Familial chylomicronemia syndrome (FCS) is an ultra-rare genetic disease characterized by extremely high plasma triglycerides (TGs). Patients with FCS have persistently elevated TGs >800 mg/dL, and are not responsive to current TG-lowering therapies, indicating low lipoprotein lipase activity.

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.\(^1\) Manifestations have a considerable impact on the daily life of a patient, translating to diminished health-related quality of life (HRQoL).\(^2\)

High levels of plasma TGs and accumulation of chylomicrons in the blood result in hyperlipidemia of blood plasma.\(^3\) Acute pancreatitis can lead to chronic pancreatitis, pancreatic insufficiency, Type 3 diabetes, organ failure and death.\(^4\) Blood and plasma viscosity measures are correlated with the level of TGs.\(^5\) TG-lowering therapy reduces plasma and serum viscosity,\(^6\) 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 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

- 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 criteria**:
  - 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

- **Systematic literature review**
  - Abstracts meeting inclusion criteria were retrieved as full text and further screened.

- **Exclusion criteria**: Not relevant for the issues under inquiry e.g.,

- **Record screening**

- **Time period**: 2003–2018

#### Inclusion criteria

- **Disease specification**: FCS, Type 1 hyperlipoproteinemia, Chylomiconemia, Chylomiconemia syndrome, Familial chylomicronemia, Familial chylomicronemia Lipoprotein lipase deficiency Type 1a, Lipoprotein lipase deficiency, Hyperlipoproteinemia type 1a, Lipase D deficiency, Familial Lipoprotein Lipase Deficiency

- **Areas of interest**: association of TGs with disease burden, reduction of TG levels as a treatment target, clinically meaningful levels of TG reduction

#### Publication types: observational studies, multicentre studies, pragmatic clinical trials, reviews, systematic reviews, meta-analysis studies, and clinical guidelines

- **Languages**: English only

- **Restriction by country**: No country limitation

#### Results

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

### Purpose

Association of TGs with disease burden

- 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, typically above 1,000 mg/dL, with this complication is well documented.\(^7\)

- High triglyceride is described as the third leading cause of AP,\(^8\) accounting for 10% of cases.\(^9\) There is some suggestion that HTG induced AP is associated with more severe complications compared to AP with other etiologies.

### Retrospective 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.

- 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.\(^10\)

### 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 specifically state that the aim of therapy should be to reduce TG levels to a level that is considered to be clinically meaningful for the patient’s particular situation.

### Conclusions

Our systematic literature review highlights an association of severe HTG with a range of clinical burdens. Through its unique form, Familial chylomicronemia Syndrome (FCS) is 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 HTG patients, particularly those with severely elevated TG levels. Patients with severe HTG may be underdiagnosed and undertreated. 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.

### References