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Review Article

Internal Medicine Section

Vascular Disease in Young Indians (20-40 years): Role of Dyslipidemia

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ABSTRACT

Dyslipidemia is an established risk factor for cardiovascular disease (CVD). Atherosclerosis begins early in life as suggested by "fatty streaks" observed in coronaries of healthy organ donors aged 20-29 years. Premature occurrence of coronary heart disease (CHD) in Indians, increases the risk for young individuals. Management of Dyslipidemia in the young Indian poses several challenges. In this article we provide in-depth review of prevalence, guidelines' perspective and expert comments on management of Dyslipidemia in the young (20-40 years) Indian.

Keywords: Diet, Epidemiology, Management

INTRODUCTION

Dyslipidemia is an established risk- factor for cardiovascular disease (CVD. Dyslipidemia is defined by abnormal levels of Total Cholesterol (TC) or Low-Density Cholesterol (LDL-C), High-Density Cholesterol (HDL-C) and Triglycerides (TGs) individually or in combination [1]. Occurrence of coronary heart disease (CHD) prematurely in Indians raises concerns for young individuals, with high TGs and/or low HDL-C [2]. Along with other risk- factors like family history, obesity, tobacco use; Dyslipidemia is also a predictor of CVD outcomes in the young as like older adults [3]. Atherosclerosis begins early in life as suggested by "fatty streaks" observed in coronaries of 37% healthy organ donors aged 20-29 years [4]. Predicting 10 years Cardio Vascular (CV) risk may underestimate the total CV risk impacted later in life. Thus a long term risk perspective becomes essential in the young [5]. Management of Dyslipidemia in the young Indian poses challenges and in this article we provide in-depth review of prevalence, guidelines' perspective, and expert comments on management of Dyslipidemia in the young (20-40 years) Indian.

EPIDEMIOLOGY

Definition of Dyslipidemia are described in [Table/Fig-1] [1,6]. In a retrospective analysis of young patients (< 40 years, n=403) with Coronary Artery Disease (CAD), Aggarwal et al., reported that low HDL (69.5%) was the most common Dyslipidemia followed by hypertriglyceridaemia (41.9%) [2]. These findings are consistent with results from a recent large scale (n=16,607) Indian Council of Medical Research–India Diabetes (ICMR-INDIAB) study which reported higher prevalence of low HDL-C in young (20-44 years) than old with greater prevalence in females than males. High rates of Dyslipidemia even in the youngest age groups (20-24 years) were observed in this study [1]. Dyslipidemia prevalence reported in different epidemiological studies among young Indians is summarized in [Table/Fig-2] [2,6-13].

MANAGEMENT OF SIMPLE DYSLIPIDEMIA

Dyslipidemia in young adults is a forerunner of high CV risk. In the Young Finns study, Nuotio et al., [14] observed that lipid measurement in early childhood improves future prediction of Dyslipidemia in adults, while Klag et al., identified a strong correlation between serum cholesterol measures in early adult life (mean age 22 years) and CV mortality in middle age life (after median follow-up of 30.5 years) [15]. Dyslipidemia has also been reported to be associated with severely impaired endothelial function and high sympathetic activity in young females [16]. Four major risk- factors which include smoking (current or past), elevated apolipoprotein B100 to apolipoprotein A-I (ApoB100/Apo-AI) ratio, history of hypertension and diabetes; showed consistent association to acute myocardial infarction (MI) among south Asian countries [17]. Non-HDL-C which measures the cholesterol content of all atherogenic lipoproteins; is considered the best discriminator to predict the presence of MI in individuals under the age of 36 years [18]. These observations reinforce the importance of Dyslipidemia screening and treatment at young age, where management of Dyslipidemia becomes more essential in the young to reduce premature CHD. Dyslipidemia intervention earlier in life is more effective than intervention later, as regards to the prevention of CVD.

Parameter	Value
Hypercholesterolaemia	Serum cholesterol ≥ 200 mg/dL (≥5.2 mMol/L)
Hypertriglyceridaemia	Serum triglyceride ≥ 150 mg/dL (≥1.7 mMol/L)
Low HDL-C	Serum HDL < 40 mg/dL (<1.04 mMol/L) in Men and < 50 mg/dL (<1.3 mMol/L) in Women
High LDL-C	Serum LDL ≥ 130 mg/dL (≥3.4 mMol/L)
High TC:HDL ratio	Ratio ≥ 4.5
Non-HDL Cholesterol	Goal non-HDL-C should be 30 mg/dL above the LDL-C goal

[Table/Fig-1]: Values of different entities for defining Dyslipidemia [1,6].

LIFESTYLE MANAGEMENT

In a recent analysis of racial/ethnic differences in Dyslipidemia, Frank et al., observed increased risk of combined hyperlipidaemias among Asian Indians. Differences in diet and physical activity probably contribute to high risk in Asians than the Western population [19]. In middle aged adults Jain et al., observed additional risk-factors like low fruit consumption, full cream, milk consumption or milk intake for CHD [20]. This suggests a changing lifestyle from young age, increases risk of CV disease.

DIETARY CHANGES FOR DYSLIPIDEMIA

Low Saturated Fat Diet

In a metanalysis, Yu-Poth et al., demonstrated that reducing saturated fatty acids in the diet primarily reduces total and LDL cholesterol whereas it has minimal effect on HDL and TG concentration [21].

Study author (year)	Population	Total number	Age (years)	Sex	Raised TC	Raised LDL	Raised TGs	Low HDL
Sawant et al., (2008) [6]	H, U	N=1805	31-40	M	42.6	77.6	47.1	65.7
				F	26.3	66.3	20.2	35.7
			≤ 30	M	27.9	65.7	30.5	61.4
				F	14.8	47.2	9.1	28.4
Estari et al., (2009) [7]	H, U	N=1496	20-39	Both	14.8		24.7	7.1
Ghosh et al., (2010) [8] Total sample=682	H	N=321	25-34	M	16	-	11	-
				F	7	-	12	-
			35-44	M	25	-	21	-
				F	27	-	23	-
Kiran et al., (2013) [9]	H, U	N=454	26*	Both	36	12	43	9
Walia et al., (2014) [10] (total sample = 2368)	H, U	N=1021	20-29	M	-	-	15.1	8.3
				F	-	-	7.3	36.7
			30-39	M	-	-	30.2	19.8
				F	-	-	27.3	50.7
Basu et al., (2015) [11] (total sample = 1621)	H, U	N=548	20-40	Both	33.5	68.6	31.2	72.9
Dwivedi et al., (2000) [12]	CAD	N=56	< 40	Both	41.6	-	44.7	37.8
Aggarwal et al., (2012) [2]	CAD, U	N=403	≤ 40	Both	-	-	74.2	83.3
				M	-	-	75.5	81.1
				F	-	-	69.2	92.3
Bhardwaj et al., (2014) [13]	AMI	N=124	<40	Both	33.0	12.9	48.3	42.7

[Table/Fig-2]: Epidemiological studies describing prevalence of Dyslipidemia in young (20-40 years) Indians.
* Mean value. H-Healthy, U-Urban, CAD-Coronary artery disease, AMI-Acute myocardial infarction. M-male, F-female.

Reduced Intake of Sugar Sweetened Beverages

Increased intake of sugar-sweetened beverages in children and adolescents has independent association with reduced HDL, increased C - reactive protein (CRP) and increased waist circumference [22]. In the United States (US), mean age of adults receiving 25% or more total energy from added sugars was 38.1 years. In such adults, Welsh et al., reported a significant linear correlation with lower HDL and higher TG levels as compared to those receiving lesser total energy. Odds of low HDL increase substantially to 300% or more among high consumers of added sugar (≥10% total energy) than low consumers [23]. Reducing intake of such beverages might help alleviate risk of Dyslipidemia. Basu et al., suggest sustained high rate of taxation on sugar-sweetened beverages can possibly help avert obesity and diabetes in Indian population [24].

Increased Fruits and Vegetable Intake

In young adults, consumption of fruits and vegetable is low as identified in Finnish young adults [25]. Increased intake of fruits and vegetables lowers risk of all-cause mortality particularly CV mortality [26]. Intake of almonds (10 g/day) significantly increased HDL cholesterol (14-16% by 12 weeks) in CAD patients [27]. Thus effective dietary interventions with increased intake of fruits and vegetable are essential to improve Dyslipidemia in young adults.

Quit All Tobacco

Risk of early onset CAD may be increased in patients with smoking associated lower levels of HDL [28]. Smoking can affect differentially the two genders; TGs and HDL impacted more in men whereas TGs mainly in females [29]. Gupta et al., observed significantly lower HDL levels in tobacco chewers than smokers and control subjects. They reported chewing tobacco is an equivalent risk-factor as smoking [30]. Neki observed similar Dyslipidemia pattern was in young smokers [31]. Quitting tobacco in all forms is essential to improve Dyslipidemia. It should be strongly emphasized in young individuals to reduce long-term CV risk.

Physical Exercise

Importance of physical exercise is universal. Combination of dietary and exercise therapy is a primary and effective means of improving *dyslipidemic* profile and should always precede drug therapy in young individuals [32].

[Table/Fig-3] provides effective dietary and exercise interventions that can be implemented in *dyslipidemic* young adults.

Intervention	Recommendation / Observations
Total calories	Restrict to biological needs
Dietary Fibers	Average intake 35 gm/day
Proteins	Up to 15% of total caloric intake
Carbohydrates	Up to 65% of total caloric intake
DASH Diet	Increase HDL by 4 mg/dL and reduces LDL by 11 mg/dL., has no effect on TG levels
DASH Diet - variant (10% calories from carbohydrates replaced with that from proteins)	Provides reduction in LDL (3 mg/dL), TGs (16 mg/dL) and increase in HDL (1 mg/dL)

[Table/Fig-3]: Dietary changes for Dyslipidemia in young DASH-Dietary Approaches to Stop Hypertension.

MEDICATIONS

Prescribing medications in Dyslipidemia management is driven by two hypothesis.

1. Goal lipid levels
2. CV risk

Achieving desired lipid levels was a strong driving force for prescribing lipid lowering medications after adult treatment panel III recommendations [33]. But this approach is now taken over by CV risk hypothesis. Recent recommendations from American lipid lowering guidelines, prescribing lipid lowering medications mainly statin is based on CV risk of an individual and not on specific LDL goal [34].

Statins

For primary prevention, any adult above 21 years of age, statin prescription was advised only if LDL levels were ≥ 190mg/dL. For LDL level below 190 mg/dL, statins were advised if 10-year atherosclerotic CVD (ASCVD) risk was above 5% (estimated from pooled cohort equations). For 10-year ASCVD risk <5%, additional factors are recommended to be considered and to be

discussed with patient namely potential risk reduction benefits, adverse effects and drug-drug interactions, etc. In case of unclear decisions, primary LDL levels ≥ 160 mg/dL, family history of premature ASCVD, lifetime ASCVD risk, abnormal coronary artery calcium score, ankle brachial index or high-sensitivity C-reactive protein (hs-CRP) levels (≥ 2mg/dL) are to be considered. A moderate intensity statin is recommended for low-risk individuals. For secondary prevention in an individual with ASCVD, a high intensity statin therapy is recommended in addition to healthy lifestyle therapy. In patients at risk for drug-drug interactions or statin intolerance, moderate intensity is recommended [34].

10-year versus 30-year (lifetime) CV risk

Commonly Framingham risk score are utilized to calculate CV risk in individuals. In a viewpoint Steinberg explains why looking at 30 years CV risk with Framingham risk score is important in young individuals. Since atherosclerosis starts early in life and stays for long with modifications in composition over time, early intervention with medications may change the future outcome. But such evidence establishing benefits for 30-year risk approach is not feasible. Starting statin treatment for familial hypercholesterolaemia is undoubted but concerns are raised for starting statin in a 25-year-old with low lifetime risk of ASCVD [5].

Non-Statin Medications

For a high risk individual deriving less than anticipated response to a maximally tolerated intensity of statin, addition of non-statin agent is to be considered only if risk reduction benefit outweighs the risk for adverse effects, and drug that has shown to reduce ASCVD risk in clinical trials is preferred [34]. Even though we identify high degree of hypertriglyceridaemia in young Indians, there are no randomized controlled trials (RCTs) or observational studies to define risk reduction benefits observed with any non-statin drug especially fibrates. A goal based approach should prevail to reduce TGs to below 150 mg/dL.

MANAGEMENT OF COMPLEX DYSLIPIDEMIA

Dyslipidemia associated with any comorbid conditions is more complex and has significant implications for management. Here we discuss Dyslipidemia associated diabetes mellitus, hypertension, and kidney disease in the young.

Dyslipidemia and Diabetes

Young individuals with type 2 diabetes mellitus are often inadequately treated for risk-factors like Dyslipidemia [35]. In Malaysian adults, Chew et al., observed that young age was the major determinant of uncontrolled lipids [36]. Interestingly, after 20 years follow-up of black and white young adults, Paynter et al., reported Dyslipidemia to be the first CV risk-factor to appear and precedes other risk-factors [37]. Comparing complications rate in type 1 and type 2 diabetes (T2DM) among young (15-40 years) diabetics, T2DM cohort had an older age with higher occurrence of Dyslipidemia (p<0.0005) [38].

The American lipid lowering guidelines advocates statin therapy for LDL levels <190 mg/dL in diabetic individuals below 40 years with due consideration of additional risk-factors as described above [34]. Applying this principle to young Indian will have to be looked upon as insulin resistance may play a central role in diabetic Dyslipidemia. Tai et al., in a National Health Survey of 3568 individuals in the general population reported that individuals with low HDL and high TGs had insulin resistant syndrome features [39]. This finding supported the fact that Asian Indians are predisposed to low HDL cholesterol and insulin resistance [39,40]. This observation correlated with epidemiological findings described in young Indians [Table/Fig-2].

Improving insulin resistance with antidiabetic medications improved hypertriglyceridaemia and HDL levels [41,42]. Reducing fasting and postprandial hyperglycaemia is an essential element in managing Dyslipidemia in diabetic individuals.

Dyslipidemia and Chronic Kidney Disease

The benefits derived with statin therapy is related to baseline CV risk than LDL levels. In individuals on dialysis, higher or lower levels of LDL and TC have higher risk adverse CV outcomes. In Chronic Kidney Disease (CKD) patients not on dialysis, linear correlation has been reported between LDL >100 mg/dL and risk of MI. Prescribing statin therapy in any individual with CKD is determined by baseline coronary risk and evidence supporting clinical benefits. A statin should be prescribed for young adults (18-49 years) with CKD not on dialysis or kidney transplantation if they have known CAD or diabetes or prior ischaemic stroke or 10 year ASCVD risk > 10% [43].

Dyslipidemia and Hypertension (HTN)

Evidence suggests that in patients with Dyslipidemia there is future risk of hypertension [44]. Dyslipidemia associated with HTN substantially increases CV risk. Dalal et al., aptly call this association as '*lipitension*' [45]. In Indian hypertensive patients (aged 18-45 years) with mean age 33.42±0.8, Naz et al., demonstrated significantly higher levels of TGs, LDL and lower levels of HDL compared to non-hypertensive controls [46]. Renin-Angiotensin-Aldosterone (RAAS) blockers and calcium channel blockers should be the preferred choice of medication in *dyslipidemic* patients. Beta blockers and thiazide diuretics tend to derange lipid levels [45]. Thus identifying Dyslipidemia in young with hypertension and treatment with statins definitely reduces future CV risk.

GUIDELINES: PERSPECTIVE FOR THE YOUNG

Dyslipidemia management guidelines are provided by different international societies and forums [34,47-52]. Recent American College of Cardiology guidelines provides specific recommendations on statin therapy for primary and secondary prevention of ASCVD. For younger patients (<40 years), guidelines identify insufficient RCT evidence and advocates clinical judgment based on lifetime ASCVD risk based on single strong factors or multiple risk-factors. Further it cites that there is no primary prevention evidence from RCTs in young individuals aged 21-39 years. The guidelines clearly says "*in adults with LDL-C <190 mg/dL who are not otherwise identified in a statin benefit group or for whom a risk-based treatment decision is uncertain after quantitative risk assessment, clinician knowledge, experience, and skill ("the art of medicine") and patient preferences all contribute to the decision to initiate statin therapy*" [34]. National lipid association guidelines also suggest lipid lowering treatment based on lifetime risk of ASCVD in young (<40 years) individuals (NLA 2014) European Society of Cardiology guidelines recommend use of relative risk chart for risk derivation in young people. Further, it identifies no need of medications in young (<40 year) with T2DM, short duration treatment, without any other risk-factor, complications and with LDL<100 mg/dL [50]. The Canadian lipid guidelines also identifies that assessing risk in young even with only one risk-factor for premature ASCVD could possibly benefit in modifying lifestyle therapy. It also recommends statin therapy for young adult of age 30 years and above with diabetes of more than 15 years duration irrespective of CV risk [47]. World Health Organization guidelines offered a different view in regards to drug treatment. Treatment benefits measured in terms of life-years gained than only avoiding CV events make an approach for drug treatment [51].

STATIN INTOLERANCE – ISSUES IN YOUNG

Statin Associated Muscle Symptoms (SAMS)

Statins are known to cause muscle symptoms with or without elevation in Creatine Kinase (CK). In general muscle symptoms

associated with 4 times elevation in CK are at increased risk of muscle damage.

Though young individuals are not at increased risk of SAMS, other risk-factors need to be looked carefully in these individuals. Asian ethnicity, female sex, low Body Mass Index (BMI), high level of physical activity, excess alcohol and drug abuse are potential risk-factors that can be attributed to higher risk of SAMS in young. Some of these factors are at peak in 20-40 years individuals so due consideration should be given to any muscle symptoms in these individuals. Vitamin D deficiency has been observed in most of the Indians and is also one of the risk-factor contributing to SAMS. Drugs like fibrates, macrolide antibiotics, azole antifungals, and warfarin can increase SAMS and may be responsible for rhabdomyolysis in rare instances [52].

Liver Toxicity

Elevation in alanine or aspartate transaminases (ALT and AST) is observed after initiation of statins. Convincing evidence supporting the fact that increase in AST or ALT with statins are associated with liver damage is lacking. There is no increased risk of liver toxicity documented in young individuals.

The evidence on safety of statins in Indian setting is limited and does not show increase in rate of adverse events.

CONCLUSION

- Dyslipidemia in young Indians vary in prevalence with some differences in males and females.
- High prevalence of low HDL and high TGs characterizes young Dyslipidemia similar to adult Indians.
- In managing simple Dyslipidemia without comorbidities, lifestyle therapy is crucial. A strict adherence to lifestyle management is mandated.
- Dietary interventions should be encouraged.
- Non-availability of specific medication to increase HDL makes management of this Dyslipidemia difficult.
- Treatment approach should be based on two parameters. LDL level approach may be considered when CV risk calculation is uncertain.
- Lifetime CV risk approach should prevail over 10-year CV risk. But lack of validated evidence with lifetime CV risk approach makes it difficult to apply in clinical practice.
- A 10-year CV risk approach with consideration of additional risk-factors should be the ideal way to justify statin prescribing in the young.
- We suggest involvement of patients to make choices after discussing risk/benefit ratio before starting statins.
- We can't comment on other lipid lowering drug use in young individuals since evidence supporting their use in young individuals to reduce CV risk is lacking.
- Use of fibrates, niacin, and other agents should be based on physician and patients' choices, clinical experience, affordability and accessibility factors.
- In diabetes, moderate to high intensity statin may be used after due consideration of adverse events risks and benefits.
- Experience with use of statins in other comorbidities especially in young is lacking. Clinical judgment and patient considerations is the best practice for such situations.
- Different guidelines suggest different approach for lipid management. 2013 ACC-AHA guidelines consider CV risk approach whereas some refer to LDL levels.
- Estimating CV risk with use of risk calculators or risk charts is advisable.
- We expect similar tolerance levels for statins in young adults.
- While using high intensity statin in young Indians, muscle symptoms/myopathies need careful observation. High level of physical exercise, alcohol, illicit drug abuse may increase risk of myopathy in young.
- For severe myopathy, discontinue statin. Reintroduce with lower dose or use other statin with low propensity of muscle symptoms.
- Limited evidence on safety even in general Indian population exists. We opine that statin discontinuation and reintroduction should be based on individual choices and clinical judgment of the treating physician.

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