Clin Investig Arterioscler. 2018;30(5):193–196

Sociedad Española de Arteriosclerosis

CLÍNICA E INVESTIGACIÓN EN ARTERIOSCLEROSIS

www.elsevier.es/arterio

EDITORIAL

The concept of severe hypertriglyceridaemia and its implications for clinical practice☆

El concepto de hipertrigliceridemia severa y sus implicaciones para la práctica clínica

Xavier Pintó Sala[a,*], **Virginia Esteve Luque**[b]

[a] *Lipid and Vascular Risk Unit, Internal Medicine Department, Hospital Universitario de Bellvitge, CiberObn., University of Barcelona, FIPEC, IDIBELL, Spain*
[b] *Lipid and Vascular Risk Unit, Internal Medicine Department, Hospital Universitario de Bellvitge, Spain*

Received 22 August 2018; accepted 27 August 2018

In the current issue of the journal, Masson et al. offer interesting information on a broad series of patients with severe hypertriglyceridaemia. This disorder of complex aetiology carries clinical significance above all because it is a cause of acute pancreatitis, which is associated with a high rate of mortality as well as a high risk of permanent sequelae.[1] In fact, this form of dyslipidaemia is the third most common cause of acute pancreatitis; 10% of all cases of this disease are attributed to it.[2] The prevalence of severe hypertriglyceridaemia varies widely depending on the population studied. In the series from Masson et al, obtained from a hospital database consisting of 162,000 electronic medical records, 2.6 cases were seen per one thousand patients. In the DRECE study,[3] with a sample representative of the Spanish population, and the ICARIA study,[4] conducted in an occupational population, the prevalence was less than 0.1%. However, it is a relatively common problem among patients with dyslipidaemia referred to specialised lipid units, such as those of the Spanish Arteriosclerosis Society SEA. Among 1394 patients with a serum triglyceride level ≥200 mg/dl who were enrolled in the SEA hypertriglyceridaemia registry, 21% had presented hypertriglyceridaemia >1000 mg/dl.[5] In the coming years, these figures may increase due to the growing epidemic of diabetes, obesity and metabolic syndrome which the global population is experiencing.[6]

A noteworthy aspect of the series reported by Masson et al. is the low frequency of pancreatitis. This was reported in 2% of cases, whereas among patients with severe hypertriglyceridaemia enrolled in the Spanish hypertriglyceridaemia registry, this percentage was 10%.[5] Hyperlipidaemic pancreatitis is a disorder of complex aetiopathogenesis influenced by a wide variety of genetic and environmental factors.[7] An awareness of the reasons for these differences would require an analysis specifically aimed at assessing whether protective circumstances or circumstances of another nature were involved. It would also require an analysis of the sensitivity of the registry. As discussed below, the risk of pancreatitis is directly related to the extent of excess triglycerides, and in the series in question, average triglyceride values were above 1500 mg/dl, thus exceeding those from the Spanish hypertriglyceridaemia registry.[5] This does not explain the low prevalence observed. Pancreatitis was also more common in other series. It affected 15% of patients from a lipid clinic with average triglyceride values similar to or somewhat higher than those from the Masson series.[8]

There is an ongoing debate with respect to the minimum serum triglyceride levels which result in a risk of acute pancreatitis.[9] It is accepted that, for this to occur,

DOI of original article:
https://doi.org/10.1016/j.arteri.2018.08.001

☆ Please cite this article as: Sala XP and Luque VE. El concepto de hipertrigliceridemia severa y sus implicaciones para la práctica clínica. Clin Investig Arterioscler. 2018;30:193–196.

* Corresponding author.
E-mail address: xpinto@bellvitgehospital.cat (X.P. Sala).

there must be a high level of chylomicrons in the pancreatic capillaries. This is unfailingly associated with very high triglyceride levels—in general, above 800–1000 mg/dl. However, it has been reported that, with triglyceride levels above 500 mg/dl, chylomicrons are already beginning to accumulate in the plasma of some individuals,[10] and that the risk of pancreatitis already appears even at lower levels.[5,11] The above-mentioned debate has most likely been influenced by the fact that triglyceride levels vary rapidly and greatly in patients with hypertriglyceridaemia. Many patients with moderate hypertriglyceridaemia may present broad and rapid variations in triglyceride levels, including hyperchylomicronaemia crises in situations of lipid overload, such as dietary transgressions, high intake of alcohol, pregnancy, taking of certain drugs such as retinoids and oestrogens, and certain associated diseases such as hyperglycaemic decompensation in diabetic patients. Although the most common criterion for defining severe hypertriglyceridaemia is a fasting triglyceride level $\geq$1000 mg/dl,[12] other recommendations and consensus documents which have had a major influence on the medical community have set out such disparate values as 500 mg/dl,[13] 885 mg/dl the result of converting 10 mmol/l of triglycerides to mg/dl 14 and 2000 mg/dl.[9] In attempting to unify the criteria for defining severe hypertriglyceridaemia, it should be noted that most patients with hyperlipidaemic pancreatitis are not affected by syndromes with a strong genetic basis of a monogenic nature, such as familial chylomicronaemia, which presents with chronically very high triglyceride levels.[15] Instead in general, patients have moderate hypertriglyceridaemia of polygenic origin which presents with sporadic hyperlipidaemic decompensation. In the Spanish hypertriglyceridaemia registry, just 6% of patients with severe hypertriglyceridaemia[5] had familial chylomicronaemia syndrome. The vast majority had been diagnosed with familial or sporadic hypertriglyceridaemia or with familial combined hyperlipidaemia. In these disorders, fasting triglyceride levels are usually below 500 mg/dl, and it may be presumed that in them pancreatitis develops in the event of the above-mentioned hyperglycaemic decompensation. In general, patients have insufficient lipolytic activity, which, in situations of lipid overload, would cause chylomicrons and other triglyceride-rich lipoproteins to accumulate. This would result in patients' triglyceride levels increasing by 10 times or more within a few hours, then decreasing within a short period of time (perhaps just one or two days) once lipid overload ceases. Therefore, it does not seem unreasonable to establish the threshold for severe hypertriglyceridaemia at 500 mg/dl. One challenge in caring for these patients is being able to identify those who are most susceptible to presenting this decompensation. In recent years, large numbers of genetic variants related to this susceptibility have been discovered. It is known that the larger the number of these genetic variants, the greater the susceptibility to having this decompensation. This is also the case in obese and diabetic patients as well as patients with other hypertriglyceridaemia-related factors.[14] In any case, genetic diagnosis tools suited to use in clinical practice are not yet available. At this time, investigation of this susceptibility requires reviewing the patient's prior laboratory results and looking for his or her highest fasting triglyceride levels. It is also useful to assess which factors increase susceptibility to development of hyperlipidaemic decompensation, including patient attitude, lifestyle, lifestyle-related circumstances, changes in body weight and associated diseases.

Another important matter related to severe hypertriglyceridaemia is its role as a vascular risk factor.[16] A few years ago, whether chylomicronaemia was associated with a higher risk of arteriosclerosis was a matter of debate.[17] Today, it is accepted that, within severe forms of hypertriglyceridaemia, a distinction must be made between those caused by severe genetic defects in triglyceride metabolism, such as familial chylomicronaemia syndrome, and less severe forms of polygenic origin associated with aggravating factors.[18] In the former group, a severe lipoprotein lipase deficiency exists, large chylomicrons accumulate and remnant particles of triglyceride-rich lipoproteins, which are those which have a high atherogenic potential, do not form. However, in moderate hypertriglyceridaemia of polygenic origin associated with aggravating factors, sufficient lipolytic activity exists for chylomicrons and VLDLs to give rise to a broad spectrum of triglyceride-rich atherogenic particles, including remnant particles and intermediate-density lipoproteins or IDLs. In the series from Masson et al., 5.5% of patients with severe hypertriglyceridaemia had a history of CVD. In the Spanish hypertriglyceridaemia registry, this percentage was 8.4%. This figure is significant considering that this population had a mean age of 47 $\pm$ 11 years,[5] an age only somewhat younger than that of the overall registry population, in which less severe forms of hypertriglyceridaemia predominated and in which cardiovascular disease affected 10.5% of the population.[19] Therefore, the possibility that most patients with severe hypertriglyceridaemia have major cardiovascular risk cannot be ruled out.

Another notable aspect of the series addressed in this article is that, in 34% of patients, no cause of secondary hypertriglyceridaemia was identified. This was probably due to a lack of information on lifestyle, especially on diet and physical activity. These are not systematically collected in medical records. Also worthy of note is the low prevalence of alcohol use—much lower than that of other series, such as the Spanish hypertriglyceridaemia registry, in which information was collected through a specific questionnaire designed for the study.[5] However, other variables which are usually collected and which are not subject to arbitrary recollection and reporting by the patient, such as diabetes, had a similar prevalence, around 30%, in both studies. As Masson et al. express in their article, observational studies based on conventional medical records are useful for detecting episodes of disease and the prevalence of a particular pathology, but provide incomplete information on certain variables related to them. It is also common for medical records to contain insufficient information on family history. This is consistent with the limited action taken with respect to first-degree relatives in disorders with a strong genetic basis, such as forms of dyslipidaemia and cardiovascular disease, which has been reported in major observational studies.[20]

Similarly, in the series of patients with severe hypertriglyceridaemia in question, a substantial treatment deficit was reported, particularly with respect to lifestyle-related measures. As mentioned, in many patients, no causes of secondary hypertriglyceridaemia were identified or

reported. The same could be said of measures to correct them. Insufficient prescription of physical activity and limited referral to dietary services were observed. These things are key to managing these patients, who usually require personalised diets, with restrictions on calories or total fat, and longer-term follow-up by nutrition experts. In fact, close to 90% of the patients from the Masson et al. study were overweight or obese. This is significant because body weight management is one of the most complex aspects of healthcare as well as one of the main factors in meeting the objectives of hypertriglyceridaemia treatment.[21]

Fibrates were seen to account for most drug treatment. This is consistent with the current recommendations for treatment of severe hypertriglyceridaemia.[22] Fenofibrate was the most commonly used fibrate, over gemfibrozil. This, as the authors have remarked, may be attributed to the fact that combining the latter with statins is contraindicated. The greater number of clinical trials conducted with fenofibrate in recent decades may be another reason why fenofibrate was used over all the other drugs in the fibrate family.[23,24] In addition, limited use of omega-3 fatty acids (seen in somewhat less than 7% of cases) as well as use of lower doses than those needed to achieve a significant decrease in triglyceride levels were reported. This is noteworthy because these agents represent a second step in treatment in patients with severe hypertriglyceridaemia in whom fibrates cannot be used, for example due to kidney failure, or in whom they are insufficient for achieving optimal management of hypertriglyceridaemia.[25] At present, many products on the market contain omega-3 fatty acids at insufficient doses. They sometimes are combined with other fatty acids and other substances without demonstrated therapeutic efficacy and come at a high cost. This may have generated a certain amount of confusion in using these agents. It should be noted that there is a need for preparations with high doses of omega-3 fatty acids for use in treating these patients, in general with a combination of docosahexaenoic acid and eicosapentaenoic acid, which enable achievement of a dose of at least 2-4 grams per day.[26]

Therefore, in relation to treatment of patients with severe hypertriglyceridaemia, it seems necessary to promote better management of lifestyle-related and aggravating factors and to optimally use drugs. In the near future, a number of therapeutic agents which are likely to represent a major advance in the management of hypertriglyceridaemia and the prevention of acute pancreatitis will appear. A wide range of drugs are being developed, including an anti-sense nucleotide against apolipoprotein C-III and a monoclonal antibody against angiopoietin-like peptide 3 (ANGPTL3).[27] For the moment, patients with severe or moderate hypertriglyceridaemia must assume that they have weak lipid metabolism, and healthcare professionals must know how to motivate them to avoid aggravating circumstances in the long term.

In conclusion, the study from Masson et al. offers very interesting information concerning patients with severe hypertriglyceridaemia, a relatively common disorder at specialised practices and on lipid units. The definition of this disorder still stirs up a certain amount of controversy. As demonstrated in the broad series of patients reported, this clinical problem is associated with several unresolved diagnostic and therapeutic issues. In many patients, aggravating and triggering causes of hypertriglyceridaemia as well as lifestyle-related measures are not identified or sufficiently emphasised, and drugs are not optimally used. These data reaffirm these patients' need to receive systematic care in accordance with a protocol from professionals with experience in lipid metabolism disorders. This would result in more effective prevention of acute pancreatitis as well as cardiovascular diseases.

References

1. Garber A, Frakes C, Arora Z, Chahal P. Mechanisms and management of acute pancreatitis. Gastroenterol Res Pract. 2018;2018:6218798, http://dx.doi.org/10.1155/2018/6218798.
2. Valdivielso P, Ramírez-Bueno A, Ewald N. Current knowledge of hypertriglyceridemic pancreatitis. Eur J Intern Med. 2014;25:689–94. Papachristou GI, Machicado JD, Stevens T, et al. Acute Pancreatitis Patient Registry to Examine Novel Therapies in Clinical Experience (APPRENTICE): an international, multicenter consortium for the study of acute pancreatitis. Ann Gastroenterol 2017;30:106–13).
3. Gómez-Gerique JA, Gutiérrez-Fuentes JA, Montoya MT, Porres A, Rueda A, Avellaneda A, et al. Lipid profile of the Spanish population: the DRECE (diet and risk of cardiovascular disease in Spain) study. DRECE study group. Med Clin (Barc). 1999;113:730–5.
4. Valdivielso P, Sánchez-Chaparro MA, Calvo-Bonacho E, Cabrera-Sierra M, Sainz-Gutiérrez JC, Fernández-Labandera C, et al. ICARIA (Ibermutuamur CArdiovascular RIsk Assessment) study group. Association of moderate and severe hypertriglyceridemia with obesity, diabetes mellitus and vascular disease in the Spanish working population: results of the ICARIA study. Atherosclerosis. 2009;207:573–8.
5. Pedragosa A, Merino J, Aranda JL, Galiana J, Godoy D, Panisello JM, et al., Registro de HTG de la SEA. [Clinical profile of patients with very high hypertriglyceridemia from the Registry of Hypertriglyceridemia of the Spanish Atherosclerosis Society]. Clin Investig Arterioscler. 2013;25:8–15.
6. Timmis A, Townsend N, Gale C, Grobbee R, Maniadakis N, Flather M, et al. European Society of Cardiology: cardiovascular disease statistics 2017. Eur Heart J. 2018;39:508–79.
7. de Pretis N, Amodio A, Frulloni L. Hypertriglyceridemic pancreatitis: epidemiology, pathophysiology and clinical management. United European Gastroenterol J. 2018;6:649–55.
8. Sandhu S, Al-Sarraf A, Taraboanta C, Frohlich J, Francis GA. Incidence of pancreatitis, secondary causes, and treatment of patients referred to a specialty lipid clinic with severe hypertriglyceridemia: a retrospective cohort study. Lipids Health Dis. 2011;10:157, http://dx.doi.org/10.1186/1476-511X-10-157.
9. Berglund L, Brunzell JD, Goldberg AC, Goldberg IJ, Sacks F, Murad MH, et al. Endocrine society. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2012;97:2969–89.
10. Lewis GF, Xiao C, Hegele RA. Hypertriglyceridemia in the genomic era: a new paradigm. Endocr Rev. 2015;36:131–47.
11. Ford ES, Li C, Zhao G, Pearson WS, Mokdad AH. Hypertriglyceridemia and its pharmacologic treatment among US adults. Arch Intern Med. 2009;169:572–8.
12. Adiamah A, Psaltis E, Crook M, Lobo DN. A systematic review of the epidemiology, pathophysiology and current management of hyperlipidaemic pancreatitis. Clin Nutr. 2017;(17):31360-2, http://dx.doi.org/10.1016/j.clnu.2017.09.028, pii:S0261-5614.

13. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Circulation 2002;106:3143–421.
14. Hegele RA, Ginsberg HN, Chapman MJ, Nordestgaard BG, Kuivenhoven JA, Averna M, et al. The polygenic nature of hypertriglyceridaemia: implications for definition, diagnosis, and management. Lancet Diabetes Endocrinol. 2014;2(8):655–66, http://dx.doi.org/10.1016/S2213-8587(13)70191-8.
15. Moulin P, Dufour R, Averna M, Arca M, Cefalù AB, Noto D, et al. Identification and diagnosis of patients with familial chylomicronaemia syndrome (FCS): expert panel recommendations and proposal of an ''FCS score''. Atherosclerosis. 2018;275:265–72.
16. Murad MH, Hazem A, Coto-Yglesias F, Dzyubak S, Gupta S, Bancos I, et al. The association of hypertriglyceridemia with cardiovascular events and pancreatitis: a systematic review and meta-analysis. BMC Endocr Disord. 2012;12:2, http://dx.doi.org/10.1186/1472-6823-12-2.
17. Rubies-Prat J, Pedro-Botet J. Premature aterosclerosis in familial chylomicronemia. N Engl J Med. 1997;336:1026–7.
18. Hegele R, Dron S. Genetics of triglycerides and the risk of aterosclerosis. Curr Atheroscler Rep. 2017;19:31.
19. Valdivielso P, Pintó X, Mateo-Gallego R, Masana L, Alvarez-Sala L, Jarauta E, et al., Registro de HTG de la SEA. Clinical features of patients with hypertriglyceridemia referred to lipid units: registry of hypertrigliceridemia of the Spanish Arteriosclerosis Society. Med Clin (Barc). 2011;136:231–8.
20. Kotseva K, Wood D, De Bacquer D, De Backer G, Rydén L, Jennings C, et al., EUROASPIRE Investigators. EUROASPIRE IV: a European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. Eur J Prev Cardiol. 2016;23:636–48.
21. Pintó X, Valdivielso P, Perez de Juan JM, Plana N, Garcia-Arias C, Fuentes FJ, et al. Spanish Registry of Hypertriglyceridemia (Spanish Society of Arteriosclerosis). Predictive factors of achieving therapeutic goals of hypertriglyceridemia. Curr Med Res Opin. 2014;30:19–26.
22. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. Atherosclerosis. 2016;253:281–344.
23. Brea A, Millán J, Ascaso JF, Blasco M, Díaz A, Hernández-Mijares A, et al. Fibrates in primary prevention of cardiovascular disease. Comments on the results of a systematic review of the Cochrane Collaboration. Clin Investig Arterioscler. 2018;30:188–92.
24. Millan J, Pintó X, Brea A, Blasco M, Hernández-Mijares A, Ascaso J, et al. Fibrates in the secondary prevention of cardiovascular disease (infarction and stroke). Results of a systematic review and meta-analysis of the Cochrane collaboration. Clin Investig Arterioscler. 2018;30:30–5.
25. Weintraub H. Update on marine omega-3 fatty acids: management of dyslipidemia and current omega-3 treatment options. Atherosclerosis. 2013;230:381–9.
26. Bowen KJ, Harris WS, Kris-Etherton PM. Omega-3 fatty acids and cardiovascular disease: are there benefits? Curr Treat Options Cardiovasc Med. 2016;18:69.
27. Chaudhry R, Viljoen A, Wierzbicki AS. Pharmacological treatment options for severe hypertriglyceridemia and familial chylomicronemia syndrome. Expert Rev Clin Pharmacol. 2018;11:589–98.