Salubris Open | IJADD

Mini-Review

The Seen and the Unseen of an Elevated Triglyceride Level

Om J Lakhani

Consultant Endocrinology, Department of Endocrinology, Zydus Hospital, Ahmedabad. Gujarat, India.

Corresponding author: Om J Lakhani, Consultant Endocrinology, Department of Endocrinology, Zydus Hospital, Ahmedabad. Gujarat, India.

Email: dromlakhani@gmail.com

Article information

Received date: 02/12/2020; **Accepted date:** 09/12/2020; **Published date:** 17/12/2020

Abstract

Amongst the parameters measured in the lipid panel, the triglyceride (TG) values are often given less importance by physicians than it deserves. It is our opinion that TG often gives multidimensional insights about the patients, and we need to pay more attention to the same. The postprandial or non-fasting value has prognostic importance in cardiovascular disease (CVD). TG is a key component of metabolic syndrome, and hypertriglyceridaemia is an important marker of insulin resistance. The TG-glucose (TyG) index has a good correlation with other measures of insulin resistance. High TG correlates with the presence of non-alcoholic steatohepatitis/non-alcoholic fatty liver disease (NASH/NAFLD). It also predicts future risk of type 2 diabetes and cardiovascular disease. Elevated TG in a non-diabetic individual must be interpreted as an opportunity to initiate or intensify the lifestyle measures to prevent type 2 diabetes and cardiovascular disease.

Keywords: Triglyceride metabolism, hypertriglyceridaemia, triglyceride-glucose index, metabolic syndrome, insulin resistance

A Clinical Vignette

A 45-year-old male comes for a routine health check-up. He fits into the category of metabolic syndrome. He is obese, with an increase in waist circumference and having impaired fasting glucose and impaired glucose tolerance. Additionally, his fasting triglyceride is 400 mg/dL.

His ultrasound suggests a grade 1 fatty liver. He is otherwise asymptomatic. What is the interpretation of this elevated triglyceride level?

Introduction

Within the lipid panel, the TG level is often given a mere cursory glance. However, we believe that an elevated TG in a lipid panel needs to be given more importance than it gets.

In this review, we shall argue that hypertriglyceridaemia (elevated triglyceride) is the "flag-bearer" of insulin resistance.[1] Elevated triglyceride is also associated with an increased risk of having NAFLD/NASH.[2] A patient with high TG is at a high risk of developing type 2 diabetes in the future.[3] For a physician, an elevated triglyceride offers more insights to a patient than we traditionally believe. It also offers an opportunity for the physician to intervene early using simple and effective lifestyle measures or medications to reduce the future risk of type 2 diabetes mellitus, NASH, and cardiovascular disease.

Metabolism of Triglycerides

Triglycerides, also called triacylglycerol, are storage forms of fatty acids. Free fatty acids (FFAs) are combined with glycerol to form triglycerides which are stored in the adipose tissues.[4]

The triglyceride has two sources. The first is the endogenous production, and the other is the exogenous dietary intake. The triglyceride obtained from the diet are carried by chylomicrons.[4]

In the adipocytes, the lipoprotein lipase metabolizes the TG to FFA for its uptake and then stores it again in form of triglycerides. The endogenous triglyceride from the liver is carried to the adipocytes and other tissue from the liver via the very-low-density lipoprotein (VLDL).[5]

During the fasting state, glucagon and other insulin counter-regulatory hormones enhance the action of hormone-sensitive lipase breaking the triglyceride to its components - the FFA and glycerol.[4]

How do We Conventionally interpret the Triglyceride Levels? (The Seen)

Most guidelines agree that normal and ideal fasting TG levels are <150 mg/dL (1.7 mmol/L). There are some minor disagreements in the classifications of higher triglyceride levels between the American and European guidelines.[6,7] Typically, the classification of triglycerides levels is as classified in Table 1.

Table 1. Interpretation of fasting triglyceride values[6]

Triglyceride (mg/dl)	Triglyceride (mmol/L)	Interpretation
<150 mg/dL	1.7 mmol/L	Normal trigl yceride
175-885 mg/dL	2.0-9.9 mmol/L	Mild-to-moderate hypertriglyceridaemia
>885 mg/dL	>10 mmol/L	Severe hypertriglyceridaemia
>1770	>20 mmol/L	Very severe hypertriglyceridaemia

It is however stressed in the guidelines to primarily differentiate the TG levels into three categories: normal - fasting TG <150 mg/dL, moderate hypertriglyceridaemia - fasting TG between 175-499 mg/L and severe hypertriglyceridaemia - fasting TG more than 500 mg/dL (American guidelines) or 885 mg/dL (European guidelines).[6,7] It is important to differentiate these three categories because of the implications of the three is very different.

The moderately elevated triglycerides are mainly carried by the VLDL and they are associated with an increased cardiovascular risk. Severely high triglycerides are carried by chylomicrons apart from VLDL and are associated with an increased risk of pancreatitis apart from the increased cardiovascular risk.[7]

Amongst the aetiology, severe hypertriglyceridaemia is associated with familial chylomicronaemia, whereas mild to moderate hypertriglyceridaemia is associated with familial hypertriglyceridaemia, dysbetalipoproteinaemia, and familial combined hyperlipidaemia.[7]

The Unconventional Interpretation of the Triglyceride Levels (The Unseen)

In the above lines, we have stated the conventional interpretation of a triglyceride value (the seen effect). However, a triglyceride tells us more about the patient than what is described above. In the next few paragraphs, we will describe the unconventional and neo interpretation of hypertriglyceridaemia.

What is the Difference Between Fasting and Post-Meal Triglyceride Level?

The normative range of triglycerides is determined based on a fasting sample. Unlike some other components of the lipid panel, the TG values are dependent on a fasting or non-fasting state. Though the prognostic importance of either of the values remains the same, there are some interesting differences between the two which we will highlight.[8]

The current trend has been towards considering a non-fasting lipid profile to help enhanced screening and convenience to the population. A recent review recommends that TG can be measured in the non-fasting state, and the test should be repeated if the TG value exceeds 400 mg/dL.[8]

There is a question often being raised about the prognostic value of TG as a marker of cardiovascular disease, but we believe that this problem arises because most of the studies mainly consider fasting TG values. The prognostic value of TG is sharpened when post-meal or non-fasting triglycerides are taken into consideration.[9]

Several studies have shown that post-meal or non-fasting TG have a strong correlation with the cardiovascular event. Experts have suggested a form of "lipid tolerance test" to standardize the measurement of post-meal triglycerides. However, a standard protocol consensus has not been reached for the same to date.[10]

Triglyceride is a Flagbearer of Metabolic Syndrome and Insulin Resistance

Hypertriglyceridaemia is a quintessential part of the definition of metabolic syndrome. The metabolic syndrome is a surrogate for clinical findings of insulin resistance.[11]

A maker called a triglyceride glucose index has been found to have a good correlation between insulin resistance markers like the HOMA-IR and hyperinsulinemia-euglycemic clamp (HIEC). HIEC is the gold standard for the measurement of insulin resistance. The triglyceride glucose index is calculated as log [fasting triglycerides (mg/dL) × fasting plasma glucose (mg/dL)/2].[12]

It is well known from the classical work done by Randle and his colleagues that fatty acid and its products, the triglyceride (triacylglycerol) and diacylglycerol impair the function of insulin in insulin-sensitive tissues like the liver and muscle. This leads to central insulin resistance in the liver and peripheral insulin resistance in the muscles. The simplest way to gauge this state is to measure triglycerides and to understand that higher circulating triglycerides point towards an overflow state of free fatty acid. It also points to the fact of the fatty acid - insulin resistance cycle is active.[13]

Triglycerides and Non-Alcoholic Steatohepatitis/Non-Alcoholic Fatty Liver Disease

The triglyceride, insulin resistance, and NAFLD/NASH constitute an unholy triad. Insulin resistance leads to the reduced ability of insulin to inhibit the lipolysis that takes place in the adipose tissue. The increased lipolysis in the adipose tissue leads to an increase in free fatty acid generation. This free fatty acid further exacerbates insulin resistance creating a vicious cycle.[2]

The free fatty acid is transported to the liver forcing the liver to generate more triglyceride from the free fatty acid. The liver triglycerides are loaded on to the VLDL and extruded into the bloodstream. Increased VLDL has been linked with increased cardiovascular disease. The excess triglyceride that cannot be extruded accumulate in the liver leads to hepatic steatosis.[4]

Hypertriglyceridaemia is a Marker of Future Risk of Type 2 Diabetes

Hypertriglyceridaemia serves as an important marker for the future risk of type 2 diabetes. An elegant study conducted in Israel showed that a baseline high triglyceride was associated with an increased risk of type 2 diabetes in men. They also showed that in men in whom the triglyceride levels increased from a baseline normal value over a span of 5 years, the risk of type 2 diabetes was 12 times higher. It was also high in men in whom the triglyceride values remained high during the half-decade. On a positive note, in men who reduced their triglyceride level from a high value within a span of 5 years using weight loss and other lifestyle measures, the risk of type 2 diabetes reduced significantly.[3]

Triglyceride is a Marker of Future Risk of Cardiovascular Disease

The triglyceride glucose index mentioned above has been found to have a good correlation with cardiovascular risk. According to a study, the prevalence of coronary artery disease (CAD) was 1.16 times higher in patients classified in the last tertile of the TyG index (9.9±0.5) compared to those in the first tertile (8.3±0.3).[12]

It is important to understand that triglyceride independently is a useful marker of future risk of cardiovascular events. However, until recently, the reduction of triglyceride was not found to be associated with the reduction of cardiovascular disease. This norm was challenged with the publication of the Reduction of Cardiovascular Events with Icosapent Ethyl - Intervention Trial (REDUCE-IT).[8]

The said trial published in 2019 showed that the use of icosapent ethyl in a dose of 4 gram/day in patients with mild to moderate hypertriglyceridaemia already on statins was associated with a significant reduction of ASCVD events.[14]

The current guidelines by the American College of Cardiology/American Heart Association (ACC/AHA) suggest that in adult patients with moderate hypertriglyceridaemia with 10 years atherosclerotic cardiovascular disease (ASCVD) risk of ≥7.5%, initiating or intensifying the dose of statins is recommended.[7] The recent review on the topic suggests that the

use of icosapent ethyl in the dose of 4 gram/day is helpful in further reduction of cardiovascular events.[8] The link between triglyceride and cardiovascular disease has been discussed in detail by Singh et al.[15]

Conclusion

An elevated triglyceride should be looked at more closely by physicians as a Sine qua non of insulin resistance and metabolic syndrome. Elevated triglycerides in a non-diabetic patient should be used as an opportunity to initiate or intensify lifestyle measures and weight loss. For those already having diabetes or other cardiovascular risk factors, an elevated TG could be an opportunity to look at intensifying the cardiovascular risk reduction strategies.

Declaration of conflicting interests

The author declares no conflict of interest.

Funding

No financial support was received for publishing this article.

References

1. Delarue J, Magnan C. Free fatty acids and insulin resistance. Curr Opin Clin Nutr Metab Care. 2007; 10(2):142-48.
2. Tacer KF, Rozman D. Nonalcoholic Fatty Liver Disease: Focus on Lipoprotein and Lipid Deregulation. J Lipids. 2011; 2011:783976.
3. Tirosh A, Shai I, Bitzur R, Kochba I, Tekes-Manova D, Israeli E, et al. Changes in triglyceride levels over time and risk of type 2 diabetes in young men. Diabetes Care. 2008; 31(10):2032-0327.
4. Alves-Bezerra M, Cohen DE. Triglyceride metabolism in the liver. Compr Physiol. 2017; 8(1):1-8.
5. Olivecrona G. Role of lipoprotein lipase in lipid metabolism. Curr Opin Lipidol. 2016; 27(3):233-41.
6. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). Eur Heart J. 2020; 41(1):111-188.
7. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019; 39(25):e1082-e1143.
8. Laufs U, Parhofer KG, Ginsberg HN, Hegele RA. Clinical review on triglycerides. Eur Heart J. 2020; 41(1):99-109c.
9. Iso H, Imano H, Yamagishi K, Ohira T, Cui R, Noda H, et al. Fasting and non-fasting triglycerides and risk of ischemic cardiovascular disease in Japanese men and women: the Circulatory Risk in Communities Study (CIRCS). Atherosclerosis. 2014; 237(1):361-68.
10. Ochiai M. Evaluating the appropriate oral lipid tolerance test model for investigating plasma triglyceride elevation in mice. PLoS One. 2020; 15(10):e0235875.
11. Samson SL, Garber AJ. Metabolic syndrome. Endocrinol Metab Clin North Am. 2014; 43(1):1-23.
12. Su W-Y, Chen S-C, Huang Y-T, Huang J-C, Wu P-Y, Hsu W-H, et al. Comparison of the effects of fasting glucose, hemoglobin a1c, and triglyceride–glucose index on cardiovascular events in type 2 diabetes mellitus. Nutrients. 2011; 11(11):2838.
13. Samuel VT, Petersen KF, Shulman GI. Lipid-induced insulin resistance: unravelling the mechanism. Lancet. 2010; 375(9733):2267-277.
14. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridaemia. N Engl J Med. 2019; 380(1):11-22.
15. Singh AK, Singh R. Triglyceride and cardiovascular risk: A critical appraisal. Indian J Endocrinol Metab. 2016; 20(4):418-428.