Role of triglyceride monitoring in patients with familial chylomicronemia syndrome

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Purpose

Familial chylomicronemia syndrome (FCS) is an ultra-rare genetic disease characterized by extremely high plasma triglycerides (TGs).[1; 2] Patients with FCS have persistently elevated TGs >880 mg/dL,[3] and are not responsive to current TG-lowering therapies, indicating low lipoprotein lipase activity.[4; 5]

Typically, FCS presents in childhood and is characterized by episodes of abdominal pain, recurrent acute pancreatitis (AP), eruptive cutaneous xanthomas, lipemia retinalis, lipemic blood and hepatosplenomegaly.[1; 6; 7; 8; 9; 10] Manifestations have a considerable impact on the daily life of a patient, translating to diminished health-related quality of life (HRQoL).[11; 12]

High levels of plasma TGs and accumulation of chylomicrons in the blood result in hyperviscosity of blood plasma.[13; 14] Acute pancreatitis can lead to chronic pancreatitis, pancreatic insufficiencies, Type 3 diabetes, organ failure and death.[15; 16] Blood and plasma viscosity measures are correlated with the level of TGs[17; 18; 19; 20] and TG-lowering therapy reduces plasma and serum viscosity,[21] suggesting that TG levels are an important clinical factor for the management of FCS.

However, due to a lack of clinical trials specifically investigating the impact of TGs and the difficulty in isolating their effects from other plasma lipoproteins, there is a lack of consensus on the role of TG reduction in the management of patients with FCS. The aim of this systematic literature review is to explore the association between chylomicronemia levels of TGs in the blood and disease burden, to further understand the importance of using TG reduction as a treatment goal in this patient population.

Methods

- A systematic literature search was conducted using electronic databases PubMed and the Cochrane Library
- The search strategy was designed to capture the impact of elevated TG levels on disease burden within the FCS patient population and investigate the role of TG reduction in disease management, namely:
    - Association of TGs with disease burden
    - Reduction of TG levels as a treatment target
    - Clinically meaningful levels of TG reduction
- The keywords were combined using appropriate Boolean operators, for example: (“FCS” OR “Hypertriglyceridemia”) AND (“Impact of” OR “Role of” AND “Elevated triglycerides”) AND (“Burden” OR “QoL” OR “Mortality”).
- Selection procedure:
    - First pass – abstracts were screened by a single investigator using predetermined inclusion and exclusion criteria
    - Second pass – abstracts meeting inclusion criteria were retrieved as full text and further reviewed
    - Table 1 summarises inclusion and exclusion criteria used in the screening process

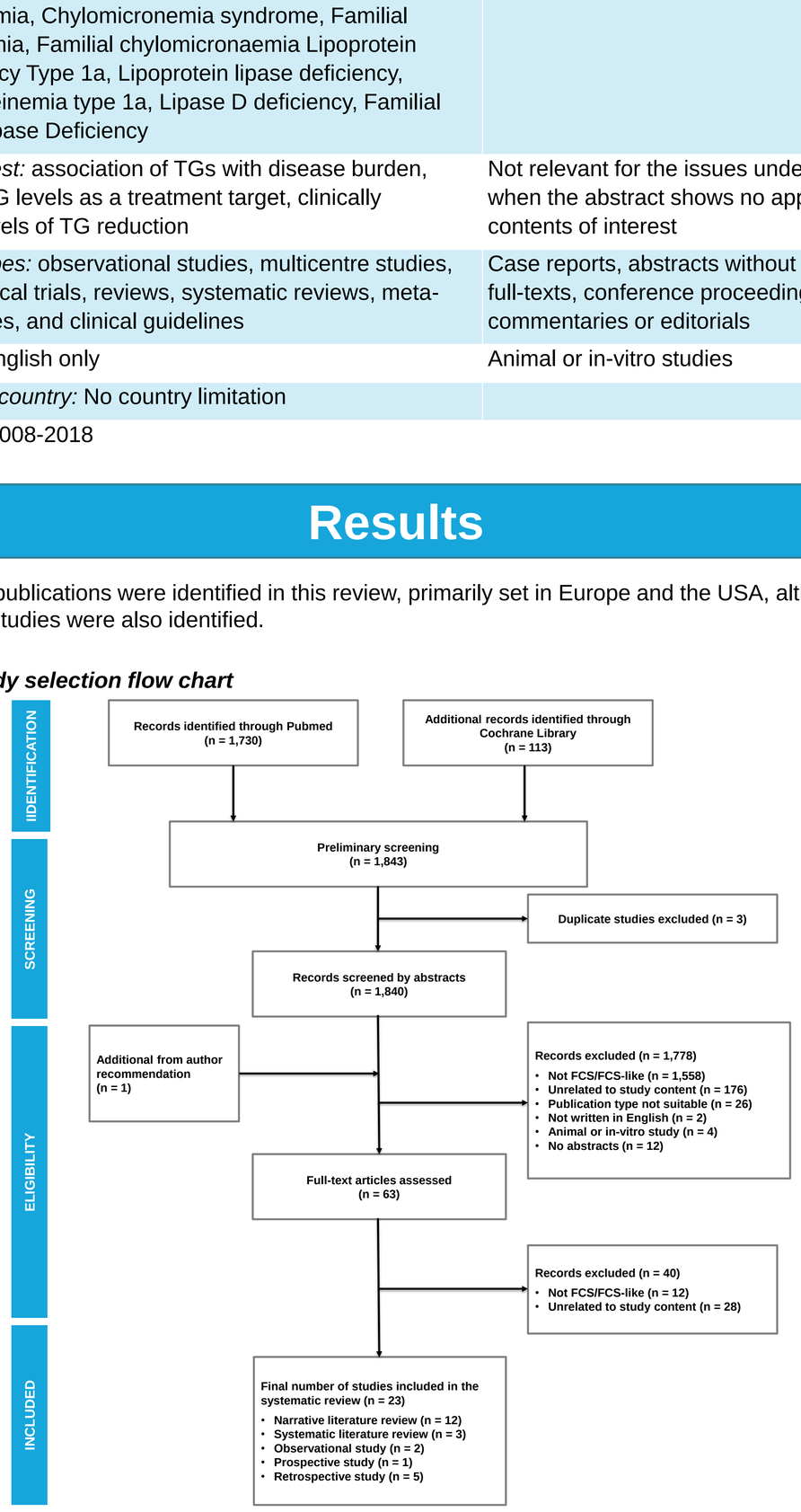
Table 1. Study inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Disease specification: FCS, Type 1 hyperlipoproteinemia, Chylomicronemia, Chylomicronemia syndrome, Familial chylomicronemia, Familial chylomicronaemia Lipoprotein lipase deficiency Type 1a, Lipoprotein lipase deficiency, Hyperlipoproteinemia type 1a, Lipase D deficiency, Familial Lipoprotein Lipase Deficiency	Not consistent with the inclusion criteria
Areas of interest: association of TGs with disease burden, reduction of TG levels as a treatment target, clinically meaningful levels of TG reduction	Not relevant for the issues under inquiry e.g., when the abstract shows no apparent contents of interest
Publication types: observational studies, multicentre studies, pragmatic clinical trials, reviews, systematic reviews, meta-analysis studies, and clinical guidelines	Case reports, abstracts without retrievable full-texts, conference proceedings, letters, commentaries or editorials
Languages: English only	Animal or in-vitro studies
Restriction by country: No country limitation	
Time period: 2008-2018	

Results

Twenty-three publications were identified in this review, primarily set in Europe and the USA, although multinational studies were also identified.

Figure 1. Study selection flow chart



Association of TGs with disease burden

- All 23 studies provided data describing positive association of elevated levels of TGs with disease burden, i.e. disease complication and manifestations. These include pancreas-related events, cardiovascular disease (CVD) events, mortality, organ failure, chronic kidney disease, diabetes, obesity, eruptive xanthomas, lipemia retinalis, neurological manifestations, fatty liver and hepatosplenomegaly.
- Acute pancreatitis was the most commonly described disease burden. The association of high TG levels, particularly above 1,000 mg/dL, with AP risk appears to be well established.
- High triglyceride is described as the third leading cause of AP,[22] accounting for 10% of cases.[6; 22; 23] There is some suggestion that HTG-induced AP is associated with more severe complications compared to AP with other etiologies. [24; 25; 26; 27]

Reduction of TG levels as a treatment target

- Out of the 23 studies, 16 included recommendations advocating for the reduction of TG levels as a treatment target for patients with hypertriglyceridemia.
- Of these, nine recommended that reduction of TG should be a primary goal for patients with severe HTG. The threshold levels for patients who should undergo immediate treatment for TG reduction varied from 440 mg/dL[28] to 500 mg/dL[29; 30; 31] to 885 mg/dL.[3; 5; 7; 10; 11; 32; 33; 34; 35; 36]
- There is a significant relationship between TG levels and prevalence of pancreatitis and pancreatitis severity. Prevalence of pancreatitis is progressively higher with increasing levels of serum TG, noticeable from 200 mg/dL.[37]

Clinically meaningful levels of TG reduction

- The reported threshold level at which risk of pancreatitis is increased varied from 200 mg/dL to 1,000 mg/dL, while for CVD events the threshold values varied from 150 mg/dL to 500 mg/dL (Table 2).
- Two studies specify that the aim of therapy should be to achieve the lowest TG values possible with currently available interventions.[38; 39] Specifically, in patients with FCS, the target level to reduce the risk of AP is 885 mg/dL.[36]

Table 2. Clinically meaningful reductions of TG levels

Reference	Study type	Patient pop	TG level (mg/dL) at which risk of pancreatitis is reported to increase	TG level (mg/dL) at which risk of CVD is reported to increase
Christian et al. 2014	Retrospective study	Severe HTG	Not specified	500
Frankova et al. 2018	Retrospective study	HTG	200	Not specified
Hegele et al. 2014	Narrative literature review	HTG	Not specified	175
Kushner & Cobble 2016	Narrative literature review	HTG	Not specified	150
Maki et al.2012	Narrative literature review	HTG	500	200
Moulin et al. 2018	Narrative literature review	FCS	177	Not specified
Rashid et al. 2016	Retrospective study	Severe HTG	1,000	Not specified
Toth 2016	Narrative literature review	HTG	500	Not specified
Viecili et al. 2017	Narrative literature review	HTG	500	Not specified

Conclusions

Our systematic literature review highlights an association of severe HTG with a range of clinical burdens. There is consensus in the field that elevated serum TGs are a prognostic risk factor for AP. Patients with HTG are at risk of more severe AP complications than non-HTG patients. Early identification and administration of TG-lowering treatment is important in patients with HTG, particularly those with severely elevated TG levels. Patients with severe HTG may be underdiagnosed and undertreated.30 Increased patient and clinician awareness are needed on the clinical burden of severe HTG and the importance of monitoring and reducing TGs to manage the disease and prevent associated complications.

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