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Insulin Resistance in End Stage Renal Disease

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Abstract
Introduction: *Insulin resistance (IR) is a risk factor for Cardiovascular mortality in ESRD patients. This study measured IR in patients with ESRD using homeostasis model assessment (HOMA)–IR model, and then derived insulin sensitivity (HOMA-%S) and beta cell function (HOMA-%B).*
Material: *The study was done between December 2016 and May 2017. Participants were divided into 2 groups: CKD stage V not on dialysis (CKDV-ND) and CKD V on hemodialysis (CKDVD). Fasting blood glucose, fasting insulin level and c-peptide were measured and IR, HOMA-%S, HOMA-%B were calculated by HOMA using Insulin level (IR-Ins) and C-peptide (IR-cp) level. GFR<15ml/min/1.73m2 was used to define ESRD.*
Observations: *The study included 20 patients in CKDV-ND and 22 patients in CKDVD group. The mean HOMA scores of IR-Ins were 0.56 ± 0.1 and 1.37 ± 0.9, while mean IR-cp were 5.1 ± 2.1 and 3.2 ± 1.7 in CKDVD and CKDVND groups respectively ($p<0.01$). Mean fasting plasma insulin levels were 9.8 ± 6.3 μU/mL in CKDV-ND, and 4.35 ± 0.7 μU/mL in CKDVD group ($p<0.001$). The HOMA-%B values were not statistically significant between groups ($p=0.16$), but HOMA-%S levels were significantly higher in the CKDVD group ($P<0.001$). The HOMA-%B using c-peptide was significantly higher in the CKDVD group ($p<0.001$). The IR-ins showed significant association with CRP levels in both the groups ($p<0.05$). IR-cp was significantly higher in the both the groups compared to IR-Ins ($p<0.001$), and was higher in the CKDVD group ($p<0.001$).*
Conclusion: *IR-Ins was decreased in CKDVD group compared to CKDV-ND, while IR-cp was higher in the dialysis group. Insulin sensitivity and beta cell function were also better in the dialysis group. This could reflect altered insulin dynamics or better control of uremia with dialysis. Measurement of IR using c-peptide could be a better method in patients with CKD.*
Keywords: *Insulin resistance, HOMA-IR, HOMA-%B, HOMA-%S c-peptide, CKD, ESRD.*

Background and Aims

Diabetes mellitus (DM) is a chronic disease which can evolve towards devastating micro- and macrovascular complications. DM is the most frequent cause of chronic kidney disease (CKD). The diabetic chronic kidney disease (CKD) is a clinical syndrome characterized by persistent albuminuria (albumin/creatinine ratio in the spontaneous urine ≥ 30 mg/g) and/or a sustained decline of the estimated glomerular filtration rate (eGFR) below 60 mL/min/1.72 m2[(1)]. Insulin resistance (IR) is a risk factor for Cardiovascular mortality in ESRD patients[(2)]. Insulin resistance is a frequent complication of uraemia, and also a risk factor for cardiovascular morbidity and mortality in patients with end stage renal disease (ESRD).

There have been few studies on insulin resistance in patients with ESRD, but data considering their correlation with insulin sensitivity and beta cell function is lacking[3,4]. This study measured IR in patients with ESRD using homeostasis model assessment (HOMA)–IR model, and then derived insulin sensitivity (HOMA-%S) and beta cell function (HOMA-%B).

Materials and Methods

This was a prospective case study carried over a period from December 2016 and March 2018. It included 42 patients of end stage renal disease out of which 22 on regular twice weekly hemodialysis and 20 were not on hemodialysis. Inclusion criteria were patients with end stage renal disease and who were receiving regular Hemodialysis. The exclusion criteria were factors or diseases affecting fasting insulin levels like congestive heart failure, patients on corticosteroids, patients on drugs like beta blockers, biguanides, ACE inhibitors, patients with end stage pulmonary disease & cancer. A total of 50 patients were enrolled for study, out of which 42 patients completed the study. 8 patients could not complete the study due to reasons like non compliance with the treatment or refusal to give informed consent etc. The remaining 42 patients were divided into two groups; Group I – CKDV-D(n=20) consisted of patients with ESRD who were on regular Hemodialysis. Group II – CKD not on hemodialysis (n=10) included patients with ESRD not on Hemodialysis.

CKDV-D included 12 patients with hypertensive nephropathy, 4 with chronic glomerulonephritis and 6 with obstructive uropathy. All these cases were receiving regular 4 hours of twice weekly maintenance Hemodialysis. The CKDV-ND included 14 patients with hypertensive nephropathy, 3 with chronic glomerulonephritis and 3 with obstructive uropathy. (Figure 1)

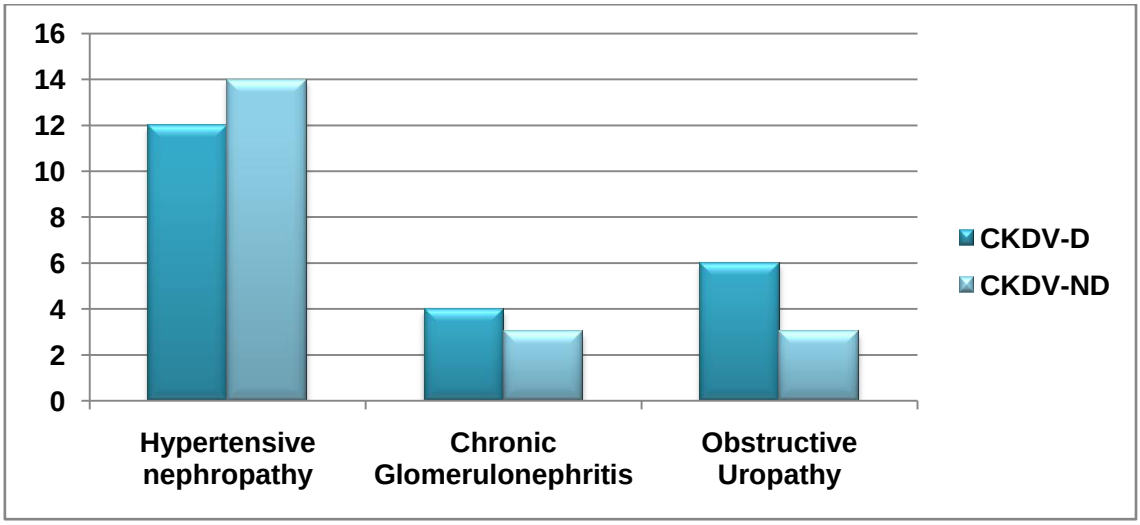

Figure 1. Showing distributions of patients in the two groups

All the patients were examined in detail and all basic laboratory investigations were done with a special emphasis on renal and various metabolic parameters. Blood samples were collected after an overnight fast of 8 hrs for basic biochemical / renal work up including serum fasting insulin levels, C-peptide levels, HBA1C, fasting and postprandial blood sugar levels at 8 AM in the morning. Adequacy of dialysis was adjudged by KT/V, which was kept above 1. (K –dialyser clearance of urea, t- dialysis time, V – patient's total body water).

Serum fasting insulin levels were measured by ADVIA CENTAUR CP model using Siemen's kit. C-peptide levels measured. Insulin resistance was calculated by HOMA-IR because of its simplicity. Data was analysed by using student t – test (paired and unpaired) and Pearson's correlation coefficient (r).

HOMA-IR [10] = Glucose X Insulin /22.5. Glucose in mmol/L (Figure 2)

Or HOMA-IR = Glucose X Insulin/405. Glucose in mass unit's mg/dL

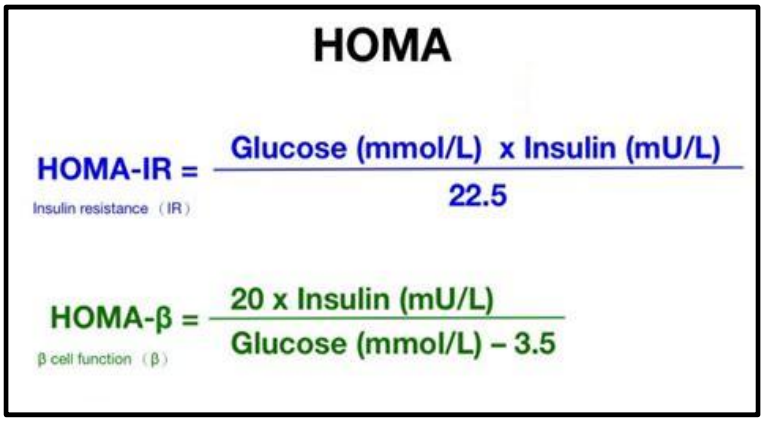

Figure 2 Formulae used for calculation of insulin resistance and Beta cell function

The area under curve for insulin, c-peptide and fasting glucose was calculated. HOMA-%S was used as marker for insulin sensitivity, while HOMA-%B was used as an index of beta cell function. Glomerular filtration rate (GFR) was calculated using the CKD-EPI creatinine equation [(5)]. A calculated GFR of 15ml/min/1.73m2 was used to define ESRD.

The main limitations of the clamp approach are that it is timeconsuming, labor intensive, expensive, and requires an experienced operator to manage technical difficulties. Thus, for epidemiological studies, large clinical investigations, or routine clinical applications (e.g., following changes in insulin resistance after therapeutic intervention in individual patients) application of the glucose clamp is not feasible.

Results

Non-diabetic ESRD patients were studied: 20 patients on HD treatment for 89.3 months, and 22 patients on conservative treatment. Mean fasting plasma insulin levels were 4.35 ± 0.7 µU/mL in dialysis group 9.8 ± 6.3 µU/mL in non-dialysis group($p<0.001$). HOMA scores for IR-Ins in dialysis group was 0.56 ± 0.1 and for non-dialysis group was 1.37 ± 0.9 and HOMA score for IR-cp was 5.1 ± 2.1 for dialysis group and 3.2 ± 1.7 for non dialysis group($p<0.01$).

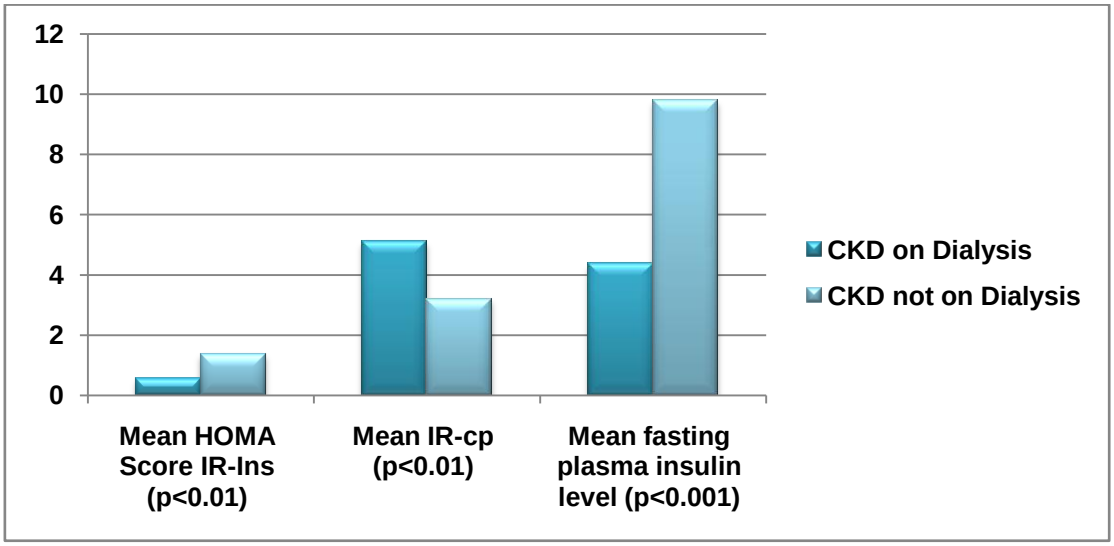

Figure 3 Observations in the Mean Insulin resistance calculated by Insulin level, C-peptide level and mean fasting insulin level in the two groups

All groups showed no significant differences for blood pressure, body weight, body mass index, fat free mass, body fat, and serum levels of albumin, total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides.

The HOMA-%B values were not statistically significant between groups (p=0.16), but HOMA-%S levels were significantly higher in the CKDVD group (P<0.001). The HOMA%B using c-peptide was significantly higher in the CKDVD group (p<0.001). The IR-ins showed significant association with CRP levels in both the groups (p<0.05). IR-cp was significantly higher in the both the groups compared to IR-Ins (p<0.001), and was higher in the CKDVD group (p<0.001).

Conclusion

IR-Ins was decreased in CKDVD group compared to CKDV-ND, while IR-cp was higher in the dialysis group. Insulin sensitivity and beta cell function were also better in the dialysis group. This could reflect altered insulin dynamics or better control of uremia with dialysis. Measurement of IR using c-peptide could be a better method in patients with CKD [(6)].

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