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Reduced Lipotoxicity Following Triple Therapy for 3 Years in New Onset T2DM

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Abstract:
We previously have shown that transition from NGT to IGT to T2DM is associated with a progressive increase in plasma FFA concentration and adipocyte insulin resistance (adipo-IR) (Diabetes 66:815-822, 2016). In the EDICT study, we demonstrated that initial Triple Combination therapy with drugs (pioglitazone, exenatide, metformin) that correct the basic pathophysiologic defects in T2DM was markedly superior than stepwise Conventional therapy (metformin → add SU → add glargine insulin) in reducing A1c and improving insulin resistance and beta cell function in newly diagnosed T2DM after 3 years (Diabetes Care 44:433-439, 2021). Herein, we compared the effect of Triple Combination therapy (n=79) versus Conventional (n=69) therapy on plasma FFA and adipo-IR and their relationship to insulin resistance, beta cell function, and hepatic steatosis/fibrosis (Fibroscan). Fasting adipo-IR (FPI x F-FFA) decreased by 50% (10.1±0.9 to 5.1±0.5, p<0.001) in Triple Therapy after 3 years and increased by 14% in Conventional Therapy (p<0.001). Adipocyte insulin sensitivity during OGTT (∆FFA/∆I) increased 3-fold in Triple Therapy (0.010±0.003 vs 0.03±0.001, p<0.001) and was unchanged in Conventional Therapy (0.12±0.001 vs 0.012±0.003) (p<0.001 vs Triple Therapy). During OGTT (0-120 min), ∆C-peptide (6.5±0.6 to 9.5±0.9, p<0.001) and Matsuda insulin sensitivity index (3.3±0.5 to 9.8±0.2, p<0.001) increased markedly in Triple Therapy, with (no change in Conventional Therapy.) and both correlated. Only insulin secretion in subjects receiving Triple Therapy measured with ∆CPEP0-120 at the end of study strongly correlated with increased FFA suppression (r=0.52 , p<0.01and r=0.59, respectively). Neither fasting FFA nor FFA during OGTTcorrelated with CAP (hepatic steatosis) or kPa (hepatic (fibrosis). CONCLUSION: reduced lipotoxicity contributes to enhanced beta cell function and insulin sensitivity following Triple Therapy.