Hepatic Steatosis, Fibrosis, and Insulin Resistance: Implications for Therapy

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Aim

To compare the efficacy of Triple Therapy (metformin/exenatide/pioglitazone) versus Conventional Therapy (metformin→glipizide→glargine insulin) on liver fat, hepatic fibrosis, and insulin resistance in newly diagnosed T2DM patients in EDICT.

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) (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. 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.
- 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 grade 3/4 fibrosis versus 2 of 29 (7%) in Triple Therapy ($p=0.003$) (Table 2).
- Triple Therapy (pioglitazone/exenatide/metformin) increased Matsuda Index of insulin sensitivity 3-fold, whereas Conventional Therapy had no effect on insulin sensitivity (Fig.1).
- 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 (Fig.2).
- Severity of steatosis by MRI-PDFF also correlated with insulin resistance (HOMA-IR and Matsuda Index) ($r=0.42$, $p<0.05$).

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.

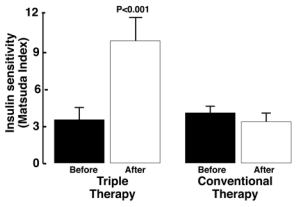
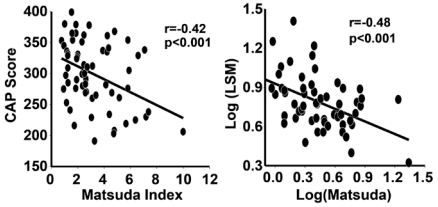


Figure 2.



Conclusion

1) T2DM subjects treated with Triple Therapy had less hepatic steatosis and fibrosis and markedly improved insulin sensitivity versus Conventional Therapy after 6 years.
2) Hepatic steatosis and fibrosis were strongly and inversely correlated with insulin resistance.
3) Antidiabetic agents that ameliorate insulin resistance reduce hepatic fat and prevent fibrosis.