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Review

Consensus clinical recommendations for the management of plasma lipid disorders in the Middle East

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ABSTRACT

Background: Plasma lipid disorders are key risk factors for the development of atherosclerotic cardiovascular disease (ASCVD) and are prevalent in the Middle East, with rates increasing in recent decades. Despite this, no region-specific guidelines for managing plasma lipids exist and there is a lack of use of guidelines developed in other regions.
Methods: A multidisciplinary panel of regional experts was convened to develop consensus clinical recommendations for the management of plasma lipids in the Middle East. The panel considered existing international guidelines and regional clinical experience to develop recommendations.
Results: The panel's recommendations include plasma lipid screening, ASCVD risk calculation and treatment considerations. The panel recommend that plasma lipid levels should be measured in all at-risk patients and at regular intervals in all adults from the age of 20 years. A scoring system should be used to calculate ASCVD risk that includes known lipid and non-lipid risk factors. Primary treatment targets include low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol. Lifestyle modifications should be first-line treatment for all patients; the first-line pharmacological treatment targeting plasma lipids in patients at moderate-to-high risk of ASCVD is statin therapy, with a number of adjunctive or second-line agents available. Guidance is also provided on the management of underlying conditions and special populations; of particular pertinence in the region are familial hypercholesterolaemia, diabetes and metabolic dyslipidaemia.
Conclusions: These consensus clinical recommendations provide practicing clinicians with comprehensive, region-specific guidance to improve the detection and management of plasma lipid disorders in patients in the Middle East.

Abbreviations: AACE, American Association of Clinical Endocrinologists; ACC, American College of Cardiology; ACE, Africa Middle East Cardiovascular Epidemiological; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CAD, coronary artery disease; CK, creatine phosphokinase; CKD, chronic kidney disease; CVD, cardiovascular disease; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; ESRD, end-stage renal disease; FCHL, familial combined hyperlipidaemia; FDA, Food and Drug Administration; FH, familial hypercholesterolaemia; FRF, Framingham Risk Factor; GFR, glomerular filtration rate; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; IAS, International Atherosclerosis Society; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); MetS, metabolic syndrome; RA, rheumatoid arthritis; TC, total cholesterol; TG, triglyceride; ULN, upper limit of normal; VLDL, very low-density lipoprotein; WC, waist circumference.

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1. Background

Disorders of plasma lipids are key risk factors for the development of atherosclerotic cardiovascular disease (ASCVD) [1,2], which is a leading cause of morbidity and mortality worldwide [3]. Typical disorders of plasma lipids include elevated levels of low-density lipoprotein cholesterol (LDL-C), elevated non-high-density lipoprotein cholesterol (non-HDL-C), elevated plasma triglyceride (TG), and low levels of high-density lipoprotein cholesterol (HDL-C) [1]. These plasma lipid disorders may be primary, occurring due to the interaction of genetic susceptibility and environmental risk factors or secondary [4,5], occurring as a result of other disorders (e.g. diabetes, hypothyroidism, nephrotic syndrome) [5–7].

Disorders of plasma lipids are a well-known problem in the Western world [8], and are an issue of increasing importance in the Middle East. Although estimates are hampered by a lack of clinical studies in the region and by inconsistencies in the definitions and thresholds used in those studies that have been conducted, the prevalence of plasma lipid disorders in the region is high [9]. Available data vary in their estimates [10–16], with prevalence as high as 50% or more in some areas. A literature review assessing the prevalence of plasma lipid disorders in Gulf countries, using studies published from 1987 to 2010, found that reported rates ranged from 3% to 52% across varying population types [10]. Similarly a further study of hypercholesterolaemia in the Gulf region, evaluating data from 1990 to 2014, found the prevalence range to be 17–55% in males and 9–54% in females [11]. A large ($n = 4378$) study in the Middle East and Africa found that 70% of stable outpatients who attended general practice clinics had disorders of plasma lipids; in all countries in the study, the prevalence of these disorders in this population was >50% [16]. Of these, only 16% of subjects were receiving lipid-lowering medications and many subjects were not achieving LDL-C goals recommended in international guidelines [16]. Large ($n > 6000$) prospective registries of patients with acute coronary syndrome conducted in Gulf countries (GULF RACE and GULF RACE-2) estimated the prevalence of plasma lipid disorders to be 31–32% [12,13].

In addition to these high prevalence rates, the profile of plasma lipid disorders observed in the Middle Eastern population differs somewhat to that seen in many other regions, with metabolic dyslipidaemia (high TG, low HDL-C and high or normal LDL-C) being one of the most common types [9]. The presentation of high TG and low HDL-C levels has also been observed among patients in the region who are already receiving chronic statin treatment; the DYSIS Middle East study ($n = 2182$) found that 62% still have high LDL-C levels, 56% have low HDL-C levels, and 49% have high TG levels [17]. A number of key risk factors for metabolic dyslipidaemia are common among the population, including type 2 diabetes mellitus (T2DM) and metabolic syndrome (MetS) [9]. There is also a high prevalence of heterozygous and homozygous familial hypercholesterolaemia (FH), possibly secondary to a high prevalence of consanguineous marriages [9]. The prevalence of many of these factors has increased in the region over recent decades [18,19]. A further characteristic of the Middle Eastern population is an earlier onset of ASCVD compared with populations in Western countries. The INTERHEART study, a case-control study conducted in 52 countries, found that the Middle East has the lowest average age to first myocardial infarction (51 years) [20].

International guidelines exist and all agree on most key recommendations [2,4,5,21], however there is lack of awareness and adherence to these international guidelines by local healthcare professionals [9]. This paper aims to provide practical recommendations for the management of plasma lipid disorders, specifically for Middle Eastern populations [9].

1.1. Aim

A multidisciplinary panel of regional experts in plasma lipid disorders was convened with the aim of developing consensus clinical recommendations for the management of plasma lipids in the Middle East.

The panel considered a number of existing international guidelines, including:

- *American College of Cardiology* (*ACC*)/*American Heart Association* (*AHA*): Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. 2013 [5].
- *European Society of Cardiology* (*ESC*)/*European Atherosclerosis Society* (*EAS*): Guidelines for the Management of Dyslipidaemias. 2011 [4].
- *International Atherosclerosis Society* (*IAS*): Global Recommendations for the Management of Dyslipidemia. 2013 [21].
- *National Lipid Association*: Recommendations for Patient-Centered Management of Dyslipidemia. 2015 [2,22].
- *Kidney Disease Improving Global Outcomes* (*KDIGO*): KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease. 2013 [23].
- *American Association of Clinical Endocrinologists* (*AACE*): Guidelines for Management of Dyslipidemia and Prevention of Atherosclerosis. 2012 [24].

There is a high degree of agreement in the recommendations proposed in these international guidelines. In cases where the international guidelines disagreed, or did not make specific recommendations of relevance to the Middle East, the panel came to consensus based on comprehensive literature searches and regional clinical experience.

The recommendations from the panel are detailed in the following sections.

2. Screening

Screening for plasma lipid disorders should be performed in all patients with T2DM [4,22], evidence of ASCVD [4,22], arterial hypertension [4], central obesity [4], chronic inflammatory autoimmune disease [4], chronic kidney disease (CKD) [4,22], a family history of ASCVD, and in the offspring of patients with severe disorders of plasma lipids (e.g. FH) [4] (Box 1). These patients are considered to be at high risk for plasma lipid disorders and the development of ASCVD. Screening should also be considered in all adults ≥20 years old and should be repeated every five years [22].

2.1. Screening endpoints

2.1.1. Assessment of lipids

Screening should include the measurement of lipid levels including LDL-C, plasma total cholesterol (TC), TG, HDL-C and non-HDL-C. Either fasting [4] or non-fasting [22,25] measurements may be used.

Direct methods for measuring LDL-C should be used if available. Calculation of LDL-C is also possible using Friedewald's formulae, although this method is subject to a number of assumptions and limitations and cannot be used if TG levels are high [4].

Measurement of non-HDL-C provides an estimate of the concentration of cholesterol in all atherogenic lipoproteins in the plasma (very low-density lipoprotein [VLDL], intermediate-density lipoprotein and LDL). Non-HDL-C is calculated by subtracting HDL-C levels from plasma TC levels [4,21,22]. Commercially available assays should be used for measuring HDL-C, TC and TG levels, including assay validation with reference and control agents [4].

Elevated plasma lipoprotein(a) (Lp(a)) levels are also indicative of an increased ASCVD risk [4,26,27] and elevated levels require a specific treatment approach (see Section 7.2). Therefore, measurement of Lp(a) should be considered in high-risk patients [4]. Lp(a) can be measured using a commercially available, size-insensitive assay – it is important to ensure assay standardisation [4].