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Review

Lipid disorders – the comparison between general population and haemodialyzed patients. Will the Oral Fat Tolerance Test improve the diagnostic?

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The cardiovascular events are frequent complications in chronic kidney disease (CKD). In the general population the risk factors of CV disease are well established and divided into two groups: non-modifiable, and modifiable. The best-known modifiable risk factors leading to the atherosclerotic plaque formation are lipid disorders. In comparison, an association between serum lipid profile in haemodialyzed patients and cardiovascular mortality is more complex and still unclear. Furthermore, it is important to note that recent studies suggest an inverse relationship between lipid disorders and CV mortality in a haemodialyzed population called 'reverse epidemiology'. The disparity between the general and haemodialyzed populations may be supported by the fact that the haemodialysis process itself contributes to the development of dyslipidaemia. Moreover, the chronic kidney disease is associated with metabolic abnormalities which can increase the risk of CVD occurrence. It is estimated that one-third of the patients on haemodialysis have lipid profile abnormalities, the most common one is hypertriglyceridemia. The assessment of the lipid profile has so far been performed in a fasting and non-fasting (postprandial) state, but both of these methods have some limitations. This review evaluates the current knowledge about lipid profile abnormalities in haemodialyzed patients and discusses a potential role of the Oral Fat Tolerance Test (OFTT) as a new tool in clinical practice that may improve the diagnosis of postprandial hypertriglyceridemia.

Keywords: chronic kidney disease, haemodialysis, cardiovascular disease, Postprandial hypertriglyceridemia, fat tolerance test

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Abbreviations: Apo, apolipoprotein; ACL, adenosine triphosphate–citrate lyase; ASCVD, Atherosclerotic Cardiovascular Disease; CKD, chronic kidney disease; CVD, cardiovascular disease; FAS, fatty acid synthase; HD, haemodialysis; HDL, high-density lipoprotein; HL, hepatic lipase; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LMWH, low molecular weight heparin; LPL, lipoprotein lipase; NADPH, nicotinamide-adenine dinucleotide phosphate; NO, nitric oxide; OFTT, The Oral Fat Tolerance Test; Oxy-LDL, oxidized low-density lipoprotein; sd-LDL, small dense low-density lipoprotein; TG, triglycerides; TRLs, Triglyceride-rich lipoproteins; VLDL, very-low-density lipoprotein

INTRODUCTION

All patients with chronic kidney disease (CKD) from early stages till renal replacement therapy are characterized by a significantly higher prevalence of cardiovascular disease (CVD), which achieved 40–50% in the haemodialyzed (HD) group. The CVD mortality is approximately 10-to 30- fold higher when compared to a general population despite the stratification by gender, age, race, and the presence of diabetes (Weiner *et al*., 2006; Harper & Jacobson, 2008; Ahmed & Khalil, 2010; Tsimihodimos, 2011). The patients diagnosed with CKD have a high prevalence of traditional risk factors of CVD such as advanced age, male gender, hypertension, diabetes, dyslipidaemia, smoking, and sedentary lifestyle (Levey & Eknoyan, 1999; Weiner *et al*., 2006; Ahmed & Khalil, 2010; Balode & Khan, 2011; Burmeister *et al*., 2014; Dušejovská *et al*., 2020). In addition, they also present non-traditional, characteristics for CKD risk factors like anaemia, mineral and bone disorders, chronic inflammatory state, oxidative stress, protein energy wasting, calcification associated with altered calcium-phosphate balance, hormonal alterations (such as deficiency of growth hormone, insulin-like growth factor, hypothyroidism, hypogonadism), and hyperhomocysteinemia (Ahmed & Khalil, 2010; Balode & Khan, 2011; Tsimihodimos, 2011; Dušejovská *et al*., 2020; Chmielewski *et al*., 2009). In addition, there are some factors linked with the haemodialysis process itself that may predispose to lipid metabolism disorders (Dušejovská *et al*., 2020).

THE COMPARISON BETWEEN CVD MORTALITY IN THE GENERAL POPULATION AND HAEMODIALYZED PATIENTS

CVD in the general population

Dyslipidaemia is one of the major risk factors for the development of cardiovascular disease (Kita *et al*., 2001; Kalantar-Zadeh *et al*., 2003; Liu *et al*., 2004; Ahmed & Khalil, 2010; Peng *et al*., 2017; Burmeister *et al*., 2014; Dušejovská *et al*., 2020). The best known pathomechanism leading to the atherosclerotic plaque formation is the accumulation of oxidized LDL (oxy-LDL) molecules in the damaged endothelium (Kita *et al*., 2001; Kwan *et al*., 2007). However, despite the prevalent use of statins, which mainly decrease the plasma concentration of this lipoprotein fraction, a relatively high residual risk of cardiovascular disease has still been reported (Peng *et al*., 2017). In further clinical studies, it has been proved that hypertriglyceridemia is an independent risk factor of cardiovascular disease (CVD), myocardial infarction, and fatal coronary heart disease (Parfrey *et al*., 1996; Cohn *et al*., 1999; Kita *et al*., 2001; Pal *et al*., 2003; Tonelli *et al*., 2006; Weiner *et al*., 2006; Ahmed & Khalil, 2010).

Atherosclerotic plaque formation has so far been associated mainly with low-density lipoproteins. There are many studies describing the penetration of LDL into the

arterial intima, accumulation of extracellular cholesterol, and formation of macrophage foam cells, which leads to increased inflammation and prothrombotic process in the arterial wall (Borén *et al*., 2020). This mechanism is also observed in haemodialysis patients. Interestingly, some papers suggest that LDL in dialysis patients showed altered composition, and its degradation was reduced compared to normal LDL (Alsayed & Rebourcet, 1991). Moreover, some recent studies suggested that high postprandial TG plasma concentration can be an independent risk factor of atherosclerosis, CVD, myocardial infarction, and ischemic stroke in patients with impaired renal function (Parfrey *et al*., 1996; Cohn *et al*., 1999; Tonelli *et al*., 2006; Harper & Jacobson, 2008; Lambert & Parks, 2012). The current knowledge about 'reverse epidemiology' and dissimilarities of serum lipid profile in haemodialyzed patients contradict this thesis.

A potential correlation between triglyceride-rich lipoproteins and an atherosclerotic plaque formation is still unclear. The possible mechanisms of atherosclerosis progression associated with TRLs accumulation include the promotion of endothelial dysfunction by diffusion into the intima and induction of inflammation, activation of monocytes to the foam cells, induction of oxidative processes, and decreasing the amount of nitric oxide (NO) (Harper & Jacobson, 2008; Talayero & Sacks, 2011; Samson *et al*., 2012; Magnifico *et al*., 2017; Peng *et al*., 2017).

Large chylomicrons and VLDL particles cannot diffuse into the arterial intima, while their smaller remnant particles enter through the vessel wall (Cohn *et al*., 1999; Pal *et al*., 2003; Talayero & Sacks, 2011; Samson *et al*., 2012). The triglyceride-rich remnant particles in human atherosclerotic plaque contain a higher amount of cholesterol per particle than LDL because of their larger size (Pal *et al*., 2003; Magnifico *et al*., 2017; Peng *et al*., 2017). Therefore, in comparison to LDL particles, they don't need to be oxidized to have strong proatherogenic properties (Peng *et al*., 2017).

On the other hand, the hypertriglyceridemia state intensifies the increased TGs removal from VLDL and chylomicrons to LDL. As the effect remnant lipoproteins: VLDL remnants, intermediate-density lipoprotein (IDL), LDL, and small dense LDL (sd-LDL) are enriched by the TGs, which may additionally promote the formation of atherosclerotic plaque (Saeed *et al*., 2019).

Lipid abnormalities in haemodialyzed patients

Dyslipidaemia in CKD patients is associated with specific qualitative and quantitative lipid abnormalities, significantly different in comparison with individuals with preserved kidney function (Balode & Khan, 2011; Dušejovská *et al*., 2020). Relatively normal or reduced total cholesterol and low-density lipoprotein (LDL), elevated triglycerides (TG), and reduced plasma high-density lipoprotein (HDL) concentration are the most common abnormalities observed in this population (Kwan *et al*., 2007; Balode & Khan, 2011; Dušejovská *et al*., 2020, Chmielewski *et al*., 2009, Szolkiewicz *et al*., 2002).

However, the association between CVD mortality and dyslipidaemia in HD patients is not as clear as in the general population. Recent studies have noted the term "reverse epidemiology" concerning total cholesterol levels and the risk of all-cause mortality (Kalantar-Zadeh *et al*., 2003; Kwan *et al*., 2007; Tsimihodimos, 2011; Dušejovská *et al*., 2020). In other words, there was a link between lower TC levels and a higher mortality rate. The etiology of this phenomenon is connected with malnutrition and inflammation observed in HD patients (Liu *et al*., 2004; Kwan *et al*., 2007; Tsimihodimos, 2011). Kilpatrick *et al*. proved in their study that a low total cholesterol level was connected with higher mortality, while the best survival was observed for total cholesterol serum level values between 225 and 254 mg/dl. What is more, a low LDL level was also associated with a high mortality hazard. To compare, patients with hypertriglyceridemia (value between 200 to 250 mg/dl) have better cardiovascular survival, while no notable trend was noticed for HDL. In this study, patients were divided into two subgroups: those with malnutrition (measured by albumin level below 3,8 mg/dl and a dietary protein intake below 1g/kg per day) and those with normal nutritional status. The trends described above were stronger in those with malnutrition (Kilpatrick *et al*., 2007). On the other hand, there are some studies that proved that 'revers epidemiology' of lipid profile can be observed not only in the group with inflammation/malnutrition syndrome. Elbert *et al*. proved that a total cholesterol, HDL, non-HDL, and LDL level was associated with higher all-cause, cardiovascular and non-cardiovascular mortality. In this study there was no correlation between mortality and an inflammation/malnutrition status for all lipid fractions (Ebert *et al*., 2021). Moreover, because of an enormous relationship between lipid serum profile and CVD risk, there is a need to find new diagnostic pathways which will improve the assessment of prognosis in dialysis patients. Cheng *et al*. tried to establish the correlation between TG and HDL levels with the cardiovascular disease risk. According to the study, the TG/HDL ratio could be a good predictor marker for detecting the risk of CV disease. In comparison to the popular generation, better CV and overall survival were observed in those dialyzed patients who had an elevated TG/HDL ratio (Chang *et al*., 2017).

Hypertriglyceridemia is predominantly present in HD patients compared with other lipid fractions (Harper & Jacobson, 2008; Balode & Khan, 2011; Tsimihodimos, 2011). It is estimated that 30% of dialysis-dependent patients have an increased TG plasma concentration (Burmeister *et al*., 2014).

Recently, clinical studies found two main processes which lead to the inappropriate TG serum amount. Delayed catabolism of Triglyceride-rich lipoproteins (TRLs) i.e. very-low-density lipoprotein (VLDL) and chylomicrons can be caused by decreased activity of hepatic triglyceride lipase (HL) and peripheral lipoprotein lipase (LPL) (Parfrey *et al*., 1996; (Kwan *et al*., 2007; Balode & Khan, 2011; Tsimihodimos, 2011; Dušejovská *et al*., 2020). The second mechanism considers increased hepatic production of TRLs (Parfrey *et al*., 1996; Kwan *et al*., 2007; Balode & Khan, 2011; Tsimihodimos, 2011; Dušejovská *et al*., 2020), however, some studies suggest that this is a less significant factor in dialysis patients compared to impaired TRL removal (Alsayed & Rebourcet, 1991; Szolkiewicz *et al*., 2002). Triglycerides are esters composed of a glycerol and three fatty acids, the production of which is catalyzed by fatty acid synthase (FAS). One of the hypotheses, which supports the theory that hypertriglyceridemia in haemodialysis patients can be caused by the overproduction of lipoproteins, assumes that the upregulation of fatty acid synthase gene expression can be observed in CKD. Szolkiewicz *et al*. measured FAS activity, FAS protein mass, and FAS mRNA level in rats after subtotal nephrectomy or sham operation. All of them were increased in response to experimental CKD, leading to the elevation of triglycerides (Szolkiewicz *et al*., 2002). Another study that focused on the lipogenesis process and CKD found the relation-

ship between FAS gene expression, mRNA abundance, adenosine triphosphate–citrate lyase (ACL) activity, enzymes participating in the reduced form of nicotinamide-adenine dinucleotide phosphate (NADPH) production activity. ACL is an enzyme catalyzing the reaction of acetyl-CoA production, which in the next step is converted into triglycerides, while NADPH is a coenzyme necessary for fatty acid biosynthesis. Both of these enzymes play a fundamental role in lipogenesis. Rutkowski and others (Rutkowski *et al*., 2003) observed in his study that rats with CKD had increased mRNA abundance and FAS gene expression. What is more, activity of ALC and all the enzymes participating in NADPH production (glucose-6-phosphate dehydrogenase; 6-phosphogluconate dehydrogenase; malic enzyme) were also elevated. On the other hand, FAS activity, protein, and mRNA abundance increased by about 30%, while the TGs level was almost 2-fold increased, which proved the hypothesis that the overproduction of lipoproteins is the only additional factor leading to hypertriglyceridemia in chronic kidney disease (Szolkiewicz *et al*., 2002; Rutkowski *et al*., 2003).

Moreover, there are a lot of indicators, which are not obtainable in routine practice, one of them being apolipoproteins - small, exchangeable glycoproteins that bind to lipids to form lipoproteins. They are involved in the transport of lipids in the blood, and some of them (such as apo-CII, apo-CIII) may influence TLR metabolism by changing lipoprotein lipase activity (Wolska *et al*., 2017). Lipoprotein lipase is responsible for triglyceride-rich lipoproteins catabolism and impaired activity of that enzyme leads to the increased VLDL and chylomicrons plasma levels. (Hiukka *et al*., 2005; Dušejovská *et al*., 2020). Blood concentrations of apolipoproteins B and C play a critical role in TRLs metabolism. Apolipoproteins CII and CIII form the structure of TLRs such as VLDL and chylomicrons (CM) and very-low-density lipoproteins (VLDL), and also high-density lipoproteins (HDL) during fasting state (Wolska *et al*., 2017). What is more, apolipoprotein CIII (Apo CIII) can concomitantly inhibit lipoprotein lipase (LPL) activity (Cohn *et al*., 1999; Hiukka *et al*., 2005; Talayero & Sacks, 2011), while ApoC-II is a cofactor of lipoprotein lipase (LPL) that enhances its action (Wolska *et al*., 2017). Some studies suggest that apolipoprotein levels may be impaired in haemodialysis patients. Alsayed *et al.* found that dialysis patients had increased apo CII level, decreased apo CII, apo E, and apo AI concentration, while apo B level was normal, this group also showed moderate hypertriglyceridemia (Alsayed & Rebourcet, 1991).

Inappropriate TG levels may be related to the progression of chronic kidney disease. For example, it has been respectively proved that secondary hyperparathyroidism and insulin resistance, often associated with CKD and haemodialysis treatment, can be involved in the impairment of TG catabolism and hepatic VLDL overproduction (Tsimihodimos, 2011; Dušejovská *et al*., 2020). Liang and others (Liang *et al*., 1998) found that high parathormone levels affect TLR metabolism. He noted that parathyroidectomy in animals with chronic kidney disease led to a significant reduction of the LPL and HL expression, resulting in lower blood triglyceride levels.

Besides these mechanisms, it was investigated that some factors strictly related to the process of HD can influence the plasma TG concentration. Some studies suggest that low molecular weight heparin (LMWH) used during haemodialysis can be associated with releasing lipoprotein lipase from the endothelial surface (Nässtrom *et al*., 2001; Nässtrom *et al*., 2004; Tsimihodimos, 2011; Dušejovská *et al*., 2020). This process leads to increased activity of lipase, resulting in lowered plasma TG concentration. It was shown that LPL-activity increased after heparin infusion and the highest peak was observed at 15 minutes and remained high at 30 minutes. The activity started decreasing at 120 minutes and after 180 min was still reduced; (Nasstrom *et al*., 2003; Nässtrom *et al*., 2004). As the result, the TGs concentration increased as expected from the low LPL activity (Nasstrom *et al*., 2003). Nässtrom and others (Nässtrom *et al*., 2001) suggest that LMW heparin infusions lead to a depletion of LPL tissue stores because of releasing it from the endothelium, whereas LPL circulating in the blood can be taken up and degraded by the liver. However, Arnadottira nd others (Arnadottir, 1994) have found that LPL activity can be released after heparin infusion but it is restored after 24–48 hours. The correlation between LMWH and TGs levels is still unclear, and it needs further examination.

Some literature data showed the possibility, that the type of dialysis membrane is connected with lipid profile abnormalities. It has been proved that the use of high-flux polysulfone membranes or cellulose triacetate membranes contributes to increased lipoprotein lipase activity resulting in improved lipolysis of the intravascular triglyceride lipoproteins. The increased apoC-II/apoC-III ratio may be involved in that process by increasing lipoprotein lipase activity and lipolysis of the triglyceride rich lipoproteins. (Ahmed & Khalil, 2010; Tsimihodimos, 2011; Dušejovská *et al*., 2020).

THE ASSESSMENT OF LIPID PROFILES

The lipid profiles are often obtained in the fasting and non-fasting/postprandial state, which usually means a random blood sample taken regardless of the time since the last meal (Kolovou *et al*., 2019a; Kolovou *et al*., 2019b). A fasting state is defined as 8–14 hours since the last meal (Kolovou *et al*., 2019a). It is known that the TG plasma concentration shows a significant rise from fasting state to the second hour after breakfast, while the maximum peak is observed at the 4th hour after breakfast. Further triglyceride level slowly decreases to the baseline at 12–14th hour of observation (Samson *et al*., 2012; Lambert & Parks, 2012; Nakamura *et al*., 2016). The triglyceride concentration shows the highest meal-dependent fluctuations during the day compared with other lipid fractions. Patients often consume more than three meals daily, so reliable assessment of a fasting lipid profile can be problematic in a clinical practice routine. Most individuals are actually in a fasting state only for a few hours in the early morning before the first meal (Lambert & Parks, 2012; Nakamura *et al*., 2016; Peng *et al*., 2017; Kolovou *et al*., 2019a). That was a reason why several societies endorse sampling non-fasting lipid profiles. Recent studies reported that consumption of a subsequent meal causes a higher TG concentration (as a result of increasing in both chylomicron particles and TG content), which is defined as a "second meal effect". It can be explained by the fact that a subsequent meal may contain a significant amount of lipid from the previous meal. This term also shows an association between previous macronutrient consumption and the metabolism of TG which are derived from meals (Lambert & Parks, 2012). It has been proved that carbohydrates and fat can decrease each other's metabolism in a non-fasting state.

Moreover, the postprandial response can be much greater and persists longer in patients with hyperlipidaemia, compared with the general healthy population (Kolovou *et al*., 2019b).

On the other hand, it is known that TG concentration shows a variability during a day, hence, the values obtained in a random blood sample can be inaccurate and difficult to compare with further assessments (Samson *et al*., 2012; Kolovou *et al*., 2019a; Kolovou *et al*., 2019b). The quantity and amount of the meal, the fat content, the time determination (breakfast, dinner, supper, etc.), the carbohydrate content, time since the last meal are taken into account for TG level variations (Samson *et al*., 2012; Kolovou *et al*., 2019a).

Many recent studies showed that fasting and postprandial hypertriglyceridemia have a causative effect on Atherosclerotic Cardiovascular Disease (ASCVD) in the general population (Sharrett *et al*., 1995; Stampfer *et al*., 1996; Tiret *et al*., 2000; Samson *et al*., 2012; Kolovou *et al*., 2019a; Kolovou *et al*., 2019b); However, both of these assessment methods have some disadvantages. Patients with an increased risk of CVD development, associated with postprandial hypertriglyceridemia, may not have been appropriately recognized in the past, while only fasting lipoprotein profiles were obtained (Kolovou *et al*., 2019a).

In the haemodialyzed population, the influence of triglycerides and other lipid fractions on the atherosclerosis process and cardiovascular disease mortality is more complex and still unclear. Some authors suggested that hypertriglyceridemia could increase CVD mortality, while according to the newest knowledge we know that the higher level of triglycerides and total cholesterol might be connected with better survival. It could be related with the inflammation and malnutrition state observed in the HD population. However current studies had some limitations. In most experiments TG level was measured in the postprandial state, or the cohort contained a mixture of fasting and non-fasting patients. The changes in TG level in serum observed during a day can disrupt the results. As above, new diagnostic methods for measuring the TRLs level should be established.

ORAL FAT TOLERANCE TEST (OFTT)

Until recently, the majority of guidelines focused on assessing postprandial hypertriglyceridemia was based on the measurements after eating a home-made meal with different type, structure, and amount of fat, carbohydrates or protein for their investigations (Sharrett *et al*., 1995; Peng *et al*., 2017; Kolovou *et al*., 2019a; Kolovou *et al*., 2019b). Therefore, obtained results were difficult to interpret and compare with other scientific data. The evaluation of postprandial hypertriglyceridemia in clinical practice is currently limited by the lack of a well-validated expected cut-off point for TG concentration after an oral fat tolerance test. Moreover, standardized OFTT meal composition is a second problem that needs to be established (Peng *et al*., 2017; Kolovou *et al*., 2019a; Kolovou *et al*., 2019b).

In published studies, researchers used a lot of variations of the test meal. The home-made meals consist of different percent of nutrients – fat, carbohydrates, and protein per kg of body mass (Kolovou *et al*., 2019a).

Due to that fact, there were difficulties associated with a comparison between obtained data, and investigators were prompted to standardize a test meal (Peng *et al*., 2017; Kolovou *et al*., 2019a; Kolovou *et al*., 2019b).

According to the expert panel recommendations, the OFTT test meal should consist of 75 g of fat, 25 g of carbohydrates, and 10g of protein (Kolovou *et al*., 2019a; Kolovou *et al*., 2019b).

In addition, there was also a necessity to establish a proper time to measure lipid profiles after the test meal intake. Based on current knowledge about the metabolism of TG rich lipoproteins and the time of the maximum postprandial TG increase, it was confirmed that triglyceride level should be obtained in the fasting state (minimum 8 h after the last meal) and at the 4th hour of observation (Kolovou *et al*., 2019a; Kolovou *et al*., 2019b).

The majority of studies indicated that prior exercise can influence the TGs response during OFTT (Samson *et al*., 2012; Kolovou *et al*., 2019b). The expert panel recommends avoiding the high-intensity exercises before postprandial hypertriglyceridemia testing (Kolovou *et al*., 2019a; Kolovou *et al*., 2019b). Moreover, the excessive consumption of alcohol can contribute to an increase of postprandial TG response. The abstinence from alcohol consumption for 20 h or even 48 h before the test should be advised (Kolovou *et al*., 2019a).

Based on the updated meta-analysis, researchers compared the response to a standardized test meal in the individuals with and without lipid profile abnormalities. They established a group that would not benefit from measuring the postprandial TG-plasma concentration (Kolovou *et al*., 2019a). The patients with fasting TG values below 1 mmol/L (89 mg/dl) have a proper response to a test meal. There is no precise evidence on the usefulness of the postprandial triglyceridemia measurement and its potential to improve clinical outcomes in this group of patients. Moreover, fasting TG plasma concentration above 2 mmol/L (175 mg/dl) and non-fasting above 2.3 mmol/L (200 mg/dl) should be considered as abnormal. Patients with these lipid profile abnormalities often have an exaggerated response during the OFTT, hence they should be excluded from further examination (Kolovou *et al*., 2019a).

The recent studies allowed to establish that the OFTT should be performed in patients with fasting TG concentrations of 1–2 mmol/L (89–175 mg/dl) or non-fasting TG concentrations 1,3-2,3 mmol/L (115–200 mg/dl), and that is the group with potential diagnostic benefit from testing in clinical practice (Kolovou *et al*., 2019a).

A response to an OFTT should be considered as incorrect when the plasma concentration of TG is higher than 2.5 mmol/L (220 mg/dl) at the 4th hour after a test meal (Kolovou *et al*., 2019a).

CONCLUSION

Hypertriglyceridemia is an independent risk factor for cardiovascular disease in the general population, while in haemodialyzed patients this correlation is not as clear. Current methods of measuring serum TG levels are insufficient and have their limitations, therefore new solutions should be introduced. The Oral Fat Tolerance Test (OFTT) may be useful to identify postprandial hypertriglyceridemia in patients who have not been recognized to have lipid profile abnormalities in the past. It can improve further investigations and enhance understanding the lipid abnormalities in haemodialyzed patients. This group may particularly benefit from OFTT because hypertriglyceridemia is one of the most common lipid disorders observed in chronic kidney disease. In conclusion, there are high hopes that OFTT will be a new diagnostic

tool of TG level measurement that will enable a better assessment of the TG level in haemodialysis patients, but the effectiveness in clinical practice and usefulness of this test requires further studies.

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