The effects of CFTR modulator therapy on endocrine pancreatic function in patients with cystic fibrosis: a systematic review and meta-analysis

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Magyar Gasztroenterológiai Társaság 66. Nagygyűlése

Introduction

CFTR modulators represent a groundbreaking therapeutic approach in cystic fibrosis (CF) management, targeting the underlying cause of the disease. These therapies have the **potential to directly influence pancreatic beta-cell function** and pathways involved in insulin secretion, thereby improving the glycemic status of people with CF (pwCF).

Aims & Methods

We aimed to evaluate the effect of CFTR modulator therapy on endocrine pancreatic function in patients with CF. **A systematic search of three databases** (PubMed, Embase, and CENTRAL) was conducted **up to March 6, 2024**, to identify studies examining the impact of CFTR modulators on glucose metabolism in pwCF comparing variables before and after CFTR modulator therapy. Outcomes of interest included measures from oral glucose tolerance tests (OGTT), continuous glucose monitoring (CGM), and glycated hemoglobin (HbA1c). Meta-analysis was initiated using random-effects models to estimate **pooled mean differences (MD) and 95% confidence intervals (CIs**). Subgroup analyses were created based on CFTR modulators elexacaftor/tezacaftor/ivacaftor (ETI), lumacaftor /ivacaftor (LUMA/IVA)) and length of therapy. **Covariate regression analyses** were made to assess the relationship between therapy length and pooled MD. A p-value less than 0.05 was considered to be statistically significant. The study protocol was registered in PROSPERO with registration number **CRD42024516198.**

Results

A total of 1081 records were identified, 73 of which proved to be eligible for inclusion. Pooled analysis of CFTR modulators did not demonstrate a significant effect on 60-minute and 120-minute plasma glucose levels (**Table 1**). However, **ETI therapy** resulted in significantly **reduced plasma glucose levels at 120 minutes (MD: -1.80 mmol/L; 95% CI -2.60, -1.00)** (**Figure 1**). Average glucose, glycemic variability, and % of time below 3.9 mmol/L interstitial glucose level were comparable before and after therapy. Meta-regression revealed no significant effect of length of therapy on 60- and 120-minute plasma glucose levels (p=0.512 and p=0.631 respectively).

Outcome		Subgroup/ Total	N° of studies (N° of patients)	Result of the meta-analysis (MD with 95% CI)	Statistical heterogeneity I^2 [95% CI]
OGTT	**60-minute plasma glucose**	Total	11 (253)	0.34 mmol/L [-0.54, 1.21]	79% [62, 88] p<0.001
		LUMA/IVA	4 (72)	1.41 mmol/L [-0.60, 3.42]	80% [46, 92] p=0.02
		ETI	6 (133)	-0.05 mmol/L [-1.28, 1.18]	81% [58, 91] p<0.001
	120-minute plasma glucose	Total	15 (338)	-0.62 mmol/L [-1.29, 0.04]	80% [67, 87] p<0.001
		LUMA/IVA	5 (116)	-0.73 mmol/L [-1.90, 0.44]	68% [18, 88] p=0.013
		ETI	**3 (86)**	**-1.80 mmol/L [-2.60, -1.00]**	**0% [0, 90] p=0.750**
CGM	**Average glucose**	Total	5 (65)	-0.16 mmol/L [-0.49, 0.17]	0% [0, 79] p=0.428
	Glycemic variability	Total	3 (30)	-0.12 mmol/L [-0.30, 0.06]	0% [0, 90] p=0.859
	% of time <3.9 mmol/L glucose	Total	4 (41)	-0.12% [-0.60, 0.37]	0% [0, 85] p=0.460

Table 1. Summary of results

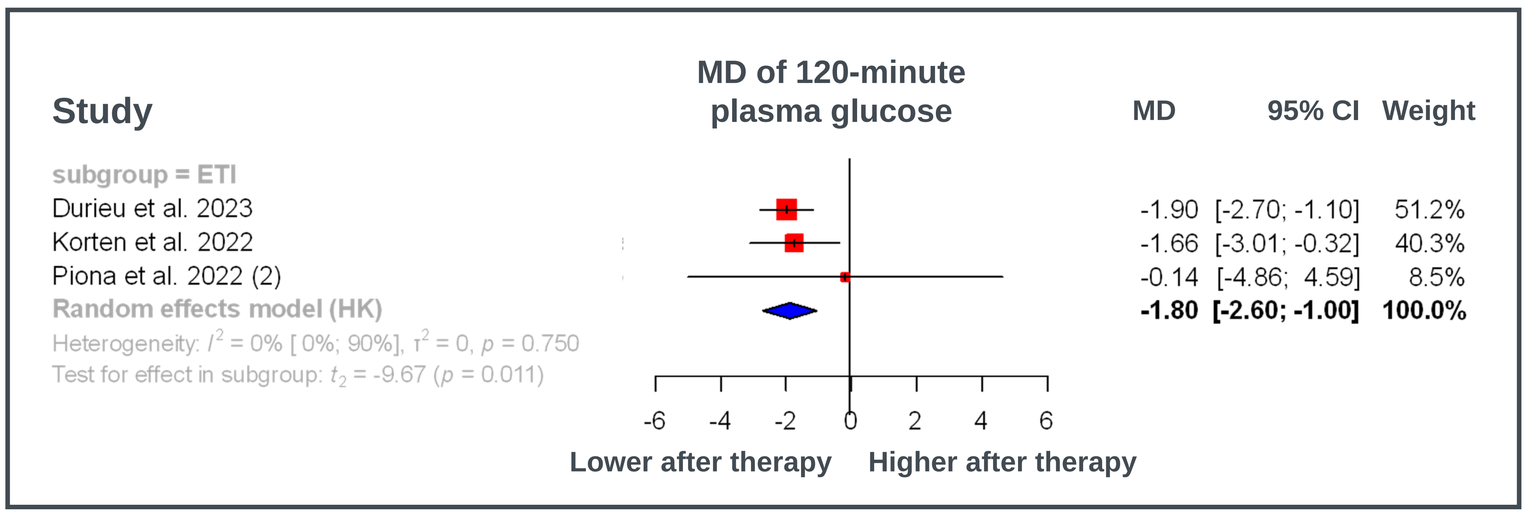

Figure 1. Effect of ETI therapy on 120-minute OGTT glucose level

Conclusions

Our results revealed an **improvement in the 120-minute OGTT plasma glucose** level in the **elexacaftor/tezacaftor/ivacaftor** subgroup. The absence of significant changes in other analyses may indicate that these medications could potentially slow or halt the deterioration of glucose metabolism. Further prospective studies are required to overcome the limitation of a relatively small patient number and to validate our findings.

National Research, Development and Innovation Fund (NRDI Fund) FK 138929.

CF Trust Strategic Research Consortium Grant NU-000600.