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Dyslipidemia in Special Ethnic Populations

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Synopsis

This manuscript reviewed racial/ethnic differences in dyslipidemia, including prevalence of dyslipidemia, its relation to CHD and stroke mortality rates, response to lipid-lowering agents, and lifestyle modification. In particular, among all racial/ethnic groups, Asian Indians, Filipinos and Hispanics are at higher risk for dyslipidemia, which is consistent with the higher coronary heart disease (CHD) mortality rates in these groups. In addition, compared to other racial/ethnic groups, statins may have a higher efficacy for Asians. Studies suggest lower starting dosage in Asians, but the data are mixed. Genetic differences in statin metabolism can in part explain this racial/ethnic difference in statin sensitivity and adverse effects. Furthermore, lifestyle modification is recommended as part of dyslipidemia control and management. Both African Americans and Hispanics have more sedentary behavior and less favorable diet profile. Hispanic subgroups (i.e. Mexican, Puerto Rican, etc.) and Asian (i.e. Chinese, South Asian, etc.) subgroups should be disaggregated for lifestyle interventions due to cultural differences among the subgroups. Further studies are needed to better understand racial/ethnic-specific risk factors contributing to the

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observed differences in dyslipidemia, CHD, and stroke. Culturally-tailored prevention and intervention should be provided to the minority populations with elevated risk for dyslipidemia and considerably more research is needed to determine the best approaches to helping specific subgroups.

Keywords

Dyslipidemia; Racial/ethnic differences; Prevalence; Mortality; Treatment; Lifestyle modification

Introduction

Dyslipidemia, including high levels of low density lipoprotein cholesterol (LDL-C) (≥ 130 mg/dL), total cholesterol (≥ 200 mg/dL), and triglycerides (TG) (≥ 150 mg/dL), or low levels of high density lipoprotein cholesterol (HDL-C) (<40 [men] and <50 [women] mg/dL), is one of the leading risk factors for coronary heart disease (CHD) and stroke.¹ A report of the National Health and Examination Survey (NHANES) from 2003–2006 estimated that 53% (105.3M) of U.S. adults have at least one lipid abnormality: 27% (53.5M) have high LDL-C, 23% (46.4M) have low HDL-C, and 30% (58.9M) have high triglycerides (TG). In addition, 21% (42.0M) of U.S. adults have mixed dyslipidemia, defined as the presence of high LDL-C combined with at least one other lipid abnormality.²

Significant heterogeneity in patterns of dyslipidemia prevalence, its relation to CHD and stroke mortality rates, and response to lipid-lowering agents has been observed across racial/ethnic groups.³ These differences in dyslipidemia provide important information that may in part explain the variation in CVD burden observed across racial/ethnic subgroups. Better understanding of dyslipidemia in special racial/ethnic populations is needed to guide prevention, screening, and treatment efforts.

Prevalence of dyslipidemia subtypes among special racial/ethnic groups

The National Health and Nutrition Examination Survey (NHANES) is the primary data source for national prevalence rates of dyslipidemia in the U.S, sampling mainly non-Hispanic whites (whites), non-Hispanic blacks (blacks) and Mexican Americans. The NHANES has very limited samples from the Asian subgroups.⁴ Other data sources, such as primary care settings and observational studies contribute to a comprehensive picture of racial/ethnic differences in dyslipidemia by providing important information about races and ethnicities that are less represented in the NHANES. One should be aware that the prevalence of dyslipidemia varies by data source. The observed differences in the prevalence rates of dyslipidemia between studies can be attributable to factors such as study design, sampling methods, time period, geographic variation, and participants' characteristics.

Low Density Lipoprotein Cholesterol

NHANES data in 2013 showed the prevalence rate of high LDL-C was highest among Mexican men (40%) and women (30%), followed by non-Hispanic black men (33%) and

women (31%). Non-Hispanic white men (30%) and women (29%) had the lowest prevalence of high LDL-C among the three racial/ethnic groups.⁵

Similarly, data from a clinic based cohort in northern California from 2008–2011 showed 63% of black men and 57% of black women had high LDL-C, which were slightly higher than the prevalence rates among non-Hispanic white men (62%) and women (53%).³ Further, Mexican American men (66%) and women (57%) also had higher prevalence of high LDL-C compared to non-Hispanic whites.³ Filipino men (73%) and women (63%) had the highest prevalence rates of high LDL-C among Asian subgroups, non-Hispanic whites, non-Hispanic blacks, and Hispanics.³

Several other studies provide further estimates for variation in prevalence among race/ethnic minority subgroups. Data from the Hispanic Community Health Study (HCHS)/Study of Latinos (SOL), an observational study in San Diego, Chicago, New York City, and Miami, showed variations among Hispanic subgroups with particularly high prevalence of dyslipidemia among Central American men (55%) and Puerto Rican women (41%).⁶ The Study of Health Assessment and Health Risk in Ethnic groups (SHARE) investigated prevalence of CHD risk factors for a multi-ethnic cohort from three Canadian cities. They found that South Asians, mainly Asian Indians, had an increased prevalence of higher total and LDL cholesterol compared to Europeans and Chinese.⁷

High Density Lipoprotein Cholesterol

NHANES data in 2013 showed 20% of black men and 10% of black women had low HDL-C, defined as less than 40mg/dL in both men and women, which were lower than the prevalence rates among non-Hispanic white men (33%) and women (12%).⁵ NHANES data also showed Mexican American men (34%) and women (15%) had higher prevalence of low HDL-C compared to non-Hispanic whites.⁵ According to NHANES data from 2011–2012, 25% of Asian American men and 5% of Asian American women had low HDL-C.⁸

Although NHANES data showed Asian Americans had the lowest prevalence of low HDL-C as an aggregated group, data from a clinic based cohort with disaggregated Asian ethnic groups in northern California between 2008–2011 found that Asian Indian men (53%) and women (55%) had the highest prevalence of low HDL-C among Asian American subgroups; their prevalence was also higher than Mexican American men (48%) and women (51%), non-Hispanic black men (34%) and women (40%), and non-Hispanic white men (36%) and women (31%).³ Similarly, data from the SHARE study showed South Asians including Asian Indians had an increased prevalence of low HDL-C compared to Europeans and Chinese.⁷

Triglycerides

NHANES data from 1999–2008 showed 35% of Mexican Americans had high TG, followed by 33% among non-Hispanic whites, and 16% among non-Hispanic blacks.⁹

Data from a clinic based cohort in northern California from 2008–2011 found Filipino men (60%) and Mexican women (45%) had the highest prevalence of high TG, compared to

Mexican men (56%) and Filipino women (42%), Asian Indian men (55%) and women (37%), non-Hispanic white men (43%) and women (28%), and non-Hispanic black men (30%) and women (18%).³

Data from the SHARE study showed South Asians had the highest prevalence of high TG among South Asians, Chinese, and Europeans.⁷

Potential explanations for racial/ethnic differences in dyslipidemia prevalence have been explored by several studies. In the Multi-Ethnic Study of Atherosclerosis (MESA), researchers found that ethnic disparities were attenuated substantially by adjusting for access to healthcare.¹⁰ The racial/ethnic differences could also be related to lifestyle, genetic, and cultural differences associated with total and LDL cholesterol concentrations.¹¹ For example, the predilection of South Asians to have lower HDL-C levels has been attributed to the higher prevalence of insulin resistance and related metabolic abnormalities, which may be the consequence of a combination of genetic predisposition, physical inactivity, and a high-carbohydrate diet.^{12,13,14}

Dyslipidemia-related mortality in special racial/ethnic groups

Dyslipidemia often results in an increased risk of premature atherosclerosis, a major risk factor for coronary heart disease (CHD).¹⁵ CHD is the leading cause of mortality for both men and women in the U.S. and worldwide with increasing evidence of gender and racial/ethnic minority disparities in CHD morbidity and mortality.^{16–19} Despite declines in CHD death rates over the past decades, CHD contributes to over one-third of all deaths for those over the age of 35 years.²⁰

CHD mortality rate differences have been found across races/ethnicities. In the U.S. CHD mortality rates are highest in blacks, intermediate in whites and Hispanics, and lowest in some Asian subgroups.^{15,21,22} These CHD rates are paralleled with observed racial/ethnic disparities in dyslipidemia prevalence, with higher CHD rates seen in Hispanics and blacks potentially due to limited healthcare access and other less favorable behavioral factors seen in these groups.¹⁰

Meanwhile, although traditionally known as the “model minority”, disproportionate mortality burden due to CHD and stroke has been shown among certain Asian subgroups such as Asian Indians, Filipinos, and Japanese.^{23,24} Of note, the landmark Ni-Hon-San study showed increased CHD mortality rates and decreased stroke rates among Japanese-American men compared to rates in Japan, suggesting a differential disease impact of acculturation to Westernized lifestyles.²⁵ A recent study found higher *proportional mortality* due to CHD among Asian Indians, especially in younger age groups, compared to all other racial/ethnic groups.¹⁷ Increased burden from CHD mortality has been well documented in both native and immigrant Asian Indian populations.^{7,26,27} This observation is consistent with the higher prevalence rates of dyslipidemia (especially low HDL-C) in Asian Indians compared to other Asian subgroups and non-Hispanic whites in the U.S.^{3,7,28}

Environmental and social factors (e.g. acculturation, socio-economic status, diet) have been known to increase CHD mortality risk.^{29,30} Cultural diets high in fat, increasing the risk for

dyslipidemia, are also of concern.³¹ Differences in susceptibility to CHD may also have a genetic basis, although this has not yet been adequately determined. Thus it is critical for clinicians to modify lipid management appropriately among these rapidly growing populations.

Treatment of Dyslipidemia

1. Overview

There are several U.S. Food and Drug Administration (FDA)-approved HMG-CoA reductase inhibitors (statins) and a variety of non-statin therapies available for the treatment of dyslipidemia, including bile acids sequestrants, cholesterol absorption inhibitors, fibrates, niacin, and omega-3 fatty acids. Statins are the most widely prescribed treatment for dyslipidemia, and one of the most commonly prescribed drugs in the U.S.³² In the most recent national cholesterol treatment guidelines, published in November 2013 by the American College of Cardiology (ACC)/American Heart Association (AHA),¹ the Expert Panel determined from robust clinical trial data that statins have the most acceptable CVD-risk reduction benefit and side-effect profile, and that the addition of non-statin therapy does not appear to provide further benefit in reducing CVD. Clinical trials on which cholesterol treatment guidelines are based have often underrepresented racial/ethnic minority groups. Accordingly, our knowledge of optimal statin treatment regimens, and the effectiveness, tolerability, and safety of these regimens in clinical practice, is limited across diverse racial/ethnic populations.

2. Racial/ethnic differences in risk stratification

The most recent ACC/AHA guidelines expand the criteria for patients who would benefit from statin treatment, and more than 80% of newly eligible patients are expected to have no prior CVD.³³ Therefore, they would be assessed for optimal statin treatment based on the new Atherosclerotic CVD (ASCVD) Risk Estimator.³³ This estimator is intended to improve upon previous CVD-risk estimators, including the Framingham³⁴ and Adult Treatment Panel III³⁵ risk algorithms. It was derived from several longitudinal epidemiologic cohort studies of non-Hispanic whites and blacks, and was externally validated in two cohort studies with similar populations (MESA and REGARDS),³⁶ as well as in contemporary samples of the derivation cohorts. However, studies among other race/ethnic minority groups are lacking. The ACC/AHA Work Group, which developed the algorithm for the ASCVD Risk Estimator, acknowledges that it should be used only in men and women of non-Hispanic white or non-Hispanic black decent, and that it may not accurately predict risk in other racial/ethnic groups.³⁷ Specifically, there is concern of overestimate of risk in Mexican Americans and East Asians and underestimate risk in other groups, such as Puerto Ricans and South Asians.^{37,38} Other countries with diverse racial/ethnic minority populations, such as the United Kingdom, have validated algorithms predicting risk for over 9 specific racial/ethnic sub-populations (<http://qrisk.org/>).³⁹

3. Race/Ethnic Differences in Statin Response

3.1 Statin metabolism and drug sensitivity—Much of the data on race/ethnic differences in statin metabolism have shown that some Asian subgroups are slower to

metabolize statins compared to non-Hispanic whites, which leads to higher systemic drug concentrations. Pharmacokinetic studies indicate rosuvastatin plasma concentrations are two-fold higher in Japanese relative to non-Hispanic white individuals. Rosuvastatin plasma concentrations have been shown to be similarly elevated in other Asian subgroups; these included Chinese, Malay, and Asian Indians, whose rosuvastatin concentrations were approximately 2 times higher relative to non-Hispanic whites/Hispanic whites.⁴⁰

There are several genetic variants that are associated with altered statin metabolism. Such variants include, but are not limited to, single nucleotide polymorphisms (SNPs) in the genes that encode the organic anion-transporting polypeptide (OATP)1B1 (521T>C), which regulates hepatic uptake of statins, and the adenosine triphosphate-binding cassette G2 (ABCG2) transporter (421C>A), which regulates hepatic efflux.^{41,42} Variants of both genes are associated with increased statin plasma concentrations within multiple race/ethnic groups.^{41–44} 421C>A has been found to be a SNP candidate to explain the observed racial differences in statin metabolism: the allelic frequency of 421C>A in ABCG2 is higher in Chinese (~35%) relative to Caucasians (9–14%).^{43,45}

Higher plasma levels of statins in Asians compared to non-Hispanic whites has led to concern about increased risk for statin-induced side effects in this population. Such concerns have led to a revised package insert recommending lower starting doses of rosuvastatin in this population (5mg, vs. 10mg for non-Hispanic whites).⁴⁶ Notably, in Japan, starting doses for most statins are half of what is recommended in the U.S.⁴⁷

There is less information on statin metabolism in other racial/ethnic minority groups. We are aware of one study that evaluated the pharmacokinetics of single-dose pravastatin in non-Hispanic blacks versus European Americans.⁴⁴ In this study, the OATP1B1 521T>C polymorphism was significantly associated with higher statin plasma concentrations in subjects of European vs. African ancestry.⁴⁴ This may be explained by the low allelic frequency of OATP1B1 521T>C in non-Hispanic blacks (~1%)⁴⁴ relative to non-Hispanic whites. To our knowledge no studies have been published on the pharmacokinetics of statins in Hispanics.

Myalgia (i.e., muscle pain) is one of the most commonly observed side effect associated with statins, but has been reported to occur at varying frequencies (5%–20%) in randomized controlled trials (RCT) and observational studies.^{48–50} More severe, but rare muscle side effects have also been reported, including myopathy (0.01%–0.3%) and rhabdomyolysis (0.003%–0.01%).⁵¹ To date, high-dose simvastatin (80mg) is the only statin to receive a U.S. FDA warning for increased risk of muscle damage.⁵² The use of statins in combination with other drugs has also been shown to increase the risk of adverse events.^{53,54} In HPS2-THRIVE, which included 25,673 adults from Europe and China on simvastatin 40mg/daily, a higher risk of adverse events, including myopathy, were reported in patients randomized to niacin-laropiprant relative to placebo.⁵⁵ Furthermore, the relative risk of musculoskeletal events (mostly myopathy) in the niacin-laropiprant versus placebo group was markedly higher among Chinese participants than European participants.⁵⁵ To our knowledge no safety concerns have been raised for statins alone or in combination with agents in non-Hispanic blacks or Hispanics.

3.2 Statin efficacy in Asian populations—Studies conducted in Asian countries have documented that lower statin doses can achieve similar therapeutic effects in Asian populations.

- In an open-label study of Japanese patients receiving simvastatin (initial dose 5 mg/daily), LDL-C decreased by 26% over six months; an effect that corresponds to simvastatin 20mg/daily in Western studies⁵⁶
- In a multicenter double-blind randomized controlled trial in six Asian countries, patients randomized to receive 10mg simvastatin or atorvastatin daily over eight weeks had an average LDL-c reduction of 35% and 43%, respectively, with more than 80% of patients achieving a National Cholesterol Education Program LDL-C target.⁵⁷ To see similar effects in non-Hispanic whites would generally require at least double this dose of simvastatin.
- In a prospective RCT of the primary prevention of CVD in Japan, pravastatin 10–20mg/daily reduced LDL-C by only 18% but reduced coronary heart disease by 33% relative to diet alone;⁵⁸ this level of risk reduction in CVD is similar to trials of predominantly non-Hispanic white populations taking higher daily doses of pravastatin (40mg)⁵⁹ or a higher potency statin (atorvastatin 10mg/daily)⁶⁰

It is tempting to speculate that the apparently increased effect of statins in Asians relative to non-Hispanic whites is due to genetic differences in statin metabolism; however, because comparisons in these studies were indirect and were conducted on ethnic populations outside of the U.S. or Europe, underlying cultural differences in diet and lifestyle cannot be ruled out as a causal factor.

In addition, other studies have failed to demonstrate differences in response to statins in Asian and non-Hispanic white populations.

- In combined analysis of two small multicenter open-label studies, GOALLS (included non-Asian and Asian participants) and STATT (included Asians only), the authors compared cholesterol outcomes among patients with coronary heart disease treated with simvastatin for 14 weeks.⁶¹ There were no differences in changes in LDL-C among Asians in the STATT study (N=133; –45.4 mg/dL) relative to Asians (N=15) or non-Asians (N=183) in the GOALLS study (–41.1 mg/dL and –41.2 mg/dL, respectively)⁶¹
- In an observational, prospective study in Canada, no difference in the magnitude of LDL-C lowering was observed among non-Hispanic whites and South Asians (–41% vs. –43%, respectively; P=0.40), taking atorvastatin or simvastatin (20 mg median dose for each) for more than three years in the secondary prevention of CVD⁶²
- Using data from an RCT evaluating atorvastatin versus placebo in a multi-ethnic population in the U.K., Chapman and colleagues matched White (N=198) and South Asian (N=76) cohorts receiving atorvastatin to evaluate the effects of statins across race/ethnic groups.⁶³ The authors again found no difference in the percent reduction in LDL-C among whites and South Asians (–40% vs. –39%; P=0.92)⁶³

To our best knowledge, no existing studies have shown differences in statin efficacy in non-Hispanic blacks, Hispanics, and non-Hispanic whites.^{63,64,65}

4. Lifestyle modification in special racial/ethnic groups

Lifestyle modification has been recommended to treat dyslipidemia and to reduce ASCVD risk, both prior to and in addition to the use of lipid-lowering agents.¹ These lifestyle risk factors include unhealthy diet, overweight and obesity, and physical inactivity. The American Heart Association has the following specific recommendations for individuals with dyslipidemia:⁶⁶

- Diet: Increase the intake of vegetables, fruits, and whole grains and limit intake of sweets; reduce the intake of saturated fat and trans fat
- Physical activity: engage in aerobic physical activity; 3–4 40-minute sessions per week; moderate-to-vigorous intensity physical activity

Racial/ethnic disparities also exist in these lifestyle risk factors. According to data from the Behavioral Risk Factor Surveillance System (BRFSS) in 2002, non-Hispanic whites had more fruits and vegetables in their diet compared to Hispanics and non-Hispanic blacks.^{6,67} According to the National Health Interview Survey (NHIS) 2008–2010, 71% of Hispanics were overweight or obese, followed by non-Hispanic blacks (70%), non-Hispanic whites (62%), and Asian Americans (42%). In addition, NHIS 2008–2010 also found that compared to non-Hispanic whites (20%), non-Hispanic black (17%), Asian American (16%), and Hispanic (13%) adults were less likely to meet the 2008 guidelines for aerobic and muscle strengthening through leisure time activity.⁶⁸ All these data indicate both non-Hispanic blacks and Hispanics are at higher risk for having both diet and lifestyle risk factors, and Asian Americans are more likely to be physically inactive.

A recent systematic review included nutrition and physical activity intervention studies in adult African Americans, from 2000 to 2011.⁶⁹ This study found both diet and physical activity interventions for weight loss improved cholesterol clinical outcomes among African Americans.⁶⁹ In particular, it provided evidence to support interventions in community-based settings among African Americans. A 2011 systematic review included intervention studies that promote physical activity in Hispanic adults published between 1988–2011.⁷⁰ This study concluded that physical activity interventions in Hispanics should include community-based settings, social support strategy, culturally sensitive intervention design, and staff from the same ethnic group. A systemic review of RCTs of lifestyle interventions for Asian Americans published between 1995 and 2013 concluded that lifestyle interventions improved physical activity, healthy diet, and weight control in Asian Americans.⁷¹ However, the studies included in this review were limited in cultural appropriateness. In particular, Asian subgroups were aggregated together although they have different cultures and health behavior patterns. Other recommendations include individual tailoring, education and modeling of lifestyle behaviors, and providing support during a maintenance phase.

Immigration and acculturation have a profound impact on lifestyle in both Hispanics and Asians in the U.S. For example, traditional Hispanic diets contain high levels of fiber.

However, studies found US-born Hispanics had a hard time retaining traditional diets and consumed more fat and sugar compared to their counterparts in their home countries.^{72,73} They have less access to high nutritional quality foods and are at risk for overweight/obesity.^{72,74} Similarly, traditional East Asian diets contain less total and saturated fat but more sodium intake compared to western diets and Asian Indian diets.^{75,76} However, Chinese immigrants who have lived in the U.S for more than ten years had more unhealthy diet and less physical activity compared to recent immigrants.³⁰ In contrast, higher acculturation levels were associated with more physical activity among Korean Americans.⁷⁷ Future studies should consider providing culturally-tailored, ethnic-specific interventions to these diverse immigrant populations.

Conclusions

There are significant racial/ethnic differences in dyslipidemia prevalence, dyslipidemia related mortality rates, and response to lipid-lowering agents. Among all racial/ethnic groups, Asian Indians, Filipinos and Hispanics are at most elevated risk for dyslipidemia, which is consistent with the higher CHD mortality rates in these groups. More attention should be paid to these at-risk groups for screening and treatment purposes. Compared to other racial/ethnic groups, statins may have a higher efficacy for Asians, which may potentially be explained by genetic differences in statin metabolism, but overall the data are mixed. At present it may be wise to start with a lower statin dose in an individual with Asian ancestry until the treatment and adverse effects can be determined. In addition, racial/ethnic differences in health behavior patterns should be taken into consideration when promoting lifestyle modification among individuals with dyslipidemia. In particular, Hispanic subgroups (i.e. Mexican, Puerto Rican, etc.) and Asian (i.e. Chinese, South Asian, etc.) subgroups should be disaggregated in lifestyle interventions. Further studies are needed to better understand racial/ethnic-specific risk factors contributing to the observed differences in dyslipidemia, CHD, and stroke. Culturally-tailored prevention and intervention should be provided to the minority populations with elevated risk for dyslipidemia and considerably more research is needed to determine the best approaches to helping specific subgroups.

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Key Points

- Among all racial/ethnic groups, Asian Indians, Filipinos and Hispanics are at higher risk for dyslipidemia, which is consistent with the higher coronary heart disease (CHD) mortality rates in these groups
- Compared to other racial/ethnic groups, statins may have a higher efficacy for Asians. Studies suggest lower starting dosage in Asians, but the data are mixed.
- Genetic differences in statin metabolism can in part explain this racial/ethnic difference in statin sensitivity and adverse effects
- Lifestyle modification is recommended as part of dyslipidemia control and management and both African Americans and Hispanics have more sedentary behavior and less favorable diet profile.