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Open label randomized controlled study to evaluate the role of Metformin to retard the progression of ADPKD

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Autosomal dominant polycystic kidney disease (ADPKD) is the most common of the inherited renal cystic diseases, contributes to 7- 10% of ESRD patients requiring dialysis. Currently the treatment for ADPKD lacks an effective therapy to retard the progression of the disease. AMPK(AMP activated protein kinase) activation may decrease cell proliferation in cyst wall and fluid secretion in cyst; thereby retarding kidney growth and disease progression. Metformin , a common oral hypoglycemic agent, activates AMPK. Though animal studies show promising result, human studies are few. Current study was planned with hypothesis that patients receiving metformin may have less increase in total kidney volume (TKV) at the end of 1 year follow up than the patients receiving placebo.
Material and methods:
70 ADPKD patients, with eGFR > 45ml/min were randomly assigned to either metformin or placebo arm in 1: 1 block. Diabetics, pregnant, breastfeeding females, patients suffering from liver disease were excluded. BP target was fixed at 130/80 and ACEI/ARB were used as 1st line antihypertensive. Primary outcome was percent change in TKV as measured by MRI with planimetry method. Secondary outcomes were percentage change in eGFR and proteinuria from baseline. difference in flank pain episodes requiring analgesic intake, numbers of minor and major adverse events. All the patients were subjected to a detailed clinical and laboratory evaluation at baseline, along with TKV estimation by MRI . In the metformin group patients were given Tab. Metformin 1000 mg/day in two divided doses to start with and increased to 1 gram twice daily. Patients in the placebo arm were given placebo tablets in BD dose. Patients were followed up at 3 monthly intervals. Physical examination and biochemical evaluation (serum creatinine, eGFR by MDRD formula, and 24 hour urine protein test) were performed at each visit. Repeat MRI were obtained at the end of 12 months. Any adverse effects reported during the study period were noted.
Results: Total 60 patients (30 patients in each group) was available for final analysis demographic and biochemical parameters like serum creatinine, eGFR and proteinuria were not different among the two groups at baseline with similar BP control in both arms. Mean TKV, as measured by MRI, at baseline, was 588.33 cc vs 563.71 cc in metformin vs control arm. At MO12 increase of TKV by 0.11% (intervention arm) and 1.01%(control arm) were observed , p value (0.001).When analysed among two age groups (< 45 and >45 years) percent change of TKV in metformin arm becomes even more significantly better (p value 0.00026) in the younger age group. Intervention arm shows better proteinuria control (M0,169.10 and M12: 141.10mg/day, 15.79% decrease and placebo arm M0:186.62 and M12 182.05 mg/day , 2.89% decrease, p value 0.00004), less eGFR decline though not significant. Pain episodes in metformin vs control arm were 72 vs 63., dyspepsia being the commonest side effect in metformin arm.
Conclusion: Treatment with metformin significantly slows the rate of growth of kidney volume and reduces proteinuria in patients with ADPKD at one year compared to the placebo group.