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Does elexacaftor-tezacaftor-ivacaftor therapy (Kaftrio™) significantly raise lipid profile parameters? A longitudinal cohort study

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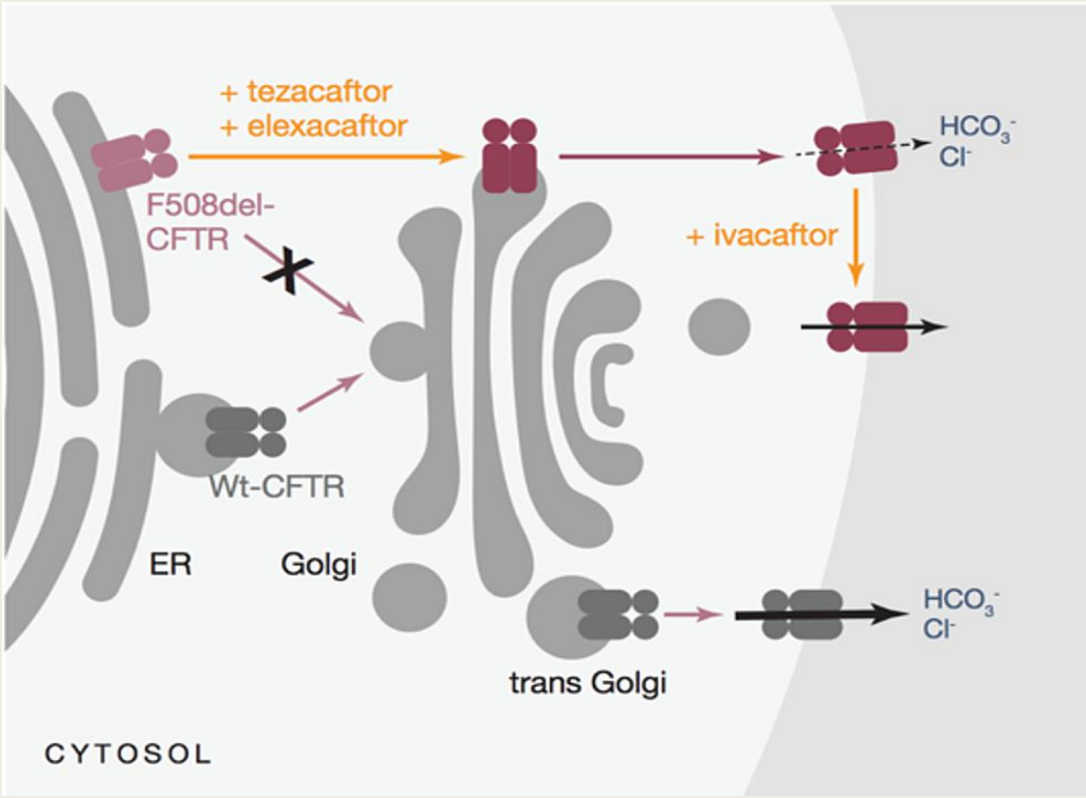
Project Origins

- Elective project as a final year medical student at Aberdeen Medical School.
- Personal interest in respiratory medicine and cystic fibrosis.
- Aberdeen Medical School – the single medical school covers Grampian, the Western Isles, the Highlands, Orkney and Shetland.
- NHS Grampian – 1 of 14 NHS health boards in Scotland, UK.

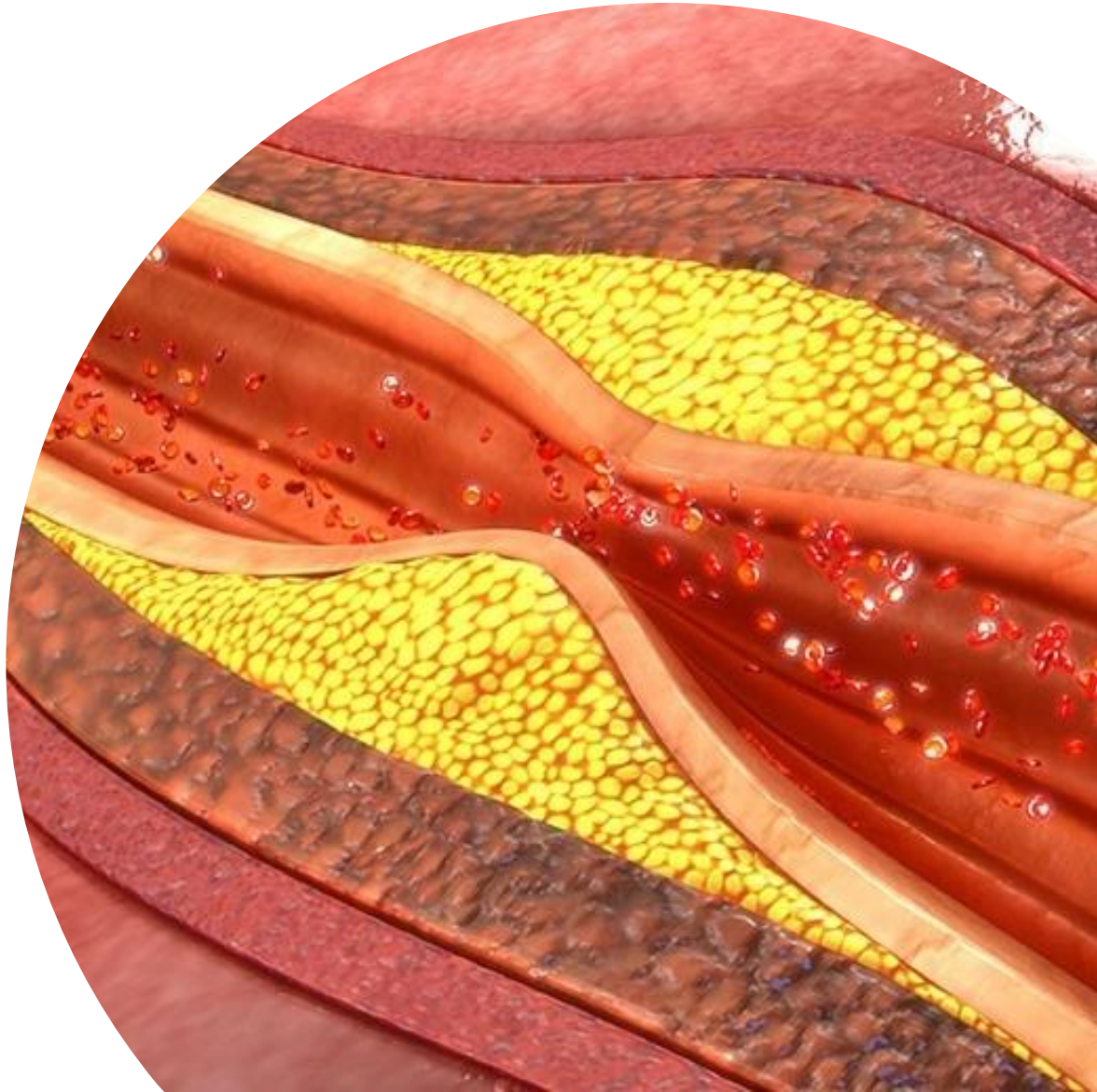
Introduction

- Kaftrio™ (Trikafta) has revolutionised cystic fibrosis (CF) treatment causing significant improvements in the quality of life and clinical outcomes (Heijerman *et al*., 2019) (Middleton et al., 2019).
- It targets the F508delta mutation of the CFTR gene. This mutation makes up around 90% of CF cases (Zaher *et al*., 2021).



The Effects of Kaftrio on the Lipid Profile

- Kaftrio™ may be associated with a rise in lipid profile parameters (Petersen *et al*., 2021).
- Rises in LDLs and total cholesterol are associated with the increased incidence and severity of atherosclerotic plaques and vascular disease.
- Uncorrected coronary artery disease and myocardial infarction are absolute contraindications for lung transplants (Weill, 2018).



The Lipid Profile

- Made up of four components –
  - **Total cholesterol** – Total amount of HDLs and LDLs within the blood. Contributes to atherosclerotic plaque formation.
  - **Low-density Lipoproteins (LDLs)** –Transports cholesterol from the liver to other body cells. Contributes to atherosclerotic plaque formation (Wadhera et al., 2016).
  - **High-density Lipoproteins (HDLs) –** Known as 'good fats' as they clear LDLs from blood vessels (Feig et al., 2014).
  - **Triglycerides –** Energy store within the body which can be split to free fatty acids and glycerol.

Total cholesterol and LDLs are the most **CLINICALLY** significant.

Aims

Aim - to determine if Kaftrio™ causes a significant rise in the lipid profile parameters of CF patients within NHS Grampians CF service.

- ***Primary outcome*** – *total cholesterol.*
- ***Secondary outcomes*** – *HDL levels, LDL levels and triglyceride levels.*

- **Novel findings** - Subgroup analysis for total cholesterol with multiple linear regression for diabetic status and sex.

Methods

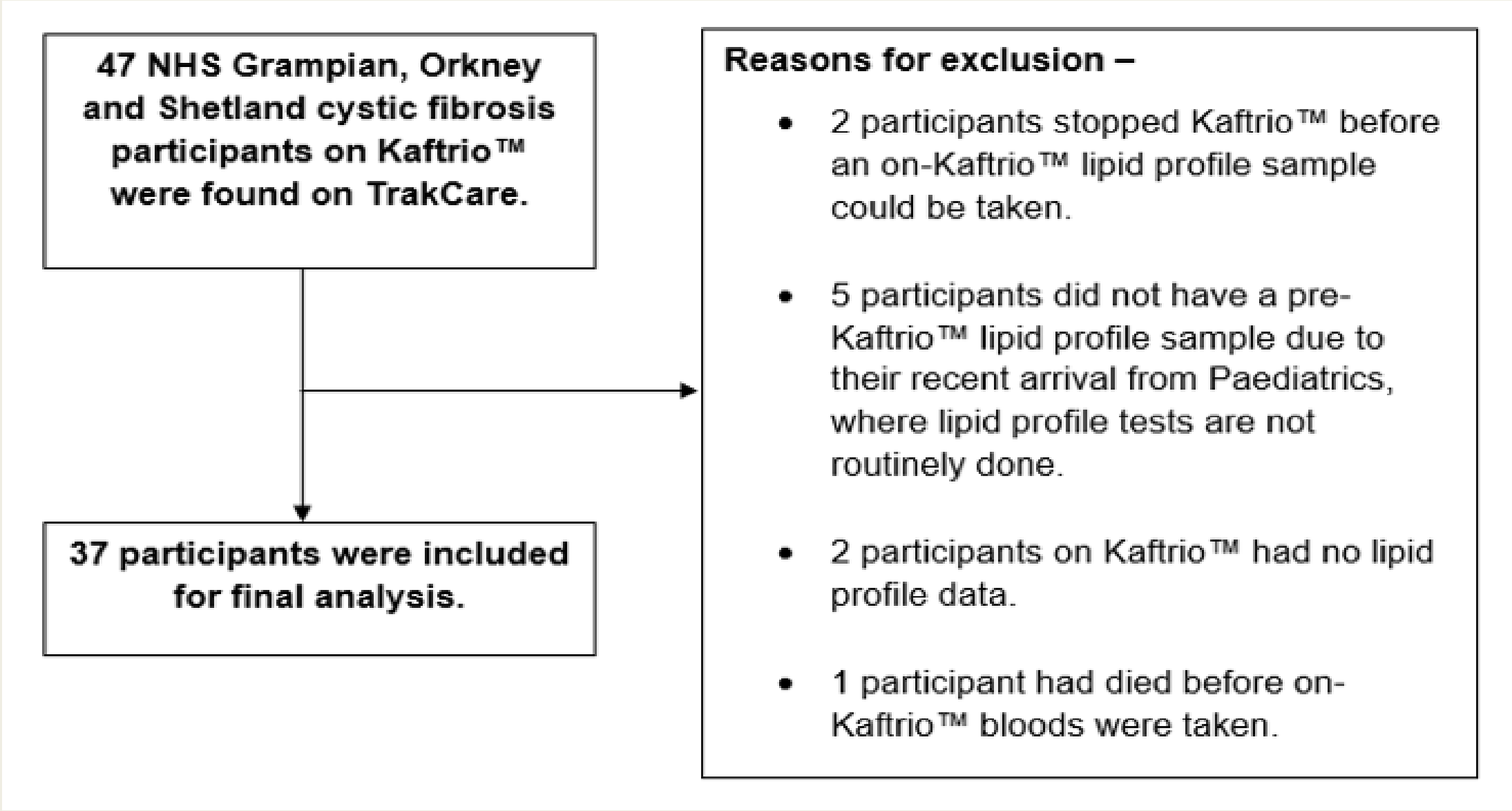
- Design – a single-centre retrospective longitudinal cohort study.
- Population – CF patients on Kaftrio that attended the CF clinic in Aberdeen Royal Infirmary (ARI).

Table 1: Inclusion criteria for the participants of this study.

Inclusion Criteria
CF diagnosis.
NHS Grampian, Orkney or Shetland patients.
On Kaftrio™ for at least one year.
Participants with a CF genotype which is compatible with Kaftrio™ administration.
Participants with exocrine or endocrine pancreatic sufficiency or insufficiency or both.
Participants of any age, sex, diabetic status and BMI.

- Outcomes measured - The most recent lipid profile test on Kaftrio and the most recent test before Kaftrio.

Results – Data Collection



Results – Participant Characteristics

Characteristic	Result (%) ± SEM n = 37
Age (years)	36 ± 2.02
The average duration of Kaftrio™ treatment since the most recent lipid profile test (years)	1.35 ± 0.06
BMI (Kg/m^2)	23.74 ± 0.73
Sex	
Male	21 (56.75%)
Female	16 (43.24%)
Pancreatic insufficiency	
Yes	34 (91.89%)
No	3 (8.11%)
Genotype (Delta F508)	
Homozygous	21 (56.75%)
Heterozygous	16 (43.24%)
Other	
Diabetes	14 (37.84%)
Percutaneous Endoscopic Gastrostomy (PEG) tube	3 (8.11%)
Port (IV access for long-term antibiotics)	13 (35.14%)
Medication associated with dyslipidaemia	
Statins	0 (0.00%)
Creon	34 (91.89%)
Steroid inhaler	19 (55.88%)
Long-term prednisolone	2 (5.41%)
Loop diuretics	1 (2.70%)

Results – Total Cholesterol

- Using the Wilcoxon test, P=0.0003 shows very strong evidence that Kaftrio™ significantly raises the total cholesterol levels in CF participants.
- A Z-score of -3.625 illustrates the null hypothesis that Kaftrio™ does not cause a rise in total cholesterol levels can be rejected.
- Both variables together showed R^2=0.008 within the model summary, showing that this model explains only 0.8% of the variation in the data.

	Pre-Kaftrio™ (n = 37) (mmol/L)	On Kaftrio™ (n=37) (mmol/L)
Mean	3.73	4.11
SEM	0.14	0.16
Wilcoxon test	0.0003	
Z-score	- 3.625	

Model Summary[b]

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.087[a]	.008	-.051	.55423

a. Predictors: (Constant), sex_numeric, diabetes_numeric

b. Dependent Variable: Total_cholesterol_change

Coefficients[a]

Model		Unstandardized Coefficients B	Unstandardized Coefficients Std. Error	Standardized Coefficients Beta	t	Sig.	95.0% Confidence Interval for B Lower Bound	95.0% Confidence Interval for B Upper Bound
1	(Constant)	.344	.397		.868	.392	-.462	1.151
	diabetes_numeric	.081	.188	.074	.431	.669	-.301	.463
	sex_numeric	-.050	.184	-.046	-.270	.789	-.423	.324

a. Dependent Variable: Total_cholesterol_change

Results – High-density Lipoproteins

- The Wilcoxon test showed P=0.363 therefore Kaftrio™ does not significantly raise the HDL levels in CF participants.
- A Z-score of -0.915 provides further evidence that the null hypothesis that Kaftrio™ does not cause a rise in HDL levels cannot be rejected.

	Pre-Kaftrio™ (n = 37) (mmol/L)	**On Kaftrio™ (n=37) (mmol/L)**
Mean	1.31	1.32
SEM	0.06	0.06
Wilcoxon test	0.363	
Z-score	-0.915	

Results – Low-density Lipoproteins

- The Wilcoxon test showed P=0.001 therefore Kaftrio™ significantly raises the LDL levels in CF participants.
- A Z-score = -3.870 shows that the null hypothesis that Kaftrio™ does not cause a rise in LDL levels can be rejected.

	Pre-Kaftrio™ (n=37) (mmol/L)	**On Kaftrio™ (n=37) (mmol/L)**
Mean	1.88	2.27
SEM	0.11	0.14
Wilcoxon test	0.001	
Z-score	-3.870	

Results – Triglyceride levels

- The Wilcoxon test was calculated to be P=0.101 therefore Kaftrio™ does not significantly raise the levels in CF participants.
- A Z-score = -1.640 conveys that the null hypothesis that Kaftrio™ does not cause a rise in triglyceride levels cannot be rejected.

	Pre-Kaftrio™ (n=37) (mmol/L)	**On Kaftrio™ (n=37) (mmol/L)**
Mean	1.26	1.13
SEM	0.12	0.10
Wilcoxon test	0.101	
Z-score	-1.640	

Discussion –Total Cholesterol

- Although a statistically significant rise was present, these levels are not currently clinically significant to require treatment.
- Further monitoring over time is required to determine whether clinically dangerous hyperlipidaemia does occur.
- Similar results of significantly higher total cholesterol of 0.21mmol/L/yr have been seen in a study of 134 adults with CF and diabetes with $P<0.0005$ (Petersen *et al*., 2021).

Discussion – HDLs and LDLs Levels

- **HDL Levels –**
  - This insignificant change is likely detrimental to these participants as HDLs have a crucial role in removing cholesterol from vessels to the liver for degradation, thus reducing atherosclerotic disease (Brewer, 2004).

- **LDL Levels –**
  - This significant rise was not deemed clinically significant. However, this rise may continue over the life-long administration of Kaftrio™.
  - Petersen et al. also showed a significant rise in LDL levels with a mean average increase of 0.47mmol/L/yr ($P<0.0005$).
  - May be due to increased oral intake and dietary fat for Kaftrio™ administration and improved pulmonary health thus less energy expenditure used on fighting infections.

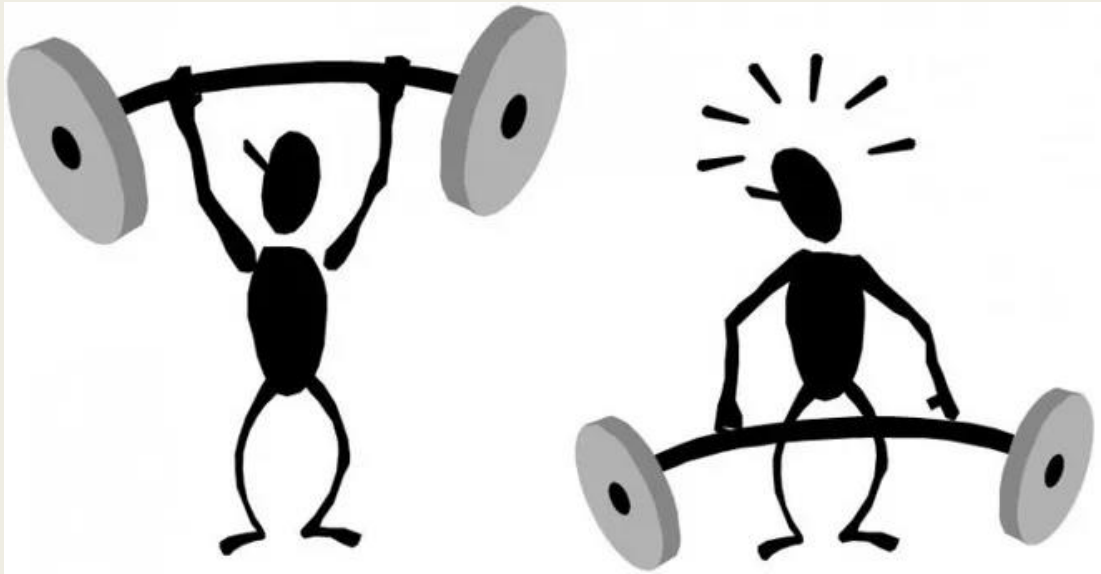
Discussion – Triglyceride Levels

Triglyceride Levels –

- Statistically insignificant results were seen by Petersen et al. (P=0.92).
- Role of triglycerides as an acute phase reactant and thus the decrease in infections may prevent an increase in the triglyceride levels of these patients (Grønholdt et al., 2001).

Discussion - Strengths and Limitations

- Strengths –
  - This study is the first of its kind to include diabetic and non-diabetic CF participants with a specific subgroup analysis of total cholesterol.
  - The 37 participants were representative of the CF population with regard to sex, diabetic status and age.
- Limitations –
  - Difficult to control variables such as medication adherence and diet.
  - Small sample size.



Discussion – Implications & Recommendations

- The data regarding Kaftrio™ and its effect on lipids is very limited and the cause of this dyslipidaemia is not yet clear.
- Further studies are required that specifically analyse multiple lipid profiles over several years to determine if this significant rise in lipid profile parameters becomes clinically significant.
- Larger cohorts of participants and further subgroup analysis may successfully determine specific groups most at risk of hyperlipidaemia.
- Any clinical recommendations based on this study alone would be too speculative at this time.

Conclusions

- Kaftrio™ is a lifelong and life-changing medication.
- The young age and the increased life expectancy of CF patients highlight the importance of rigorous monitoring of the biochemical impact that triple therapy may have on its patient cohort.
- Long-term studies with larger cohorts and more rigorous subgroup analysis are needed to determine the true clinical impact of Kaftrio™ on the lipid profile and vascular health of these patients.

References and Questions

Scan this QR code for references.