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ORIGINAL RESEARCH & CONTRIBUTIONS

Study of the Use of Lipid Panels as a Marker of Insulin Resistance to Determine Cardiovascular Risk

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ABSTRACT

Context: When assessing the lipid panel, practical physicians tend to focus on the low-density lipoprotein cholesterol (LDL-c). However, an elevated triglyceride/high-density lipoprotein cholesterol (HDL-c) ratio, suggesting insulin resistance, also effectively predicts cardiovascular outcomes but requires different treatments than an elevated LDL-c. We tested whether high triglyceride/HDL-c ratios are associated with more risk than high LDL-c concentrations or other lipid markers of atherogenicity.

Methods: We followed 103,646 members aged 50 to 75 years without cardiovascular disease or diabetes in a community health plan. Subjects were categorized as insulin sensitive or insulin resistant on the basis of triglyceride and HDL-c in the index year. The primary outcome was ischemic heart disease. The percentage of subjects with a primary outcome after 8 years was stratified by insulin category, lipid measures, and blood pressure. Hazard ratios (HR) for insulin resistance, LDL-c, age, sex, and the presence of hypertension were determined in a multivariate analysis.

Results: Subjects with insulin resistance but lipid measures healthier than the median had worse outcomes than those who were insulin sensitive but had unhealthier lipid measures such as non-HDL-c and the ratios of total cholesterol/HDL-c and LDL-c/HDL-c. The HR for a 60 mg/dL increase in LDL-c was 1.14 (95% confidence interval [CI], 1.10-1.18); the HR for an LDL-c greater than 160 mg/dL was 1.19 (95% CI, 1.12-1.28). In contrast, the hazard ratio for having an insulin-resistant triglyceride/HDL-c ratio was 1.68 (95% CI, 1.57-1.80), compared with an insulin-sensitive ratio. There was no difference in outcomes between insulin-resistant but normotensive patients and insulin-sensitive but hypertensive patients.

Conclusion: Insulin resistance, as manifested by a high triglyceride/HDL-c ratio, was associated with adverse cardiovascular outcomes more than other lipid metrics, including LDL-c, which had little concordance. Physicians and patients should not overlook the triglyceride/HDL-c ratio.

INTRODUCTION

Predicting patients' risk for cardiovascular disease (CVD) is an important function of medicine. The risks of high concentrations of low-density lipoprotein cholesterol (LDL-c) are well recognized. Treatment of LDL-c with 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) reduces the incidence of myocardial infarctions.[1] Both the number of LDL-c measurements in high-risk patients and the percentage of those whose LDL-c is below 100 mg/dL were used until 2015 as quality metrics for health care facilities.[2-4] Until the latest 2013 cholesterol guidelines advocated that we dose statins according to overall CVD risk, we were encouraged to dose statins according to the absolute LDL-c concentration.[5] So, until recently, busy, practicing physicians were encouraged to focus on the LDL-c.

Other components of the lipid panel provide information for assessing CVD risk, although these risk factors are not well understood by many physicians. For example, the ratio of triglycerides to high-density lipoprotein cholesterol (HDL-c) reflects the presence of insulin resistance. A ratio greater than 3.0 has been measured as 64% sensitive and 68% specific for insulin resistance compared with the gold standard insulin suppression test. [6] The extreme manifestation of insulin resistance is better known as the metabolic syndrome.[7] Insulin resistance develops in the presence of both a genetic predisposition and excess adiposity—usually frank obesity.[8,9] The resulting insulin resistance is associated with much hypertension, diabetes, atherosclerosis and its complications, and even many cancers.[9] In addition to being a good measure of insulin resistance, the ratio of triglycerides to HDL-c is a powerful predictor of CVD.[10-13] Yet insulin resistance, even when manifested by the metabolic syndrome, is often unrecognized in clinical practice.[14-16] The only American study that showed good recognition of the metabolic syndrome was based on a survey with only a 30% response rate.[17] Furthermore, the best treatment for insulin resistance is weight loss and exercise, yet neither the Joint Commission nor the principal evaluator of the quality of American hospitals (Healthcare Effectiveness Data and Information Set) mentions exercise. The measures of the Healthcare Effectiveness Data and Information Set only recently started requiring that body mass index be documented for a fraction of adults.[18] Many physicians do not even discuss obesity with their obese patients.[19,20]

When reviewing the lipid panel, physicians often address the LDL-c but neglect the triglyceride and HDL-c ratio. Yet, multiple small and moderately sized studies suggest that the triglyceride to HDL-c ratio is more predictive of cardiovascular events than the LDL-c,

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non-HDL-c, total cholesterol/HDL-c ratio, and LDL-c/HDL-c ratio.[21-24] We undertook a large, retrospective study to assess which metric better predicts the risk of ischemic heart disease among members of an American community Health Plan, Kaiser Permanente Northern California (KPNC).

METHODS

Patient Selection

We conducted a retrospective cohort study among members of KPNC, a nonprofit, prepaid Health Plan that serves more than 3 million people.[25] The Kaiser Foundation Research Institute's institutional review board approved this study and waived informed consent.

Inclusion criteria were adults age 50 to 75 years, the presence of a fasting lipid panel in the year 2000, a minimum of 12 months' continuous membership in the year before the index lipid panel, and at least 10 months of membership in each of the 3 years preceding the year before the index lipid panel. Exclusion criteria were members who had triglycerides greater than 400 mg/dL, who were prescribed at least a 180-day supply of a statin in the year before the lipid panel, who had diabetes before the index lipid panel, or who had evidence of significant atherosclerosis (Figure 1). Refer to Table 1 (available online at: www.thepermanentejournal.org/files/Fall2015/ICD9.pdf) for the International Statistical Classification of Diseases, Ninth Revision, codes describing the inclusion, exclusion, and censorship criteria.

Definitions of Outcomes and Risk Factors

The primary outcome was any ischemic heart disease (International Statistical Classification of Diseases, Ninth Revision, codes 410 through 414), including death caused by any of those codes after the index lipid panel.

The patient was deemed insulin resistant if the triglyceride level was in the highest tertile of the cohort and the HDL-c was in the lowest tertile of the cohort. The patient was deemed insulin sensitive if the triglyceride level was in the lowest tertile of the cohort and the HDL-c level was in the highest tertile. Patients not meeting criteria for insulin resistance or insulin sensitivity were put in a single intermediate category.

The diagnosis of hypertension required that a primary care clinician had included hypertension as a diagnosis for at least two visits in the two years before the lipid panel or one visit in the previous two years coupled with one of the following: 1) one or more inpatient hypertension diagnoses in the past two years; 2) a filled prescription for hypertension medication in the previous six months; or 3) a history of diabetes, CVD, heart failure, or stroke.

Statistical Analysis

For the bivariate analysis, we excluded patients with a gap of more than 4 months in membership. Thus, we included only patients who had died of ischemic heart disease during the 8 years after the first lipid panel in 2000 or patients who had 8 years of complete follow-up from the time of the first lipid panel in 2000 (n = 80,328). We used χ^2 analysis to look for differences in the primary outcome of ischemic heart disease among the 3 insulin groups, stratified by various parameters of the lipid panel or hypertension. The lipid

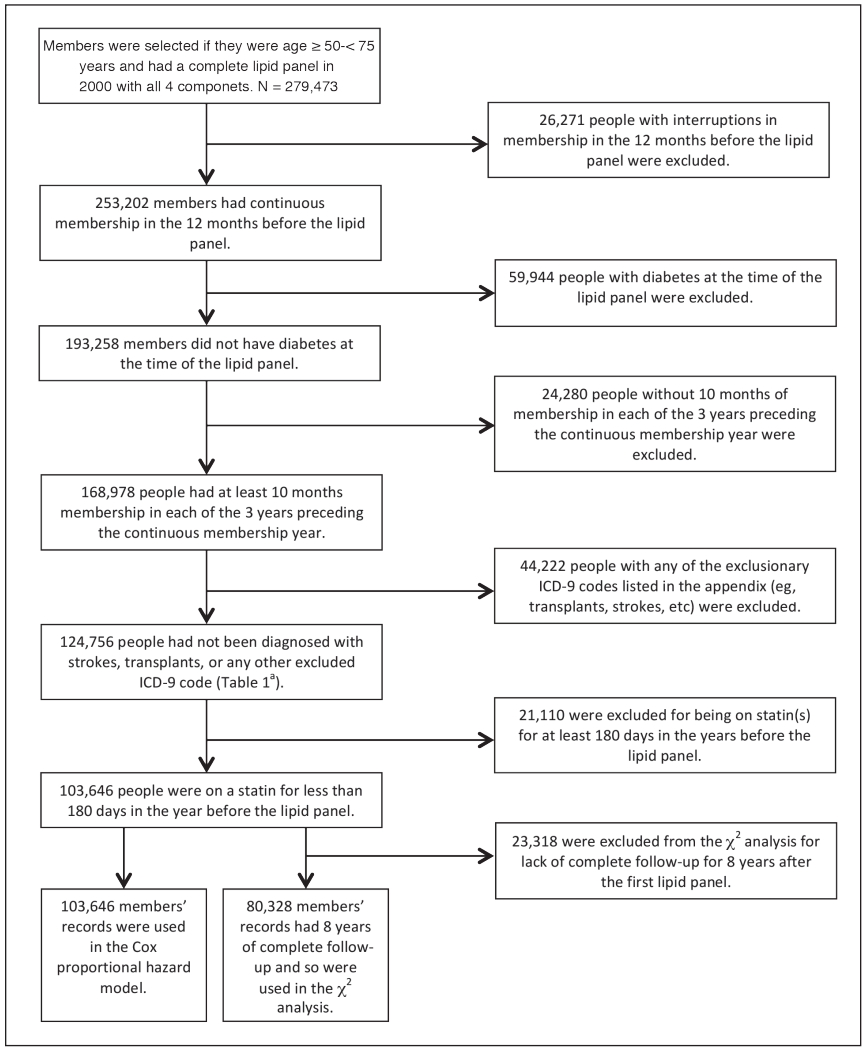

Figure 1. Quality of reporting of meta-analyses statement flow diagram. Selection of the cohorts for univariate and bivariate analyses.

[a] Available from: www.thepermanentejournal.org/files/Fall2015/ICD9.pdf.

ICD-9 = International Statistical Classification of Diseases, Ninth Revision.

parameters were dichotomized at the median values of the cohort. The Fisher exact test was used to compare the incidence of ischemic heart disease between the 2 main groups of interest: those with insulin resistance but lipid or blood pressure measures below the median, and those with insulin sensitivity but lipid or blood pressure measures above the median. The results were adjusted for multiple comparisons using the permutation method; p values < 0.05 indicated a significant difference.

The Cox proportional hazard model was used for the multivariate analysis. Our outcome variable was again diagnosis of ischemic heart disease or death therefrom subsequent to the first lipid panel in 2000. The main predictors were insulin resistance and LDL-c; covariates included sex, age (per year), and being hypertensive. The full cohort of 103,646 people was included in the analysis with follow-up ending at death; organ transplant; diagnosis of end-stage renal disease; diagnosis of or death resulting from CVD; a gap of more than 4 months of membership; or December 31, 2008, whichever came first. We tested the proportional hazard assumptions for our main predictors, insulin resistance and LDL-c, using Schoenfeld residuals because our large sample size was not conducive to using the computing-intensive Martingale residuals. Neither variable violated the proportional hazard assumption.

RESULTS

Table 2 describes the final cohort of 103,646 patients: 16.7% were insulin resistant and 17.8% were insulin sensitive. The cutoff lipid values of the insulin resistant group turned out to be ≥ 176 mg/dL for the triglycerides and ≤ 46 mg/dL for the HDL-c. For the insulin sensitive group, the cutoffs were ≤ 112 mg/dL triglycerides and ≥ 60 mg/dL HDL-c. The distribution of insulin responsiveness varied significantly by age, sex, self-identified race, blood pressure, and various lipid values. Men were more insulin resistant than women. Insulin resistance was associated with high blood pressure, as expected.[26,27]

For the population with at least 8 years of follow-up (n = 80,328), the incidence of ischemic heart disease was significantly higher in insulin-resistant patients with lower LDL-c (17.7%) than in insulin-sensitive patients with higher LDL-c (10.0%) (p < 0.001; Figure 2). Similarly, insulin-resistant patients with a lower LDL-c/HDL-c ratio had a significantly higher incidence of ischemic heart disease (16.2%) than insulin-sensitive patients with a higher LDL-c/HDL-c ratio (9.96%) (p < 0.001; Figure 3). A similar pattern emerged with total cholesterol/HDL-c and non-HDL-c (Table 3). Thus, being insulin resistant carried a significantly

Table 2. Cohort characteristics by degree of insulin responsiveness

Characteristic	Insulin sensitive (n = 18,418)	Indeterminate insulin sensitivity (n = 67,878)	Insulin resistant (n = 17,350)	Total population (N = 103,646)	p value
Age, mean years (SD)	60.3 (7.1)	60.5 (7.1)	59.8 (7.0)	60.3 (7.1)	< 0.001[a]
Sex, %					
Male	26.2	43.7	67.8	44.6	< 0.001[a]
Female	73.8	56.3	32.3	55.4	
Race, %					
White	66.8	65.2	66.1	65.7	< 0.001[a]
Asian	10.2	11.1	11.0	10.9	
Black	9.3	6.1	3.4	6.2	
Hispanic	5.6	8.7	9.9	8.3	
Other/unknown	8.2	8.9	9.6	8.9	
Blood pressure, %					
Normotensive	74.7	65.0	58.3	66.6	< 0.001[a]
Hypertensive	25.3	35.0	41.7	34.4	
Lipid values, mean (SD)					
LDL-c, mg/dL	134 (34)	146 (35)	140 (37)	143 (36)	< 0.001[b]
Triglycerides/HDL-c	1.1 (0.3)	2.9 (1.2)	6.7 (2.0)	3.2 (2.1)	< 0.001[b]
Total cholesterol, mg/dL[c]	225 (36)	231 (41)	230 (38)	230 (40)	< 0.001[b]
Triglycerides, mg/dL[c]	80 (19)	152 (61)	255 (60)	157 (76)	< 0.001[b]
HDL-c, mg/dL	75 (13)	54 (12)	39 (4)	55 (16)	< 0.001[b]
Total cholesterol/HDL-c	3.1 (0.6)	4.4 (1.0)	6.0 (1.1)	4.4 (1.3)	< 0.001[b]
Non-HDL cholesterol, mg/dL	150 (35)	176 (39)	191 (37)	174 (40)	< 0.001[b]
LDL-c/HDL-c	1.8 (0.6)	2.8 (0.9)	3.6 (1.0)	2.8 (1.0)	< 0.001[b]

[a] p values were calculated using the $\chi 2$ test.
[b] p values were calculated using the General Linear Model.
[c] SI conversion factors: To convert cholesterol values to millimoles per liter, multiply by 0.02586. To convert triglycerides to millimoles per liter, multiply by 0.01129.
HDL-c = high-density lipoprotein cholesterol; LDL-c = low-density lipoprotein cholesterol; SD = standard deviation.

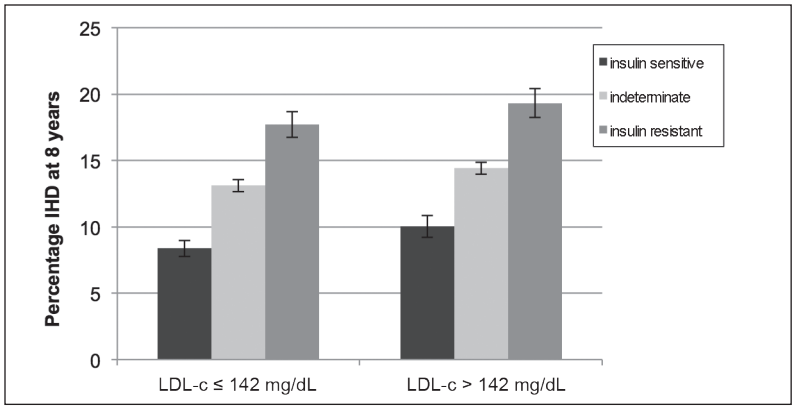

Figure 2. Incidence of ischemic heart disease (IHD) stratified by insulin resistance and low-density lipoprotein cholesterol (LDL-c). Insulin resistance and low LDL-c (≤ 3.66 mmol/L [142 mg/dL]) was associated with higher incidence of IHD than insulin sensitivity and high LDL-c ($p < 0.001$, Fisher exact test). Error bars show the 95% confidence limits.

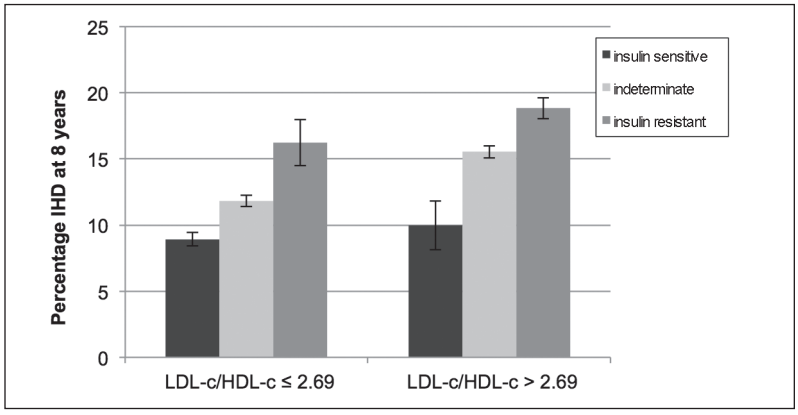

Figure 3. Incidence of ischemic heart disease (IHD) stratified by insulin resistance and the low-density lipoprotein cholesterol (LDL-c)/high-density lipoprotein cholesterol (HDL-c) ratio. Insulin resistance and a low LDL-c/HDL-c ratio (less than or equal to 2.69) was associated with higher incidence of IHD than insulin sensitivity and a high LDL-c/HDL-c ratio ($p < 0.001$, Fisher exact test). Error bars show the 95% confidence limits.

higher risk of ischemic heart disease than having an LDL-c, LDL-c/HDL-c, total cholesterol/HDL-c, or non-HDL-c cholesterol higher than the median values of 142 mg/dL, 2.69, 4.30, and 173 mg/dL, respectively. However, there was no difference in the incidence of ischemic heart disease between insulin-resistant but normotensive patients and insulin-sensitive but hypertensive patients (Table 3).

For the full cohort of 103,646 patients, the mean follow-up was 7 years (median, 8.3 years). We ran 2 models; in the first we used LDL-c as a categorical variable using LDL-c ≤ 100 mg/dL as the reference and compared this with both the LDL-c between 101 mg/dL and 160 mg/dL and the LDL-c ≥ 161 mg/dL. In the second model we used LDL-c as a continuous variable and calculated the hazard ratio on the basis of increases in increments of 60 mg/dL. Both models give identical results for male sex, hypertension, age, and insulin resistance. All conferred 60% to 72% greater risk of ischemic heart disease than female sex, having normal blood pressure, and being insulin sensitive, respectively (Table 4). In contrast, LDL-c > 160 mg/dL conferred a 19% risk. In the second model a 60-mg/dL increase in LDL-c conferred a 14% greater risk of developing ischemic heart disease. The 68% risk of ischemic heart disease for insulin-resistant patients is much higher than the LDL-c in both models. For every 1 year of increased age, a person was 5.9% more likely to develop ischemic heart disease, assuming all other measured variables did not change. This does not scale linearly with additional years (because the hazard ratio is the exponent of beta [the point estimate] for age in the model).

DISCUSSION

In this large-scale analysis of members of a Health Plan, we found that insulin resistance, as defined by high triglycerides and low HDL-c, was more predictive of ischemic heart disease than LDL-c among 50 to 75 year olds who had not had a major cardiovascular event or acquired diabetes. Also, the people in the worst tertile of triglycerides and HDL-c had worse ischemic heart disease than those with elevated non-HDL-c, total cholesterol/HDL-c ratios, or LDL-c/HDL-c ratios.

Our population provides several advantages. First, it is a community cohort, not a study group, which may enable the results to apply more generally. Second, the cohort is ethnically heterogeneous. Third, it is a large population; more than 100,000 individuals were included in this study. Finally, a large study in an American population may have greater potential to affect the behavior of Americans, who underestimate the danger of insulin resistance and often overestimate the effect of total cholesterol or LDL-c on their cardiovascular health. In one study, a group of New Englanders thought that cholesterol levels (ie, total cholesterol or LDL-c) were more important to cardiovascular health than blood pressure, smoking, or exercise.[28] In another study, more people in underserved, rural Pennsylvania identified high cholesterol as a risk factor than identified smoking or diabetes.[29]

Our results showed that being insulin resistant (as suggested by a high triglyceride/HDL-c ratio) and having LDL-c ≤ 142 mg/dL conferred a higher risk of CVD than being insulin sensitive and having an elevated LDL-c.

… the treatment of a high LDL-c/HDL-c ratio depends on its exact problem—whether the LDL-c is too high or the HDL-c is too low. In contrast, the triglyceride/HDL-c ratio is relatively specific to insulin resistance.

The same was true for being insulin resistant and having an LDL-c/HDL-c ratio ≤ 2.69, a total cholesterol/HDL-c ratio ≤ 4.30, or a non-HDL-c concentration ≤ 173 mg/dL. These results suggest that LDL-c is not a dominant predictor of cardiovascular outcomes in this study. Consistent with these results, the Cox proportional hazard model identified insulin resistance, hypertension, and male sex as the risk factors most important in predicting cardiovascular outcomes in our cohort. An increase in LDL-c of 60 mg/dL conferred only 14% more risk of ischemic heart disease.

Similar to our study, the Copenhagen Male Study sorted approximately 3000 Danish men into 3 groups based on triglycerides and HDL-c levels and found that high triglycerides and low HDL-c were more predictive of subsequent ischemic heart disease than LDL-c.[21] However, the results of our χ^2 analyses were even stronger than those from the Copenhagen Male Study, likely because our population has more people from ethnic groups more likely to be insulin resistant than the Danish population.

Other studies have also shown that the triglyceride/HDL-c ratio is more predictive than the LDL-c level, including the Metabolic Syndrome in Active Subjects in Spain study,[23] the Boston Area Health Study,[24] the Women's Ischemia Syndrome Evaluation,[22] and the study by Bampi et al.[10]

Table 3. Incidence of ischemic heart disease within 8 years of the index lipid panel stratified by insulin resistance and by various components of the lipid panel or hypertension

Parameter	Insulin sensitive (n = 14,411), %	Indeterminate insulin sensitivity (n = 52,515), %	Insulin resistant (n = 13,402), %	p value
Total cholesterol/HDL-c				
≤ 4.30	9.0	11.7	20.6	< 0.001[a]
> 4.30	9.3	15.8	18.4	
Non-HDL-c				
≤ 173 mg/dL[b]	8.6	13.1	16.7	< 0.001[c]
> 173 mg/dL	10.3	14.5	19.3	
Blood pressure				
Normotensive	7.1	11.1	15.2	0.52[d]
Hypertensive	14.7	18.8	22.9	

[a] Fisher exact test p value compares 9.3 with 20.6.
[b] To convert milligrams of cholesterol per deciliter to SI units, multiply by 0.02586.
[c] Fisher exact test p value compares 10.3 with 16.7.
[d] Fisher exact test p value compares 14.7 with 15.2.
HDL-c = high-density lipoprotein cholesterol.

Table 4. Hazard ratios for risk factors predicting ischemic heart disease at 8 years after the index lipid panel

Parameter	Hazard ratio	95% CI	p value
Insulin resistance (compared with insulin sensitivity)	1.68	1.57-1.80	< 0.001
LDL-c[a] (> 160 mg/dL compared with ≤ 100 mg/dL)	1.19	1.12-1.28	< 0.001
Age, years	1.06	1.06-1.06	< 0.001
Male sex	1.72	1.65-1.79	< 0.001
Hypertension	1.60	1.54-1.66	< 0.001

[a] To convert milligrams of cholesterol per deciliter to SI units, multiply by 0.02586.
CI = confidence interval; LDL-c = low-density lipoprotein cholesterol.

Data from larger trials are also consistent with our findings. The Helsinki Heart Study showed that LDL-c was a poor predictor of myocardial risk, but that triglycerides and HDL-c were good predictors.[30] Using the Framingham risk algorithm to evaluate people with the metabolic syndrome, Wong et al[31] calculated the percentage of CVD that would be prevented if the LDL-c or the HDL-c could be optimized. They found that HDL-c was a more powerful risk factor among patients with the metabolic syndrome than LDL-c and that an optimal HDL-c would prevent more events than an optimal LDL-c.[31] The Physicians' Health Study found that both HDL-c and the total cholesterol/HDL-c ratio were effective predictors of myocardial infarction but that a potential surrogate for LDL-c, apolipoprotein B-100, was not.[32] Data from the Framingham Study and the Coronary Primary Prevention Trial showed that the ratios of cholesterols (total/HDL-c and LDL-c/HDL-c) were superior to LDL-c for prediction, but the study did not test the predictiveness of the triglycerides or HDL-c alone.[33] In the Prospective Study of Pravastatin in the Elderly at Risk trial, LDL-c was not predictive of CVD and stroke, but HDL-c, LDL-c/HDL-c, and total cholesterol/HDL-c were.[34]

Other smaller studies also partially support our findings. A study evaluated the first 100 nondiabetic patients who presented for coronary angiography at the time of their first heart attack and who had never received treatment that might have affected the evolution of coronary artery disease. The HDL-c was significantly predictive of coronary artery disease, whereas the LDL-c, triglycerides, and total cholesterol were not.[35] A case-control study of 180 Taiwanese hospitalized patients showed the HDL-c was more associated with coronary artery stenosis than the LDL-c.[36] A study of 900 diabetic patients in a Japanese clinic that used ultrasound of the carotid artery to assess atherosclerosis showed that LDL-c, total cholesterol, and triglycerides were not significantly predictive; however, HDL-c, LDL-c/HDL-c, total

cholesterol/HDL-c, and non-HDL-c were predictive.[37]

Our findings might contradict the prevailing wisdom that LDL-c is a powerful risk factor for ischemic heart disease. There are several possible explanations for these data. First, LDL-c >142 mg/dL may not be dangerous enough to statistically demonstrate excessive ischemic disease. The Copenhagen Male Study used a cutoff for high LDL-c of 170 mg/dL[21]; in contrast, 66% of the KPNC population with "high" LDL-c had LDL-c values < 171 mg/dL. Nonetheless, the Copenhagen Male Study found that the triglycerides/HDL-c ratio was more predictive than even these higher levels of LDL-c.

Second, the index lipid panel in this study was acquired in the absence of statin use. However, our results could be explained if most people in the cohort started using statins immediately after the index measurement. This could have mitigated the deleterious effects of elevated LDL-c, thereby nullifying the negative predictive value of the initially untreated LDL-c. These results would support the continued clinical evaluation of LDL-c to assess whether a statin should be administered. However, the results would then suggest that clinicians should also focus on insulin resistance because it remains a powerful risk factor even after treatment of high LDL-c.

Alternatively, KPNC may have waited until after approximately the early 2000s (until after the majority of the big statin trials were released) before ramping up statin prescriptions for primary prevention. Thus, this cohort may not have been on statins long enough for the drugs to reduce ischemic outcomes substantially. Approximately half the diagnoses of ischemic heart disease occurred within the first year after the index lipid panel. If KPNC did not start aggressively treating LDL with statins until late in the decade, then approximately half the events would have occurred in the absence of statin treatment. If so, our results would indicate that an untreated LDL-c is not as dangerous as insulin resistance. In fact, Yeh et al[38] have already published the rate of statin use in the KPNC members more than 30 years of age who developed their first myocardial infarction between 1999 and 2008. Statin use was starting to ramp up in 2000 but did not reach peak penetration until 2005.[38] More investigations are currently in progress to determine the role of statins in this cohort.

By better understanding the risks conferred by the various components of the lipid panel, physicians and patients can do more to mitigate those risks. In addition to the triglyceride/HDL-c ratio, the LDL-c/HDL-c and the total cholesterol/HDL-c ratio are very predictive of CVD risk.[30,33,39,40] Many clinicians like the LDL-c/HDL-c ratio because the results generally range from 2 to 10, numbers that are easy to remember. However, the treatment of a high LDL-c/HDL-c ratio depends on its exact problem—whether the LDL-c is too high or the HDL-c is too low. In contrast, the triglyceride/HDL-c ratio is relatively specific to insulin resistance.

This study would have confirmed that a high triglyceride/HDL-c ratio is a good surrogate for insulin resistance if other metrics of insulin resistance had been measured also. Hypertension was measured and was virtually as strong a risk factor for CVD outcomes as the high triglyceride/HDL-c ratio. Body mass index, weight, actual blood pressures, blood sugars, and hemoglobin A_{1c} would also have been relevant to this study. Unfortunately, the accuracy of the body mass index and weight data in 2000 needs clarification. The other metrics were beyond the scope of this study.

CONCLUSION

Physician counseling can change patients' behaviors if effective techniques are used.[41,42] If more physicians understood that insulin resistance is a huge risk factor for ischemic heart disease, we could potentially do more to motivate our patients. More than two-thirds of Americans are overweight or obese,[43] and a large fraction of these have insulin resistance.[44] Currently, we may be missing opportunities, because a sizable fraction of patients don't recall hearing their physicians address their obesity.[45] Focusing on LDL-c levels is not sufficient; triglycerides and HDL-c should also be routinely monitored and problematic values addressed to decrease the associated risks. ❖

Disclosure Statement

The author(s) have no potential conflicts to disclose.

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