

TWO ADULTS WITH HYPERTRIGLYCERIDEMIA

How should one manage these persons?#

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Editor's note: Dr Prabha Nair and Dr Maile Nyon provided the following two scenarios and Professor Jayasinghe was invited to respond.

ABSTRACT

The paper discusses the management of two individuals with asymptomatic hypertriglyceridemia, a common problem faces by Family Physicians in Malaysia. In such instances it is advisable to exclude an underlying disorder (e.g. metabolic syndrome) and take a pragmatic approach.

Keywords: Dyslipidemia, hypertriglyceridemia, guideline

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Published guidelines state that very high levels (>5.65 mmol/L) confers a risk for acute pancreatitis and should be treated. Therapy includes, diet, weight reduction, exercise, niacin, fibrates and even statins. The indications and treatment regimes for TG levels <5.65 mmol/L are less well defined, mainly because there is uncertainty on the role of TG in coronary artery disease. For example, recent evidence suggests that high fasting and non-fasting TG are risk factors for coronary artery disease. The clinician should therefore consider among other factors, the level of TG and other lipoproteins (e.g. LDL), evidence that some drugs (e.g. statins and n-3 fatty acids) improve mortality rates, and the potential susceptibility of certain ethnic groups (e.g. southern Asian groups) to develop coronary artery disease.

Case 1

Mr X, 47-years-old Chinese businessman, was diagnosed to have hypertriglyceridaemia since age 30. He seldom exercises, is a non-smoker and a social drinker of wine. Mr X's sister, his only sibling, has hyperlipidaemia. His parents died of "old age". He does not have hypertension, diabetes or ischaemic heart disease. He was treated before with simvastatin-ezetimibe and fenofibrate but his serum triglyceride remains unchanged.

<u>Fasting serum lipid</u>	<u>Result</u>	<u>Desirable values</u>
Total cholesterol	4.9	<5.2 mmol/L
Triglycerides	4.7	<1.7 mmol/L
HDL-C	1.0	>1.0 mmol/L
LDL-C	*	<2.6 mmol/L
Total cholesterol/HDL-C	5.1	<4.5

*serum slightly lipaemic. LDL-C inaccurate when TG >4.5

Case 2

Mr Y a 36-year-old was detected to have hypertriglyceridemia during a health screening. He is otherwise healthy. Clinically there is no xanthoma. His BMI is 22 kg/m². [His family is being screened for hyperlipidemia]. There is no family history of heart disease.

<u>Fasting serum lipid</u>	<u>Result</u>	<u>Desirable values</u>
Total cholesterol	7.1	<5.2 mmol/L
Triglycerides	17.0	<1.7 mmol/L
HDL-C	0.5	>1.0 mmol/L
LDL-C	*	<2.6 mmol/L
Total cholesterol/HDL-C	14.2	<4.5

*serum lipaemic. LDL-C inaccurate when TG >4.5

Fasting glucose 6.3 mmol/L, 2-hour post-meal glucose 5.5 mmol/L

Principles of care

Both these persons appear to be healthy, but with fasting dyslipidemia with no evidence of coronary artery disease. They lack a clinical disease and should not be considered as "patients". (#)

The initial step in the management of hypertriglyceridemia is to rule out contributory causes, such as diabetes mellitus, alcohol intake, nephrotic syndrome and chronic renal disease, hypothyroidism and metabolic syndrome. The fact that Mr X's sister has hyperlipidemia indicates a familial dyslipidemia. More details are also required about his social drinking pattern to rule out excess alcohol intake. A normal BMI, mentioned in Mr

Y, is inadequate to detect abdominal obesity (a feature of metabolic syndrome) and waist circumference should be measured in both.

Asymptomatic persons with deranged biochemical tests require interventions only if they are at higher risks of diseases in the future (i.e. primary prevention). When one considers medium to longer-term risks of dyslipidemias, the main concern is coronary artery diseases. Quantifying the risks enables the physician to decide on therapy. Risk assessment is based on analysis of longitudinal follow-up of large-community cohorts (e.g. Framingham study) and the derivation of scoring schemes or algorithms. Risks are often expressed for different age groups, sex and at for a defined period (e.g. risks for the next 10 years).

Approach used to decide on therapy

A commonly used approach to decide on treatment of dyslipidemia is to follow the guidelines of the Coordinating Committee of the National Cholesterol Education Program

(NCEP).^{1,2} The NCEP third Adult Treatment Panel report (ATP III) is summarized as an "At-A-Glance Quick Desk Reference" by the National Institute of Health, and accessible via the internet.³ ATP III and other guidelines estimate risks based on age, sex, total cholesterol or low density lipoprotein cholesterol levels (LDL-C), systolic blood pressure, treatment for hypertension, diabetes mellitus status, and smoking, and attach less importance to triglyceride levels.^{2,4} (An alternative graphic method described in the British National Formulary uses different criteria).⁵

The goal of therapy in ATP III is mainly to achieve appropriate LDL levels, and less is mentioned of triglyceride (TG) levels. This situation may change in future, because of our understanding of the role of TG and apolipoproteins in premature atherosclerosis.^{6,7} There is fresh evidence that non-HDL-C and apolipoprotein B levels are even better predictor of cardiovascular risk than LDL.⁷ Table 1 applies the steps proposed in reference 3, in order to answer the management issues in the two scenarios.

Table 1. Summary of steps involved in assessing risks

STEPS ADAPTED FROM GUIDELINES ³	Mr X	Mr Y
Step 1: Determine lipoprotein levels	Borderline HDL-C	Elevated serum cholesterol and low HDL-C.
Step 2: Identify presence of clinical atherosclerotic diseases that confers high risk for coronary artery disease events ^a	None	None.
Step 3: Determine presence of major risk factors ^b	Two major risk factors: low HDL-C; age (>45 years).	One major risk factor: the low HDL-C.
Step 4: If 2+ risk factors are present without CHD, assess 10-year (short-term) CHD risk using Framingham tables (see reference 3)	Score of 8, equivalent to a 10-year risk of 4%.	Not applicable as he has only one major risk factor.
Steps 5-7: Determine risk category, and establish the target LDL	Not available	
Step 8: Identify metabolic syndrome and treat, if present after 3 months of therapeutic lifestyle change	Thus the importance of measuring if waist circumference	
Step 9: Treat elevated TG based on levels with appropriate LDL, non-HDL cholesterol targets. For TG, 1.7 -2.26 mmols/L = borderline high; 2.27-5.64 mmol/L = high and > 5.65 mmol/L = very high	TG 4.7 mmol/L. Requires only lifestyle change.	TG 17.0 mmol/L. First lower TG. Lifestyle changes, with drugs (fibrates, nicotinic acid or fish oils).
Step 10: Goals for LDL <3.36 mmol/L for 2+ risk factors and 10-year risk ≤20% <4.14 mmol/L for 0-1 risk factors	Recheck LDL later. Goal <3.36 mmol/L	Recheck LDL later. Goal <4.14 mmol/L
Step 11: Goals for non-HDL-C <4.14 mmol/L for 2+ risk factors and 10-year risk ≤20% <4.91 mmol/L for 0-1 risk factors	Non-HDL-C is 3.9 mmol/L. Has reached goal of <4.14 mmol/L	Non-HDL-C 6.6 mmol/L. Aim to reduce to <4.91 mmol/L
Step 12: Goals for HDL-C >1.0 mmol/L	Already achieved	HDL-C 0.5 mmol/L. Aim to increase to above 1 mmol / L

^aDiseases that that confer high risk for events: clinical coronary heart disease, symptomatic carotid artery disease, peripheral arterial disease, abdominal aneurysm, and diabetes

^bMajor risk factors: cigarette smoking, BP ≥140/90 or on antihypertensive, low HDL (<1mmol / L), family history of premature coronary heart disease (first degree relatives male ≤55 years and female ≤65 years), age ≥45 years for males and ≥ 55 years for females

Summary of treatment

A crucial question in the management of hypertriglyceridemia is whether treatment should focus on reducing TG levels or towards modification of other lipids that confer a risk for coronary artery diseases.⁷ Both require appropriate lifestyle changes. Mr X should be advised to reduced intake of fat, replace saturated fat with complex carbohydrates and mono- and poly-unsaturated fats (favourable effect on HDL), avoid simple sugars particularly fructose (they lead to postprandial hypertriglyceridemia), weight management, and advised to increase physical exercise.⁷ Once TG is below 4.5 mmol/L, LDL could be measured and a goal of <3.36 mmol/L achieved.

Mr Y needs drugs to rapidly reduce TG levels and prevent acute pancreatitis. His lifestyle changes ($\leq 15\%$ of calories from fat, intensive control of weight, increased physical exercise) should be combined with fibrates (e.g. gemfibrozil), nicotinic acid or fish oil.⁷

The risk of coronary artery disease does not increase as result of very high concentrations of triglycerides, because the molecule is being transported by chylomicrons (as indicated by the very high TG levels together with lipemia). Chylomicrons rarely produce premature atherosclerosis because the particles are too large to enter into the intima and induce atheroma formation.⁶ However, the high non-HDL-C concentration of 6.6 mmol/L (i.e. 7.1-0.5) and low HDL are of concern. Therefore one could add a statin. The combination of nicotinic acid and simvastatin has been shown to reduce the progress in atherosclerosis in those with low HDL-C and borderline TG.⁷ Once TG is below 4.5 mmol/L, LDL should be measured and treated if >4.14 mmol/L. There is increasing evidence that in primary prevention of coronary heart diseases, statins (e.g. simvastatin), and n-3 fatty acids reduce mortality, in contrast to fibrates where the mortality outcomes are less convincing.⁷⁻⁹

A final point to be aware is the considerable ethnic variation in severity and outcomes of coronary artery disease. Studies in Singapore suggest that persons of southern Asian origin are at higher risk, while Malays have a poorer prognosis.¹⁰ Thus the physician may err on the side of caution when using scoring systems adapted from studies such as Framingham where the population consists mainly of Caucasians.

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