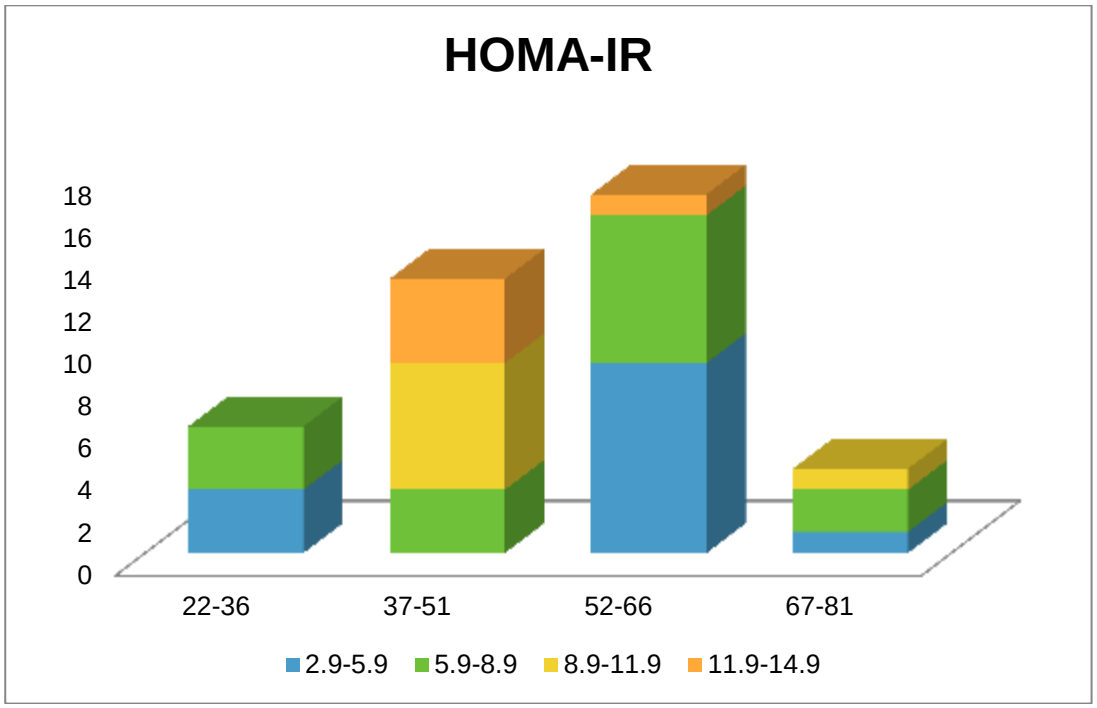
Sl.No	Age	1.22-7.22	7.22-13.22	13.22-19.22	19.22-25.22	Grand Total
1	22-36	4	2	0	0	6
2	37-51	11	2	0	0	13
3	52-66	9	4	3	1	17
4	67-81	3	1	0	0	4
	Grand Total	27	9	3	1	40



ISSN: 0975-3583,0976-2833 VOL15, ISSUE 01, 2024

HOMA-IR:

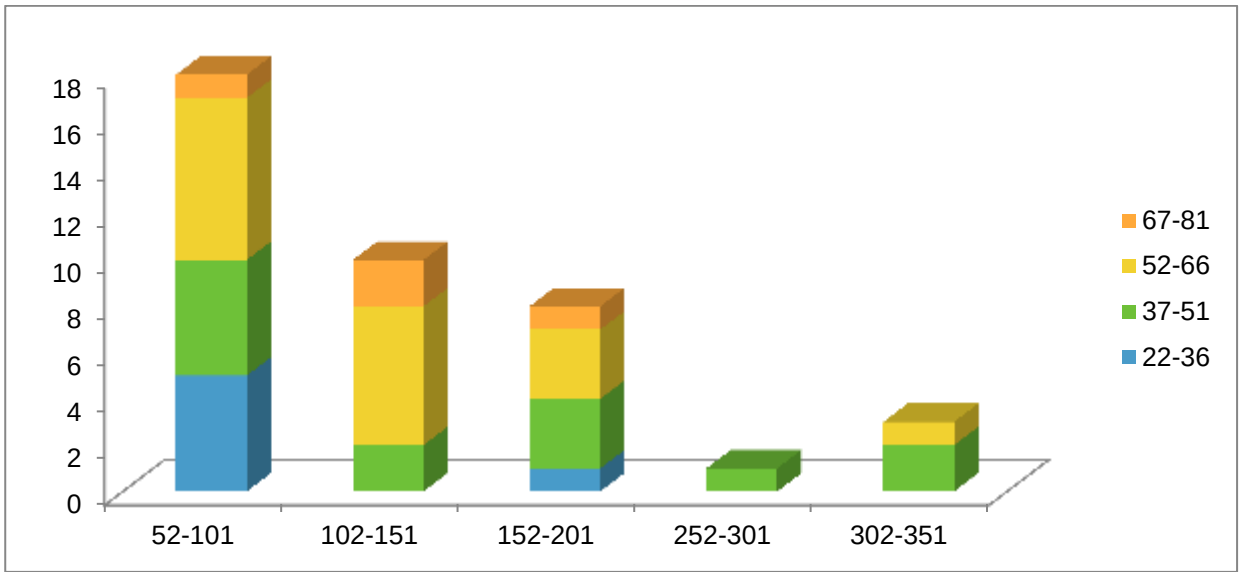
Sl.No	Age group	0.16-3.16	3.16-6.16	9.16-12.16	Grand Total
1	22-36	6	0	0	6
2	37-51	13	0	0	13
3	52-66	14	2	1	17
4	67-81	4	0	0	4
	Grand Total	37	2	1	40



UREA:

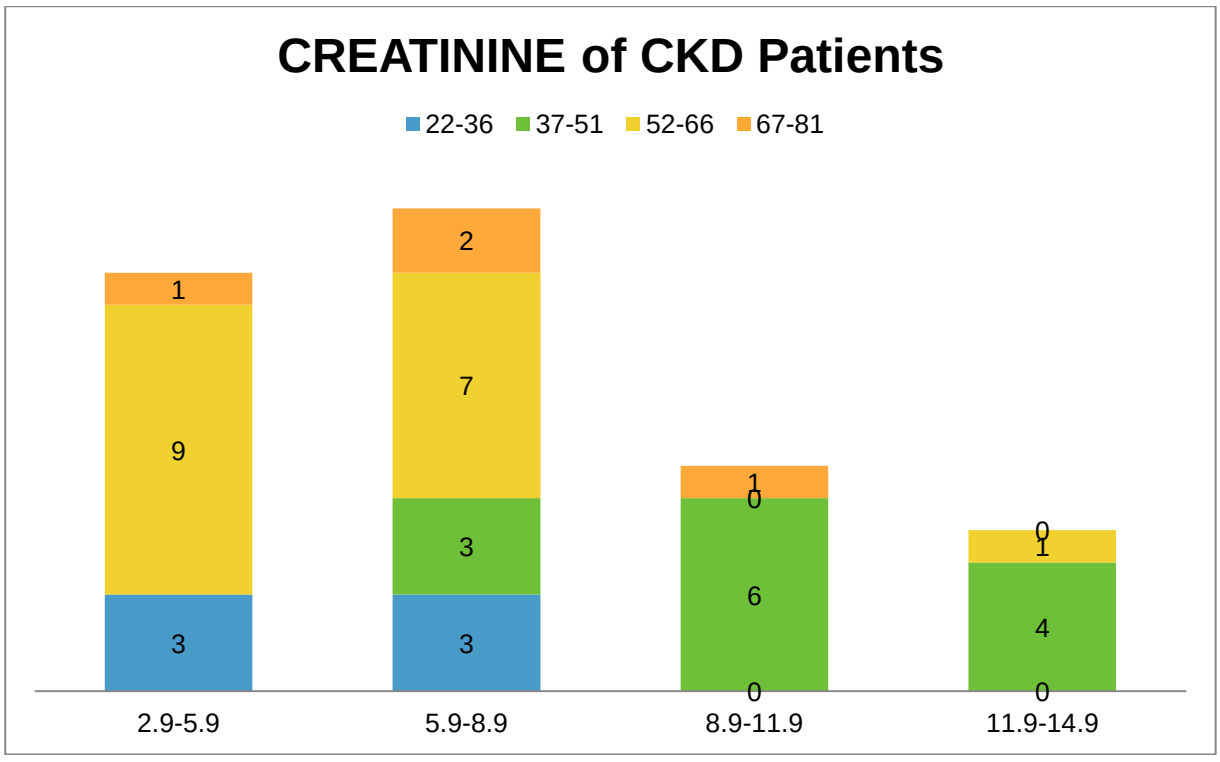
Sl. No	Age group	52-101	102-151	152-201	252-301	302-351	Grand Total
1	22-36	5		1			6
2	37-51	5	2	3	1	2	13
3	52-66	7	6	3		1	17
4	67-81	1	2	1			4
	Grand Total	18	10	8	1	3	40

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 01, 2024



CREATININE:

Sl.No	Age group	2.9-5.9	5.9-8.9	8.9-11.9	11.9-14.9	Grand Total
1	22-36	3	3	0	0	6
2	37-51		3	6	4	13
3	52-66	9	7	0	1	17
4	67-81	1	2	1	0	4
	Grand Total	13	15	7	5	40



ISSN: 0975-3583,0976-2833 VOL15, ISSUE 01, 2024

Results:

In the present study , 40 cases of CKD in which 20 are with dialysis and 20 are without dialysis were studied for the association of insulin resistance. controls were taken 20 each in men and women irrespective of the age. insulin resistance was calculated from the 2 parameters, blood glucose and serum levels of insulin , estimating the HOMA-IR.

HOMA-IR was one of the established marker for the insulin resistance the average fasting blood sugar mg/dl In normal individuals was 77.63 with SD +/- 1.97 whereas in cases of CKD patients the same parameter was 105.20 with SD +/- 75.48.

Another important component of HOMA IR is serum insulin (IU/ml) in Normal individuals was mean 5.12 with SD +/- 3.83 whereas in CKD patients mean 6.09 with SD+/- 5.21

The marker of insulin resistance HOMA- IR in normal individuals with mean 0.99, with SD +/- 0.79
On comparison the mean of CKD. HOMA-IR is 1.62 with the SD +/- 1.81.

The P value is significant at 0.023941 (less than 0.05) in case of normal individuals, on comparison with cases of CKD patients with and without dialysis.

Creatinine is the supporting parameter which is statistically significant.

HOMA- IR comparison within the 2 groups of CKD with Dialysis mean of 1.57 on comparison without dialysis mean of 1.68 the P value is 0.42308 which is not significant.

Discussion

In the present study of insulin resistance, in cases of chronic kidney disease with hemodialysis, without hemodialysis on comparison with normal individuals there is a statistically significant increase in insulin levels and HOMA-IR (p value = 0.023941, p value significant at $p < 0.05$) in concurrence with the established fact that IR is a cause of cardiovascular morbidity in cases of CKD end stage[27] and early cases of CKD[19,20,21]
No statistical significance found between the two groups of CKD with dialysis and without dialysis.
(the p value = 0.422308 , p value significant at $p <0.05$)
IR in CKD treated by Vit- D Supplementation, Correction of metabolic acidosis,anemia & treatment by gliptins causes increased insulin sensitivity in peripheral tissues thereby increases HDL-C & circulating adiponectins ,Decreased TGL and circulating inflammatory mediators. [37]Vitamin D supplementation improves short term insulin secretion and insulin sensitivity in ESRD [38,39]
Intravenous nutrition treats malnutrition along with amino acid supplementation [40]. Leucine rich supplements in the management of uraemia & muscle wasting were suggested in CKD patients [41]

Summary and conclusion.

IR maybe the cause or effect of CKD and plays a role in declining renal function,
IR is multifactorial in its cause and associated with chronic inflammation, oxidative stress, Vit-D deficiency, anaemic and malnutrition. These factors associated with elevation of TNF Alpha,IL-6 & other cytokines along with adepokines & increased ER.Proper nutrition and prevention of uraemia associated complications. including dyslipediemia , Vit- D, EPO deficiency and anaemia may also improve insulin sensitivity among the CKD population.

References:

1. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resist- ance. Science 1993; 259: 87–91
2. Turnbaugh PJ, Ley RE, Mahowald MA et al. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature 2006; 444: 1027–1031
3. Bammens B, Evenepoel P, Verbeke K et al. Impairment of small intestinal protein assimilation in patients with end-stage renal disease: extending the malnutrition-inflammation-atherosclerosis concept. Am. J. Clin. Nutr. 2004; 80: 1536–1543

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 01, 2024

4. Vaziri ND, Wong J, Pahl M et al. Chronic kidney disease alters intestinal microbial flora. Kidney Int. 2013; 83: 308–315
5. Aronov PA, Luo FJ-G, Plummer NS et al. Colonic contribution to uremic solutes. J. Am. Soc. Nephrol. 2011; 22: 1769–1776
6. D'Apolito M, Du X, Zong H et al. Urea-induced ROS generation causes insulin resistance in mice with chronic renal failure. J. Clin. Invest. 2010; 120: 203–213
7. Koppe L, Pillon NJ, Vella RE et al. p-Cresyl sulfate promotes insulin resistance associated with CKD. J. Am. Soc. Nephrol. 2013; 24: 88–99
8. Zhao H-L, Sui Y, Guan J et al. Fat redistribution and adipocyte transformation in uni-nephrectomized rats. Kidney Int. 2008; 74: 467–477
9. Samuel VT, Shulman GI. Mechanisms for insulin resistance: common threads and missing links. Cell 2012; 148: 852–871
10. Fox TE, Houck KL, O'Neill SM et al. Ceramide recruits and activates protein kinase C zeta (PKC zeta) within structured membrane microdo- mains. J. Biol. Chem. 2007; 282: 12450–12457
11. Plomgaard P, Fischer CP, Ibfelt T et al. Tumor necrosis factor-alpha modulates human in vivo lipolysis. J. Clin. Endocrinol. Metab. 2008; 93: 543–549
12. Tuncman G, Hirosumi J, Solinas G et al. Functional in vivo interactions between JNK1 and JNK2 isoforms in obesity and insulin resistance. Proc. Natl. Acad. Sci. USA 2006; 103: 10741–10746
13. Bak JF, Schmitz O, Sørensen SS et al. Activity of insulin receptor kinase and glycogen synthase in skeletal muscle from patients with chronic renal failure. Acta Endocrinol. 1989; 121: 744–750
14. Cecchin F, Ittoop O, Sinha MK et al. Insulin resistance in uremia: insulin receptor kinase activity in liver and muscle from chronic uremic rats. Am. J. Physiol. 1988; 254: E394–E401
15. Aksentijević D, Bhandari S, Seymour A-ML. Insulin resistance and altered glucose transporter 4 expression in experimental uremia. Kidney Int. 2009; 75: 711–718
16. Witasp A, Carrero JJ, Heimbürger O et al. Increased expression of pro-in- flammatory genes in abdominal subcutaneous fat in advanced chronic kidney disease patients. J. Intern. Med. 2011; 269: 410–419
17. Bailey JL, Zheng B, Hu Z et al. Chronic kidney disease causes defects in signaling through the insulin receptor substrate/ phosphatidylinositol 3-kinase/Akt pathway: implications for muscle atrophy. J. Am. Soc. Nephrol. 2006; 17: 1388–1394
18. Thomas SS, Dong Y, Zhang L et al. Signal regulatory protein-α interacts with the insulin receptor contributing to muscle wasting in chronic kidney disease. Kidney Int. 2013; 84: 308–316
19. Xu H, Huang X, Arnlöv J, Cederholm T, Stenvinkel P, Lindholm B, Risérus U, Carrero JJ: Clinical correlates of insulin sensitivity and its association with mortality among men with CKD stages 3 and 4. *Clin J Am Soc Nephrol* 9: 690–697, 2014 [PMCID: PMC3974352][PubMed: 24436478]
20. Shinohara K, Shoji T, Emoto M, Tahara H, Koyama H, Ishimura E, Miki T, Tabata T, Nishizawa Y: Insulin resistance as an independent predictor of cardiovascular mortality in patients with end-stage renal disease. *J Am Soc Nephrol* 13: 1894–1900, 2002 [PubMed: 12089386]
21. Becker B, Kronenberg F, Kielstein JT, Haller H, Morath C, Ritz E, Fliser D; MMKD Study Group: Renal insulin resistance syndrome, adiponectin and cardiovascular events in patients with kidney disease: The mild and moderate kidney disease study. *J Am Soc Nephrol* 16: 1091–1098, 2005 [PubMed: 15743998]
22. Bishop, Michael L., et al. *Clinical Chemistry: Principles, Techniques, and Correlations.* 7th ed. Philadelphia, Wolters Kluwer Health/Hippincott Williams & Wilkins, 2013. Page no : 585

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 01, 2024

23. Ralston, Stuart H., et al., editors. *Davidson's Principles and Practice of Medicine*, Elsevier Health Sciences, 2018. Page no : 484
24. Pham H, Utzschneider KM, de Boer IH. Measurement of insulin resistance in chronic kidney disease. Current opinion in nephrology and hypertension. 2011 Aug 31
25. de Boer, Ian H et al. "Insulin resistance, cystatin C, and mortality among older adults." *Diabetes care*vol. 35,6 (2012): 1355-60. doi:10.2337/dc11-1657
26. De Cosmo S, Menzaghi C, Prudente S, Trischitta V. Role of insulin resistance in kidney dysfunction: insights into the mechanism and epidemiological evidence. Nephrol Dial Transplant. 2013 Jan; 28(1):29–36. [PubMed: 23048172]
27. DeFronzo RA, Alvestrand A, Smith D, Hendler R, Hendler E, Wahren J. Insulin resistance in uremia. J Clin Invest. 1981 Feb; 67(2):563–568. [PubMed: 7007440]
28. Koppe L, Pillon NJ, Vella RE, et al. p-Cresyl sulfate promotes insulin resistance associated with CKD. J Am Soc Nephrol. 2013 Jan; 24(1):88–99. [PubMed: 23274953]
29. Jia T. Kidney Int. 2014
Kidney Int. Author manuscript; available in PMC 2015 February 01.
30. Chen J, Muntner P, Hamm LL, et al: The metabolic syndrome and chronic kidney disease in U.S. adults. Ann Intern Med 2004;140:167–174.
31. Yamagata K, Ishida K, Sairenchi T, et al: Risk factors for chronic kidney disease in a community-based popu- lation: a 10-year follow-up study. Kidney Int 2007;71:159–166.
32. Soltani Z, Washco V, Morse S, Reisin E: The impacts of obesity on the cardiovascular and renal systems: cascade of events and therapeutic approaches. Curr Hypertens Rep 2015;17:7.
33. Pulakat L, DeMarco VG, Whaley-Connell A, Sowers JR: The impact of overnutrition on insulin metabolic signaling in the heart and the kidney. Cardiorenal Med 2011;1:102–112.
34. Aroor AR, McKarns S, Demarco VG, Jia G, Sowers JR: Maladaptive immune and inflammatory pathways lead to cardiovascular insulin resistance. Metabolism 2013;62:1543–1552.
35. Ferdinand KC, Rodriguez F, Nasser SA, et al: Cardiorenal metabolic syndrome and cardiometabolic risks in minority populations. Cardiorenal Med 2014;4:1–11.
36. Zhan, J, Bottiglieri T, McCullough PA: The central role of endothelial dysfunction in cardiorenal syndrome. Cardiorenal Med 2017;7:104–117.
37. R. H. K. Mak, "Effect of recombinant human erythropoietin on insulin, amino acid, and lipid metabolism in uremia," *Journal of Pediatrics*, vol. 129, no. 1, pp. 97–104, 1996.
38. R. H. K. Mak, "1,25-Dihydroxyvitamin D3 corrects insulin and lipid abnormalities in uremia," *Kidney International*, vol. 53, no. 5, pp. 1353–1357, 1998.
39. K. C. Lu, S. D. Shieh, S. H. Lin et al., "Hyperparathyroidism, glucose tolerance and platelet intracellular free calcium in chronic renal failure," *Quarterly Journal of Medicine*, vol. 87, no. 6, pp. 359–365, 1994.
40. J. M. Church and G. L. Hill, "Impaired glucose metabolism in surgical patients improved by intravenous nutrition: assessment by the euglycemic-hyperinsulinemic clamp," *Metabolism: Clinical and Experimental*, vol. 37, no. 6, pp. 505–509, 1988.
41. Y. Chen, S. Sood, K. McIntire, R. Roth, and R. Rabkin, "Leucine-stimulated mTOR signaling is partly attenuated in skeletal muscle of chronically uremic rats," *American Journal of Physiology - Endocrinology and Metabolism*, vol. 301, no. 5, pp. E873–E881, 2011.