Carotid Atherosclerosis Is Not Related to Hepatic Steatosis or Fibrosis in EDICT

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Background

The prevalence of nonalcoholic fatty liver disease (NAFLD) has increased dramatically over the last two decades and commonly is associated with type 2 diabetes (T2D), obesity, insulin resistance, and metabolic syndrome. In the EDICT (Efficacy and Durability of Initial Combination Therapy) trial we compared the efficacy of Triple (pioglitazone/ exenatide/ metformin) versus Conventional (metformin, sulfonylurea/ insulin) Therapy in newly diagnosed T2D patients.

Research Design

The EDICT study is an ongoing single center (Texas Diabetes Institute), randomized controlled trial (NCT01107717) designed to compare two therapeutic approaches for the management of patients with new onset T2DM: (1) initial combination therapy with medications (metformin/pioglitazone/exenatide) that correct core metabolic defects present in T2DM (Triple Therapy) versus (2) stepwise addition of medications that lower plasma glucose without correcting the underlying pathophysiologic abnormalities (Conventional Therapy) (metformin → glipizide →glargine insulin up to 60 units/day). If the HbA1c was > 6.5% on maximum therapy, the subject was considered to be a treatment failure. Interim analysis of the study results focusing on glycemic control, physiologic measurements of beta cell function, and insulin sensitivity previously have been reported (Diab Ob Metab 17:268-275, 2015; Diabetes Care 44:433-439, 2021). The initial study protocol was designed for 3-years of follow-up and was extended to 6-years of follow-up.

Participants

Participants were drug naïve, new onset T2DM. The current study includes 68 patients who completed the 3-year follow-up, entered the 3-year extension phase and had the measurements of hepatic fat content and liver fibrosis done at end of study (EOS). The mean follow-up was = 5.4±0.2 years (Table 1).

Table 1.

	Conventional Therapy	Triple Therapy	P Value
Number	39	29	
Age (years)	52±2	50±2	NS
Gender (% female)	41	51	NS
BMI (kg/m^2)	33.2±1.6	35.3±1.4	NS
Diabetes Duration (months)	4.5±1.1	5.4±1.4	NS
Baseline HbA1c (%)	8.6±0.4	8.7±0.4	NS
AST (IU)	28±3	26±2	NS
ALT (IU)	37±3	41±4	NS
AST/ALT Ratio	0.78±0.04	0.76±0.08	NS
Albumin (g/dl)	4.5±0.1	4.3±0.1	NS
Platelet count x 10^3	247±14	267±14	NS
Matsuda Index	2.9±0.4	3.3±0.6	NS
HOMA-IR	7.2±1.0	7.1±1.1	NS

Patient characteristics and laboratory tests at study end. Treatment failure represents the percentage of patients with HbA1c > 6.5% despite maximum therapy.

Methods

- FPG, FPI, HbA1c, OGTT, body fat (DEXA) at baseline and study end.
- Liver function tests, AST, ALT, platelets, albumin, were obtained in all subjects at baseline and annually for 6 years.
- Both plasma AST and ALT decreased significantly ($p<0.01$) with Triple therapy, while in Conventional Therapy neither ALT or AST changed significantly.
- Carotid intima media thickness, a well documented measure of atherosclerotic cardiovascular disease, was obtained at baseline and at study end.
- The increment in carotid IMT above baseline was significantly less in Triple versus Conventional Therapy (+5±2 vs +15±2 um, $p<0.0001$).
- Subjects received a vibration-controlled transient elastography (VCTE) (FibroScan) measurement at the end of study to provide a measure of liver fibrosis (LSM) and hepatic steatosis (CAP). Based upon the LSM value (kPa,) the severity of fibrosis was graded as: <6 (F0, normal), 6-8 (F1/2), 8-12 (F3), and 12+ (F4, cirrhosis); based upon the CAP value (dB/m) the severity of hepatic steatosis was graded as: 100-233 (S0), 234-268 (S1), 269-300 (S2), and 300+ (S3).
- Measurement of hepatic fat with MR spectroscopy (MRS) is the gold standard, and quantitation of hepatic fat content (MRS-PDFF) was performed using a 3- Tesla MRI Scanner. At the time that EDICT was initiated the importance of NASH as a complication of T2DM was less well established. Moreover, the FibroScan was not approved for clinical use by the FDA (April, 2013) until after the study was initiated (2010). Therefore, baseline measurements of hepatic fat content and fibrosis were not performed.

Results

- 27 of 39 (69%) subjects receiving Conventional Therapy had grade 2/3 steatosis compared to 9 of 29 (31%) in triple Therapy ($p<0.01$) (Table 2).
- 10 of 39 (26%) receiving Conventional Therapy had 3/4 fibrosis versus 2 of 29 (7%) in Triple Therapy ($p=0.003$) (Table 2).
- Severity of steatosis, measured by CAP ($r=0.42$, $p<0.001$), and severity of fibrosis, measured by LSM ($r=-0.48$, $p<0.001$), correlated inversely with Matsuda Index of insulin sensitivity.
- No correlation was observed between carotid IMT and CAP score, when the triple and Conventional Therapy groups were analyzed collectively (or individually) (Figure 1).
- Similarly, no correlation was observed between carotid ITM or change in carotid IMT versus severity of hepatic fibrosis (Figure 2).

Table 2. Liver fibrosis and steatosis scores determined by FibroScan in type 2 diabetes patients at study end (5.4 years)

Fibrosis Grade	Conventional Therapy	Triple Therapy	Steatosis Grade	Conventional Therapy	Triple Therapy
F0/F1	28	27	S0	7	14
F2	1	0	S1	5	6
F3	7	2	S2	9	2
F4	3	0	S3	18	7
F3/F4 (N,%)	10/39 (26%)	2/29 (7%)**	S2/S3 (N,%)	27/39 (69%)	9/29 (31%)*

* $p<0.01$ and **$p=0.003$ vs Conventional Therapy

Figure 1.

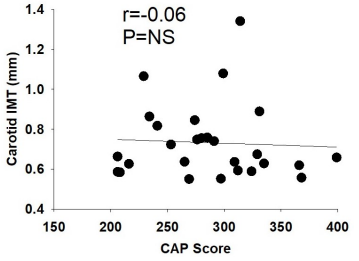
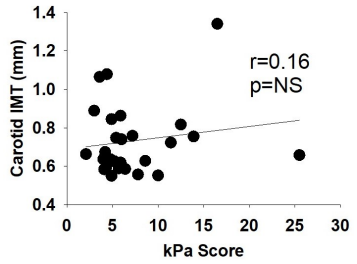


Figure 2.



Conclusion

Severity of atherosclerosis, measured by carotid IMT, is not related to either severity of hepatic steatosis or fibrosis in EDICT.