New NCEP Cholesterol Guidelines

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Introduction

On May 15, 2001, the National Cholesterol Education Panel (NCEP) issued major new clinical practice guidelines on the prevention and treatment of high cholesterol levels in adults. This was the first major update of the NCEP guidelines since 1993. An executive summary of the Third Report of the NCEP Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (a.k.a., Adult Treatment Panel III or ATP III) appeared in the May 16, 2001 issue of the Journal of the American Medical Association. The NCEP has predicted that the new ATP III guidelines will increase the number of Americans requiring treatment for elevated cholesterol levels (from 52 million to 65 million) and nearly triple the number of Americans who will need to take cholesterol lowering drugs (from 13 million to 36 million Americans). This is in order to reach the more aggressive blood cholesterol-lowering treatment goals established by the ATP III.

The Key Changes

The key changes established by the ATP III from the previous NCEP guidelines (set by the ATP II) include the following:

1. More aggressive cholesterol-lowering treatment goals

2. Use of a lipoprotein profile as a first test for diagnosing dyslipidemia and myocardial infarct (MI) risk

3. New more aggressive dietary guidelines for lowering elevated low density lipoprotein cholesterol (LDL-C) levels with diet and other lifestyle changes known as Therapeutic Lifestyle Changes (TLC)

4. Better diagnosis of those at high-risk for a MI)

5. Recognition that people with Type 2 diabetes mellitus (DM) are at very high risk of MI and require more aggressive treatment of elevated LDL-C levels

6. Increased focus on elevated triglycerides (TG) levels and their treatment

7. A new higher cutpoint for establishing a low high density lipoprotein cholesterol (HDL-C) level as a major risk factor for MIs

8. New guidelines for treating those with the metabolic syndrome, (a.k.a., "insulin resistance syndrome", "syndrome X")

From the perspective of this reviewer, the ATP III guidelines represent:
a) several steps forward in the prevention and treatment of atherosclerotic related cardiovascular disease
b) a few missteps by ignoring important research
c) a few steps that are probably warranted but not taken

More Aggressive Cholesterol-Lowering Goals (Change #1)

The new ATP III guidelines do not change the total cholesterol (TC) level categories. They continue to define a TC below 200 mg/dl as "desirable" even though about 30% of all MIs occur in Americans with a "desirable" TC.[1]

However, the new ATP III guidelines have established goals for LDL-C levels that are much more aggressive than the earlier ATP II goals. These more aggressive LDL-C lowering goals, if achieved, will be much more likely to prevent or treat successfully atherosclerotic cardiovascular disease than the ATP II goals. These new cholesterol-lowering goals should help prevent many more MIs and strokes than the older goals. The new LDL-C categories are shown in Table 1.

Table 1. ATP III LDL-Cholesterol Categories

LDL-Cholesterol level	LDL-Cholesterol Category
<100 mg/dl	Optimal
100-129 mg/dl	Above Optimal
130-159 mg/dl	Borderline High
160-189 mg/dl	High
>190 mg/dl	Very High

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In ATP II, an LDL-C level below 130 mg/dl was categorized as "desirable" but an LDL-C of 100-129 mg/dl is often associated with progression of atherosclerotic lesions particularly when several other coronary heart disease (CHD) risk factors are present. So while a LDL-C of <130 mg/dl was more "desirable" than even higher levels, it was certainly not "optimal" for either the prevention or treatment of atherosclerotic disease. A meta-analysis of 14 cholesterol-lowering trials calculated that atherosclerotic plaque progression ceases around a LDL-C of 100 mg/dl.[2] No doubt it was this type of data that convinced the ATP III to lower their LDL-C targets for people at high-risk of CHD.

It should be noted that nearly 10% of CHD patients still have LDL-C levels below 100 mg/dl although most of these have several other risk factors for CHD.

Therefore, in patients deemed at very high risk for MIs due to advanced atherosclerosis, an LDL-C clinical target even lower than 100 mg/dl may be warranted in some, if not most, patients.[3] Several intervention trials are now being conducted to determine if there is clinical benefit to lowering LDL-C well below 100 mg/dl in patients with clinical evidence of atherosclerotic disease. Clearly the ATP III's new focus on the measurement of LDL-C in all adults over age 20 years, along with lower targets for "safe" LDL-C levels for many patients, is warranted by the bulk of the scientific research. Whether even lower target levels for LDL-C are clinically warranted awaits results of ongoing clinical trials. However, the more generous LDL-C targets for people deemed to be at lower risk of atherosclerotic disease will certainly allow this disease to progress in many, if not most, people.

If the ATP III now states that an LDL-C of less than 100 mg/dl is "optimal" for people at high risk of CHD why is it not the optimal goal for those at lower risk of CHD? After all, several hundred thousand Americans will have MIs and strokes each year even though they are not deemed to be in the high-risk category by the new NCEP guidelines. Perhaps the ATP III believes that recommending a diet sufficiently low in animal products and hydrogenated fat and sufficiently high in minimally processed fruits, vegetables and whole grains in order to achieve the "optimal" LDL-C level is too drastic a change in diet to expect most people to comply with. Nevertheless, it seems that health professionals should be in the business of educating people about what the scientific evidence suggests is an optimal LDL-C level and what is the safest and most effective dietary approach to achieving this optimal LDL-C goal.

Fasting Blood Lipid Profile Now Used To Screen For Dyslipidemia (Change #2)

The ATP III now recommends that a fasting blood lipid profile measures serum TC, HDL-C and TG levels in all adults age 20 years and older. They say this is needed to better screen for dyslipidemia and to assess the risk of a MI. Earlier NCEP guidelines required a non-fasting TC and HDL-C measurement only because there was no consensus on the value of measuring TG levels. However, under the old guidelines, if the TC was 200 mg/dl or higher and/or if HDL-C was under 35 mg/dl then the measurement of fasting TG levels was recommended at a follow-up blood test. This became necessary because the older as well as the new treatment guidelines use the LDL-C level as the primary treatment target. Most clinical labs do not measure LDL-C directly. Therefore, without measuring fasting TG level it is not possible to calculate the LDL-C level. LDL-C is usually calculated as follows:

LDL-C = TC - HDL-C - TG/5 (all values in mg/dl)

In truth, what is called LDL-C actually includes both LDL-C plus intermediate-density-lipoprotein-cholesterol (IDL-C). There is also cholesterol in very-low-density-lipoprotein particles (VLDL), chylomicrons and their remnants. VLDL particles generally have about 1/5 as much cholesterol as they do TG. After a 10-12 hour fast there is very little chylomicron remnant particles in the blood. For people who have very high TG levels, this ratio changes and so LDL-C is generally not estimated if TG levels are over 400 mg/dl.

The ATP III now appears to believe that elevated fasting TG levels (>150 mg/dl) are an established risk factor for CHD. In fact this is still a matter of much debate. For example, a comprehensive secondary statistical analysis of data from the Multiple Risk Factor Intervention Trial (MRFIT), the Lipid Research Clinics Coronary Primary Prevention Trial (LRCPPT), and the Lipid Research Clinics

Prevalence and Follow-Up Study found, "with few exceptions, no significant interactions between cholesterol subfractions and triglyceride levels were found … and triglyceride measurements did not improve discrimination between those subjects who did and those who did not suffer coronary heart disease events."[4] Simply put, in studies of Americans, there is no consistent relationship between serum TG levels and the risk of CHD after adjusting the data for confounding variables like HDL-C, BMI, smoking, etc. For example, the risk of CHD is higher in those who have higher TG levels but these people often have lower HDL-C levels. Clearly there is nothing close to a scientific consensus to support the contention that fasting TG levels are an independent risk factor for CHD. Unfortunately the ATP III's growing but unfounded focus on serum fasting TG levels as a CVD risk factor appears to be playing a role in moving the NCEP dietary recommendations in the wrong direction. This is particularly true for people who have insulin resistance and elevated fasting serum TG levels. This will be discussed later.

The ATP III's recommendation to continue using LDL-C as the primary clinical target for treating dyslipidemia is also becoming more questionable. This is because very low density lipoprotein cholesterol (VLDL-C) also appears to be atherogenic or at least is associated with an increased risk of CHD. A recent analysis of the Lipid Research Clinics Follow-Up Study found that non-high-density lipoprotein cholesterol (non-HDL-C) was actually a somewhat better predictor of CVD risk than was LDL-C.[5] Simply put, non-HDL-C rather than LDL-C should be the primary therapeutic target for reducing the risk of CVD rather than just the LDL-C.

The ATP III does set a secondary goal of achieving a non-HDL-C level no more than 30 mg/dl higher than the primary LDL-C goal (see Table 1) in people who have a fasting TG level of 200 mg/dl or higher. However, most of the subjects in the LRC Follow-Up Study discussed above had TG levels below 200 mg/dl and in these subjects non-HDL-C was a significantly better predictor of dying from CVD than was LDL-C. Simply put, research shows that lowering non-HDL-C reduces the risk of CVD more than lowering LDL-C. No doubt this is because non-HDL-C includes LDL-C, IDL-C, VLDL-C and chylomiron-C. All of these lipoprotein subfractions can be associated more atherosclerosis so why should the NCEP continue to focus primarily on the LDL-C level?

Some members of the ATP III panel have argued that there is not yet sufficient data to switch from LDL-C to non-HDL-C as the primary target for treating patients with dyslipidemia. However, the bulk of the data available suggests that non-HDL-C is a more superior predictor of atherosclerotic disease than is LDL-C alone. The ATP III's main argument against switching appears to be that they have recommended using LDL-C for so long that switching to non-HDL-C would confuse physicians and the public.[6] Non-HDL-C is easy to calculate and does not even require a fasting blood lipid panel. Non-HDL-C = TC - HDL-C. Because non-HDL-C does not require a fasting blood sample to measure it would be easier on patients and a little less expensive than using LDL-C to monitor therapeutic success. This does not mean fasting TG levels should not be measured. If very elevated they can cause pancreatitis and are often associated with other metabolic problems like renal disease, alcoholism, hypothyroidism and poorly controlled diabetes. However, when it comes to atherosclerotic disease, fasting TG levels are of little, if any, diagnostic value. The ATP III does recommend the use of non-HDL-C as a secondary target of treatment.

So what is an optimal non-HDL-C level? To establish a secondary treatment target, the NCEP now recommends adding 30 to their LDL-C target. So if a patient's LDL-C target was less than 100 mg/dl then his non-HDL-C target would be less than 130 mg/dl. The ATP III has lowered the "normal" range for fasting TG levels from less than 200 mg/dl to less than 150 mg/dl. It is the opinion of this reviewer that an optimal fasting TG level is below 100 mg/dl although a somewhat higher level may still be optimal if the patient is consuming a very-low-fat (VLF) diet (under 20% of energy from fat). The reason for this is that elevated fasting TG levels correlate with elevated postprandial TG levels. Most research suggests that any CVD risk associated with higher fasting TG levels would be primarily due to the higher postprandial lipemia. Higher postprandial TG levels are often closely correlated with higher fasting TG levels. Higher postprandial TG levels are associated with more atherogenic lipoprotein particles. This will be discussed in detail later. In this reviewer's opinion, an optimal non-HDL-C level is below 120 mg/dl and perhaps up to 130 mg/dl if the patient is consuming a VLF, high-carbohydrate diet.

More Aggressive Dietary Guidelines for LDL-C Lowering (Change #3)

ATP III appears to have abandoned the terminology for the "Step 1 Diet" and "Step 2 Diet" for lowering LDL-C levels. What was once the Step 1 diet is now referred to as a "Heart Healthy Diet" and is recommended for people at a lower risk of atherosclerotic disease. The Heart Healthy Diet is basically the same as the old "Step 1 Diet" except the percent of calories from total fat is now 25 to 35% of energy rather than less than 30% under the older guidelines. The higher intake of fat is achieved by increasing the amount of monounsaturated fatty acids up to 20% of the total calories. The intake of saturated fatty acids (SFA) and polyunsaturated fatty acids (PUFA) and cholesterol on the Heart Healthy Diet are the same as the old Step 1 diet.

Therapeutic Lifestyle Changes (TLC) are now recommended for people whose LDL-C remains above the target level. TLC puts more emphasis on losing excess body fat and increasing daily activity than the earlier ATP II guidelines. The old "Step 2 Diet" used to lower elevated LDL-C levels in patients who fail to achieve treatment goals on the Step 1 Diet has also undergone a few changes. As with the "Heart Healthy Diet", this new therapeutic diet (called the TLC Diet instead of Step 2 Diet) also adopts a fat range of 25-35% of energy instead of the old guideline of less than 30% of energy from fat. The TLC Diet targets for SFA (<7% en) and cholesterol (<200 mg/d) remain the same as the old Step 2 Diet. However, the TLC Diet recommends a couple of new twists for lowering elevated LDL-C levels.

One is to eat more soluble fiber rich foods. The goal is to increase soluble fiber intake to 10 to 25g daily by eating more soluble-fiber rich foods.

The second new twist is the recommendation to consume 2 grams daily of plant sterol and stanols by consuming food products enriched in these cholesterol-lowering phytochemicals such as margarine and salad dressings (e.g., "Benecol" and "Take Control").

Increasing dietary soluble fiber and plant sterols and stanols, in the diets of patients with elevated LDL-C, makes the TLC Dietary approach potentially more effective than the old ATP II Step 2 Diet approach. However, reducing dietary saturated fat and cholesterol to even lower amounts than the targets for the TLC Diet would certainly make it easier for more people to achieve their LDL-C goal without cholesterol-lowering medications. There is every reason to believe that a VLF (<15% en), high-fiber, more vegetarian diet can lower LDL-C more than the new TLC Diet. This is because such a diet can supply less than 3.5% of calories from saturated and trans fatty acids and keep daily cholesterol intake well below 100 mg. No one doubts that greater reductions in SFA, trans fatty acids (TFA) and cholesterol would lead to greater reductions in LDL-C levels. A diet higher in carbohydrate and lower in fat would also tend to have more dietary fiber and this helps lower elevated TC, LDL-C and non-HDL-C levels.

It should also be obvious that achieving a 25g intake of soluble fiber would be far more difficult on a 35% fat diet than a diet with only 10-15% of calories from fat. Vegetable oils have no soluble fiber and most high-fat vegetarian foods (e.g. nuts, seeds, tofu, avocados) have less soluble fiber for a given energy content than do most fruits, vegetables, beans, peas, lentils and many grains (especially oats and barely). It should also be noted that all vegetable oils contain SFA. If one added enough olive oil to increase the % fat calories from 10% to 35% of energy then the SFA content of the diet would double (from 3.5% to 7% en.). This extra oil could displace a lot of fiber-rich foods assuming that energy intake was the same on the diet higher in fat. Of course, there is growing evidence that higher fat diets tend to promote excessive energy intake and weight gain over time.[7] [8]

Even though the NCEP ATP III's new guidelines put more emphasis on the importance of weight loss for reducing CHD risk factors, they ignore growing evidence linking higher fat diets with increased energy intake and weight gain. The ATP III even recommends reducing the calorie density of the diet to help achieve greater satiety and make weight loss easier. Calorie density appears more important than % energy from fat in determining ad libitum calorie intake.[9] [10] However, nearly all foods high in monounsaturated fat (i.e. oils and nuts) also have a high calorie density whereas all fresh fruits, vegetables, legumes and many whole grain products (e.g., hot cereals, pasta, corn, brown rice) have a low to moderate calorie density. Therefore, if one were to switch from a VLF diet consisting largely of fruits, vegetables, beans and high-water content whole grain products to a diet with more monounsaturated fat, the calorie density of the diet would surely increase. This is why this reviewer believes that a diet lower in fat, saturated fat and cholesterol and higher in fruits, vegetables and whole grains is preferable to the ATP III's TLC Diet, at least for patients who are overweight, for reducing the risk of CHD.

Better Diagnosis of Risk of MI (Change #4)

The earlier ATP II guidelines recommended patient were to be initially screened by simply measuring TC and HDL-C in the non-fasting state. Only when the HDL-C was less than 35 mg/dl and/or the TC was 200 mg/dl or higher is more extensive blood lipid measurements recommended. However, many MIs are known to occur in individuals with a "desirable" TC (of < 200 mg/dl) and a HDL-C of 35 mg/dl or higher. The new ATP III guidelines call for a complete fasting (9-12 hours without food) blood lipid profile (TC, LDL-C, HDL-C and TG) for everyone 20y or older. By recommending a complete blood lipid panel on all adults and setting more aggressive LDL-C goals the new ATP III guidelines have taken a step in the right direction. This step should reduce the number of people at high-risk for a MI who "slipped through the cracks" of the older ATP II guidelines.

The ATP III continue to make LDL-C levels the primary focus for preventing and treating CHD. This is probably not the best treatment target. To compound the problem the NCEP ATP III guidelines use data from the long running Framingham Heart Study to assess risk of CHD based on TC rather than either LDL or non-HDL-C levels. Both LDL-C and non-HDL-C are better risk predictors than TC levels. So why did the ATP III elect to access risk using TC instead? This was because they had much more long-term data available (from the long-running Framingham Heart Study) associating risk of MI with TC rather than LDL-C level.

The most aggressive treatment goals for LDL-C levels are reserved for those patients deemed to be at highest risk of future CHD events. These patients have a 20% or greater risk of a CHD event within the next 10y according to the statistics and data generated from the Framingham Heart Study. The 10y risk of CHD events is calculated based on a risk point system using only the following CHD risk factors: age, cigarette smoking, gender, systolic blood pressure level (with or without drug treatment) and the level of TC and HDL. In determining the treatment goal for LDL-C level the presence of either clinical atherosclerotic disease and/or diabetes puts the patient in the highest risk category (regardless of the number of calculated risk points). Family history of early cardiovascular disease also counts as an additional "risk factor" along with smoking, age 45+ for men and 55+ for women, low HDL-C (<40 mg/dl), hypertension and elevated TC. An HDL-C of 60 mg/dl or more is considered to be a negative risk factor.

Both cost/benefit analysis and risk/benefit analysis was no doubt used to set the LDL-C treatment goals for initiating TLC and drug therapy. However, it is likely that many fatal cardiovascular events could be prevented in patients deemed to be at lower risk if the TLC dietary guidelines were recommended for all adult Americans (with the exception of the plant sterol/stanol fortified foods). The TLC diet is not the most effective diet for reducing LDL-C (or non-HDL-C levels) to the optimal range now recognized by the NCEP.

The failure to recommend the most efficacious diet for lowering LDL-C levels coupled with the delay of dietary treatment until the patient is already at fairly high risk of CHD are two of the major short-comings of the new ATP III guidelines. No doubt, factors such as the added cost of dietary counseling for millions of Americans, current well-entrenched food habits, preferences and the potential problems with compliance, with more aggressive dietary guidelines than those advocated in ATP III, were used in setting the TLC dietary guidelines. It also appears that the potential for economic harm to the food industry may have been considerations of the ATP III as well. It also appears that the ATP III failed to fully understand the "big picture" relationship between diet, insulin resistance, body weight regulation and the atherosclerotic disease process. As a result, the TLC dietary guidelines still do not represent the best approach to prevent and treat CVD.

Twenty-five-year follow-up data from the Seven Countries Study continues to show dramatic differences in the incidence of CHD mortality between countries. Migration studies have shown that little, if any of these major differences in CHD mortality between countries can be explained by genetic differences. Compared to Japan and Southern (Mediterranean) European countries, the death rate for CHD was far greater in Northern European countries and the United States. To be sure much of the difference between countries in terms of the incidence of CHD could be explained by the higher saturated fat intake and higher TC and LDL-C levels in Northern Europe and the U.S. compared with the Mediterranean region and Japan. However, the incidence of fatal CHD was still at least 2-3 times higher in the U.S and Northern Europe than in Southern Europe or Japan, even in individuals with similar fasting blood lipid levels. The increased risk of CHD mortality was also adjusted for differences in age, smoking status and systolic blood pressure (SBP). These adjustments also did not remove the much higher risk of CHD death in the U.S and Northern Europe than in Japan or the Mediterranean region of Europe.[11]

The major differences in the relative risk of fatal CHD events in people having similar TC levels but very different diets should make it clear the Framingham Heart Study risk data are far from perfect. Admittedly, these data when coupled with fasting blood lipid levels do a fairly good job of predicting the relative risk of developing CHD in people consuming a typical American diet. However, they appear to grossly over estimate the relative risk of CHD in people who are consuming either a Mediterranean-style diet or low-fat Japanese-style diet. As one's diet deviates from a typical American diet to one with much less saturated fat from red meat and dairy products, it appears the predictive value of the data from the Framingham Heart Study diminishes. Reasons for this are not clear but probably include a higher intake of omega 3 fatty acids and phytochemicals in the Mediterranean and Japanese diets that reduce the propensity of LDL particles to oxidize, reduce inflammatory reactions and thrombosis.

Recognition of Type 2 DM as a Major MI Risk Factor (Change #5)

People with Type 2 DM almost always have some insulin resistance and frequently dyslipidemia, hypertension and abdominal obesity. As a result of these and other factors, patients with Type 2 DM have at least 2-3 times the risk of fatal CVD as people without diabetes but with similar risk factors for CVD. According to the ATP III, the 10 year risk of a fatal MI in someone with Type 2 DM is similar to that of someone who as already has evidence of clinical atherosclerosis (i.e. nonfatal MI, angina, symptomatic carotid artery disease, peripheral arterial disease, abdominal aortic aneurysm). However, the risk of death from CHD is actually significantly higher for men with a history of CHD than those with diabetes but without a history of CHD. The presence of both diabetes and a history of CHD identifies a particularly high-risk group for death from CHD.[12]

Both the American Diabetes Association and the NCEP now recommend lowering LDL-C levels to less than 100 mg/dl in those with Type 2 DM. About two-thirds of patients with Type 2 DM die of CVD compared to a little less than half the general population. Aggressively lowering LDL-C levels of patients with Type 2 DM has been shown to reduce their risk of fatal MI. Clearly, more aggressive control of CVD risk factors in patients with Type 2 DM is scientifically justifiable. In recognizing diabetes, a major risk factor for developing CVD, the ATP III has taken a step in the right direction. However, there is reason to question the use of the TLC Diet as optimal for treating overweight and obese Type 2 DM patients. This diet recommends 25-35% energy as fat. Diets higher in fat have several drawbacks in such patients. First, increasing dietary fat will generally be expected to increase energy density and reduce satiety. Therefore, a higher fat diet is more likely to promote weight gain and/or make weight loss more difficult due to increased hunger compared to a higher carbohydrate diet with a lower ED and higher fiber content.[13]

A second concern is that diets with a higher fat content tend to increase free fatty acid levels. Increased free fatty acid (FFA) levels are associated with increased insulin resistance (IR). Greater IR appears to play a role in the development of Type 2 DM. Replacing dietary carbohydrate with dietary fat has been shown to increase FFA levels in non-diabetic subjects.[14] Other studies have shown that the fall in FFA levels in the blood is greatest when the diet is high in fiber and is composed largely of slowly digested high-carbohydrate foods (low-glycemic index foods). Of course, the surest way to lower FFA levels in the blood is to increase activity and lose excess body fat.

While the TLC guidelines do stress the need for regular exercise in patients with Type 2 DM, these new guidelines also recommend a moderately high-fat diet (up to 35% en.). Higher fat diets tend to have a higher energy density and a lower fiber and satiety value than diets higher in minimally processed plant foods. Because most Type 2 DM patients are overweight and would benefit from increased fiber intake and weight loss there is reason to question the wisdom of the ATP III's TLC Diet for such patients. However, if the Type 2 DM patient is thin and has lost a lot of beta-cell function then such patients may do better with even more than 35% energy from fat. For more detailed information about medical nutrition therapy for the treatment and prevention of CVD in people with Type 2 DM see Diabetes CPE course at www.foodandhealth.com.

More Focus on Insulin Resistance and Dyslipidemia (Changes #6,7 & 8)

Type 2 DM nearly always starts with insulin resistance. The insulin resistant state is associated with many metabolic changes. Some of these metabolic disturbances develop long before Type 2 DM or even before fasting blood sugar levels begin to rise above the normal range. These metabolic changes can increase the risk of CVD even if they never lead to a diagnosis of Type 2 DM. This IR metabolic state often includes lower HDL-C levels and higher fasting and postprandial serum TG levels. It also generally includes more atherogenic small dense LDL particles, higher insulin levels and an increased tendency for blood clots to form. While most patients with low HDL-C levels and elevated TG levels do show evidence of insulin resistance it should be noted that genetic factors and/or lifestyle factors can result in low HDL-C levels and/or high fasting TG levels in people with normal insulin sensitivity as well.

The ATP III correctly puts more emphasis on the risk of CHD due to insulin resistance and the metabolic disturbances associated with it. This insulin resistant condition is known as the metabolic syndrome (a.k.a., syndrome X, insulin resistance syndrome, insulin resistance metabolic syndrome). However, the ATP III's dietary recommendations for most patients with this metabolic syndrome suggest to this reviewer some failure to fully understand the role of diet in causing the metabolic syndrome to develop in genetically susceptible individuals.

There is compelling scientific evidence that excessive energy intake, particularly when coupled with an inactive lifestyle, can lead to excessive body fat stores, IR, impaired glucose tolerance (IGT), Type 2 DM, increased blood pressure (BP) and dyslipidemia. The adverse changes in blood lipids (dyslipidemia) that typically accompany IR include elevated fasting and postprandial serum TG levels, reduced HDL-C and an increasing ratio of small dense LDL particles (a.k.a., Phenotype B or Pattern B). Small dense LDL particles are believed to be much more atherogenic than larger LDL particles. In addition, the metabolic syndrome also promotes thrombosis. All of these metabolic changes have been associated with an increased risk of a fatal MI or stroke. Clearly there is a need to diagnose and treat the metabolic syndrome whenever it exists. Waiting for Type 2 DM to develop or clinical signs of CVD makes no sense.

Unfortunately, there is no simple, cost effective test that directly measures the presence of insulin resistance or small dense LDL particles. However, the metabolic syndrome is frequently associated with an increased waist to hip ratio and other easily measured metabolic changes that can be used to predict its presence. ATP III establishes risk factors for identifying the likely presence of the metabolic syndrome using 5 clinical indicators or risk factors. Table 3 shows how these 5 clinical indicators are used to identify the metabolic syndrome according to the new NCEP ATP III guidelines. The ATP III guidelines are a step in the right direction because they do provide a reasonably accurate way to identify those patients most likely to have insulin resistance and the associated metabolic syndrome.

Table 3. Clinical Identification of the Metabolic Syndrome Requires the Presence of 3 or More of These Risk Factors

Risk Factor	Defining Level
Abdominal obesity	Waist Circumference
Men	>40 inches
Women	>35 inches
Triglycerides	150 mg/dl or higher
HDL-C	
Men	<40 mg/dl
Women	<50 mg/dl
Blood pressure	130/85 mmHg or higher
Fasting glucose	100 mg/dl or higher

This classification system will certainly miss many younger and some older people with clinically significant insulin resistance, small dense LDL particles and a heightened risk of CHD. It will also misclassify some people who do not have insulin resistance as having the metabolic syndrome. Nevertheless, given the current problems in directly measuring and diagnosing insulin resistance, the use of the ATP III's method of assessing the presence of the metabolic syndrome seems reasonable. What appears to this reviewer to be less reasonable are the recommended by ATP III's TLC for people who are identified with the metabolic syndrome. Specifically, the TLC Diet for patients identified as having the metabolic syndrome appears to be based on an incorrect interpretation of the scientific evidence.

The NCEP has taken several steps forward with recommendations aimed at reducing morbidity and mortality form CVD associated with the metabolic syndrome. However, this reviewer believes the ATP III has also made a few missteps with the TLC Diet, which makes it less than optimal for promoting weight loss and preventing CVD in patients with the metabolic syndrome. What follows is a critical review of scientific evidence that calls into question some of the recommendations made by ATP III.

How Did the ATP III Go Wrong?

The ATP III's dietary guidelines for treating patients whom have been identified as having the metabolic syndrome, is based primarily on short-term clinical trials. These studies have consistently shown higher fasting TG levels and lower HDL-C levels when dietary carbohydrate displaces dietary fats rich in monounsaturated fatty acids. More recently, the isoenergetic substitution of carbohydrate with unsaturated fat was also shown to increase small dense LDL particles. On the surface, these studies do seem to suggest that people with the metabolic syndrome would be better off with more dietary unsaturated fat and less dietary carbohydrate. These studies are no doubt the primary reason the ATP III decided to increase the NCEP's recommendation for dietary fat to 35% of the energy for patients with elevated TG levels, low HDL-C and other features of the metabolic syndrome. However, there is reason to believe that such a recommendation may actually end up increasing the very metabolic disturbances the ATP III believes it will correct. A critical review of the type of research studies that have misled the NCEP to recommend a higher intake of unsaturated fat and a lower intake of carbohydrate will reveal where they went wrong.

Much of the research behind the NCEP's recommendation to increase dietary fat at the expense of carbohydrate comes from studies conducted at Stanford University. Other researchers at other institutions have duplicated most of the results from the Stanford group using a similar experimental design. Unfortunately the experimental design of these studies makes their result of questionable clinical value. For example, there are serious design flaws in a study that supposedly demonstrated that a diet higher in carbohydrate and lower in unsaturated fats alters blood lipids in such a way that the risk atherosclerosis is increased.[15] This study showed a lower HDL-C (39 vs. 44 mg/dl) and higher fasting triglycerides (TG) (206 vs. 113 mg/dl) in 8 healthy subjects fed a high-carbohydrate (25% fat) diet compared to those same subjects fed a high-fat (45% fat) diet for 2 weeks. This type of finding is similar to earlier studies done by these researchers and others in patients with Type 2 DM.[16]

In addition to the presumably adverse effects on fasting blood lipids seen in both of these studies, these researchers also examined postprandial remnant lipoprotein particles (RLP) and found they too were higher on the high-carbohydrate diet compared to the diet higher in unsaturated fat. Numerous studies have shown that elevated postprandial TG levels increase the risk of CHD.[17] All of the changes in blood lipids (both fasting and postprandial) seen when dietary carbohydrate replaces unsaturated fat in short-term clinical trials are presumably associated with an increased risk of coronary artery disease (CAD). This is because lower HDL-C and higher fasting TG levels have been consistently correlated with a higher risk of CHD in epidemiological studies of Americans.

The changes in blood lipids that often result from the isoenergetic exchange of dietary carbohydrate for monounsaturated fat are also similar to what is typically seen in people with the metabolic syndrome (i.e., increased fasting TG and decreased HDL-C). Because the metabolic syndrome is associated with an increased risk of CAD the authors concluded, "Given the atherogenic potential of these changes in lipoprotein metabolism, it seems appropriate to question the wisdom of recommending that all Americans should replace dietary saturated fat with carbohydrate."[18] Is such a conclusion justified? There are many reasons to believe such a conclusions is at best premature and more likely incorrect. Nevertheless it was no doubt the results of this and similar studies that convinced the ATP III to recommend a higher fat intake for most people with the metabolic syndrome.

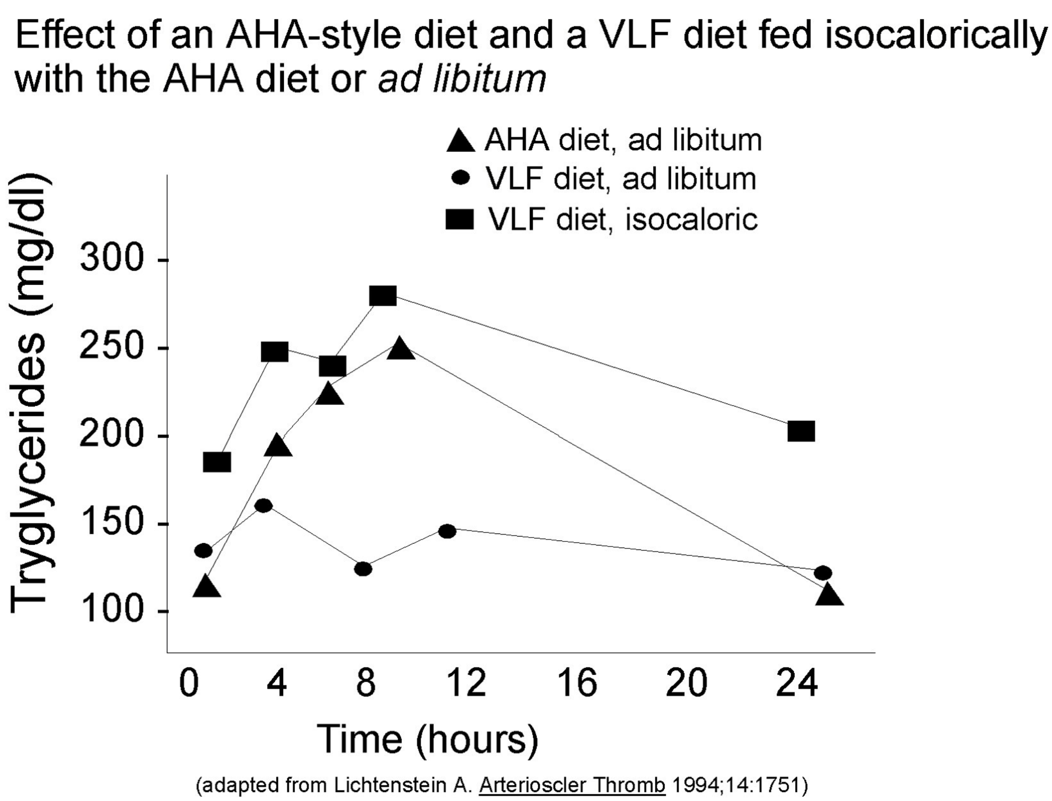
Do High-Carbohydrate Diets Necessarily Increase Fasting TG and RLP?

Scientific evidence is accumulating implicating higher postprandial TG levels with an increased risk of developing CHD.[19] [20] However, while postprandial TG levels do correlate fairly closely with fasting TG levels among people who are consuming similar diets, this is not necessarily the case when if the diets differ dramatically in the fat to carbohydrate ratio and/or energy intake.

A crossover design study, that compared the effects of a VLF diet to a diet higher in fat on blood lipids, may help put the results of the Stanford study in better perspective. In this study, a VLF (15% fat calories), high-carbohydrate diet was compared to a higher fat diet (30% of calories). The VLF diet was fed isocalorically with the more moderate-fat diet (as was done in all the Stanford studies). However, in this same study, the high-carbohydrate diet was also fed ad libitum. Both fasting and postprandial lipids were measured.

When the VLF diet was fed isocalorically with a moderate fat diet, the fasting TG levels were much higher (188 vs. 115 mg/dl) on the higher carbohydrate diet than on the moderate fat diet.[21] Just as the Stanford researchers observed in their recent study, the results of this study also showed that postprandial TG (and presumably RLP) were also much higher on the higher carbohydrate diet than on the diet higher in unsaturated fat (see Figure 1 below). HDL-C was also lower (42 vs. 35 mg/dl) on the higher carbohydrate diet just as it was in the Stanford study. LDL-C was somewhat higher on the VLF (134 vs. 128 mg/dl) than the moderate fat diet when both diets were fed isocalorically. However, when the VLF, high-carbohydrate diet was fed ad libitum, the LDL-C was now lower (119 vs. 128 mg/dl) than on the 30% fat diet. Remarkably, this was despite a much higher PUFA content (11.2% vs. 2.5% energy) and P/S (1.6 vs. 0.5) on the 30% fat diet compared to the VLF diet. The P/S ratio in the Stanford study was also higher on the higher fat diet. And while the fasting TG levels were still a little higher (130 vs. 115 mg/dl) on the VLF fed ad libitum compared to the moderate fat diet, the postprandial TG level was already considerably lower on the VLF diet compared to the 30% fat diet.

Figure 1. Effect of an AHA-Style Diet and a VLF Diet (Fed either Ad Libitum or Isocalorically with the AHA-Style Diet) on Serum TG Levels



Adapted from Lichtenstein. Arterioscler Thromb. 1994;14:1751

As we have seen, an increased fasting and postprandial TG level may be associated with more potentially atherogenic RLP. As Figure 2 above clearly shows, even when fasting TG levels are somewhat higher on a higher carbohydrate diet, they may still be much lower during most of the day on such a diet. Because most people spend most of the day in the postprandial state, it seems clinically more relevant to study the impact of dietary changes on postprandial blood lipids rather than just fasting blood lipid levels. Unfortunately, the ATP III apparently ignores the fact that when diets are fed ad libitum the postprandial TG level is often lower on VLF diets than diets high in monounsaturated fat even when the fasting TG level is somewhat higher on the higher carbohydrate diet.

Data from The Atherosclerosis Risk in Communities (ARIC) Study found that fasting TG levels were the strongest predictor of postprandial lipids. The ARIC Study also found that elevated postprandial TG levels were a better predictor of the amount of atherosclerosis than were fasting TG levels.[22] More recently, data from the ARIC Study were used to demonstrate that the determinants of fasting and postprandial blood lipids differ.[23] Among middle-aged Americans it is clear that fasting TG levels do correlate fairly well with postprandial TG and this appears to be why fasting TG level is also a fairly good predictor of atherosclerotic disease. So the ATP III is correct to be concerned about Americans who do have elevated fasting TG levels (150 mg/dl or more). However, if two people have the same fasting TG level and they consume diets that differ dramatically in fat and carbohydrate content then it should be clear that the rise in postprandial TG levels will be much greater (and probably more atherogenic) on a high-fat than a very-high-carbohydrate diet.

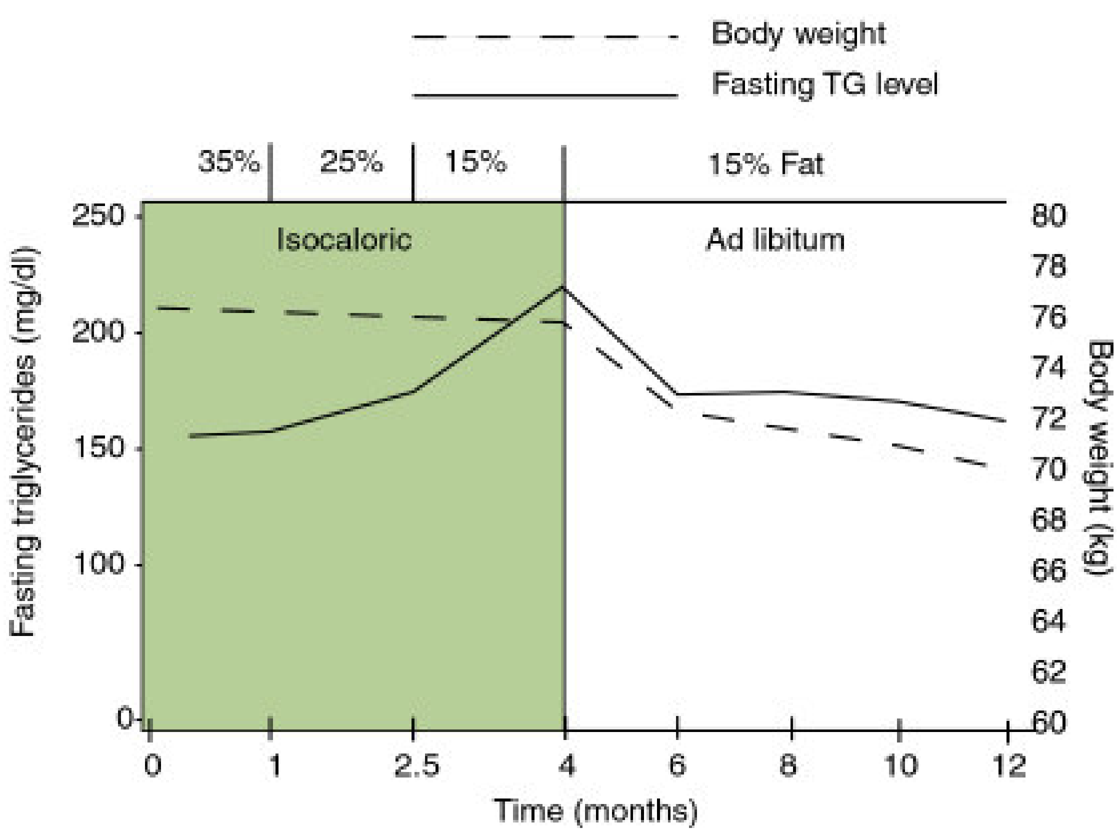
Most people spend most of their lifetime in a postprandial state. Typically 18 or more hours a day is the norm. Therefore it may be inappropriate to claim that finding higher fasting TG levels as a result of adopting a higher carbohydrate diet causes an increased risk of CAD. This is because the increase in postprandial TG levels (and presumably RLP) would be much less with an ad libitum VLF, high-fiber diet than it would be on an ad libitum diet, which contains more monounstaturated fat. It should be clear that clinicians cannot assume the higher risk of CVD often associated with higher fasting and postprandial TG levels (in people consuming high-fat Western-style diets) would be comparable to the risk of CVD with a similar fasting TG level in people consuming a VLF diet. While it seems likely that atherogenic RLP would fall along with postprandial TG levels on a low-fat diet if fed ad libitum compared to a diet higher in unsaturated fat over the long-term this remains to be proven. This is an area that deserves more attention from researchers.

Fasting TG Levels Often Return To Normal On A High-Carbohydrate Diet

Initially, when dietary carbohydrate replaces UFA and body weight and dietary energy intake are held constant it is generally true that most people do experience a rise in fasting TG levels. This is particularly true if the high-carbohydrate diet is high in refined sugars and low in fiber. Virtually all the studies which have shown elevated fasting TG levels on a higher carbohydrate than a diet higher in monounsaturated fat have used primarily refined carbohydrates and have been very short-term, typically lasting no more than a few weeks. However, epidemiological studies have shown that neither CHD nor elevated fasting TG levels are common in human populations consuming diets very high in carbohydrate but with little refined sugar.[24]

Studies that last much longer than 2-3 weeks typically find little or no sustained rise in fasting TG levels as a result of increasing the percent of energy from dietary carbohydrate. When a low-fat, high-carbohydrate diet consisting largely of whole natural foods is fed to people accustomed to a typical modern diet it typically takes 4-6 weeks for their fasting TG levels to stabilize. However, in a few subjects it can take as long as 10 to 18 weeks for fasting TG levels to stabilize after a switch to a diet much higher in carbohydrate.[25] **Figure 2** below shows what happened to fasting serum TG levels in a group of 54 postmenopausal women who were placed on a low-fat, high-carbohydrate diet consisting largely of whole foods.[26]

Figure 2. Effect of increasing dietary carbohydrate at the expense of fat on fasting plasma triglyceride levels and body weight in postmenopausal women.



Adapted from Kasim-Karakas SE, et al. Metabolism 1997;46:431

During the first 4 months of this study, dietary carbohydrate gradually replaced dietary fat in the diet but subjects were required to consume enough calories to prevent weight loss. During this time, fasting serum TG levels rose from 151 to 204 mg/dl. In this study, the increase in average fasting TG levels was much less than that observed in most studies lasting only a few weeks or less. This was the case, even though the difference in carbohydrate content of the two diets used in this study (20% increase in calories from carbohydrate) was similar to that used in most shorter term studies. In the Stanford study, fasting TG levels increased nearly twice as high on the high-carbohydrate diet compared with the high monounsaturated fat diet (113 vs. 206 mg/dl) as observed in this study (151 vs. 204 mg/dl). This was the case even though both high-carbohydrate diets had the same percent difference in dietary carbohydrate content (20% more of energy).

There are two likely explanations. First, four months is long enough for more physiological adjustment to the higher carbohydrate intake to occur. However, as can be seen from **Figure 2**, there was a small amount of weight loss on the VLF diet despite the researchers best efforts to control body weight. During the second phase of the study, when food intake was ad libitum, fasting TG levels returned close to baseline within two months. If fasting TG levels are similar on diets with large differences in carbohydrate and fat content then postprandial TG levels will always be much lower on the lower fat diet.[27]

Another reason for the greater initial rise in fasting TG levels observed in the Stanford researchers' study and others like it was that these researchers used more refined sugar in the high-carbohydrate diet (which tend to raise TG levels more than natural high-carbohydrate foods). For example, sucrose and fructose appear to increase fasting and postprandial TG levels more than starch or glucose, particularly in men. Replacing sucrose and fructose with starch of glucose has been shown to increase fasting TG levels.[28] [29] Another study showed that both fasting and postprandial TG levels were significantly higher when dietary sucrose displaced starch isocalorically in normal weight women.[30]

Another reason the Stanford study observed elevated fasting TG levels was that their subjects were on the experimental diets for only 2 weeks. Two weeks is not long enough for the body to biochemically adapt to a higher carbohydrate intake. Also, the subjects in this study lost a little weight during the first 4 months of the study despite the researchers best attempts to get them to maintain their initial body weights. Weight loss tends to lower TG levels so even the loss of a few pounds can blunt the TG raising effects of adopting a higher carbohydrate diet. The inability of researchers to control body weights effectively over long periods of time when they differ dramatically in fat content may be another reason that nearly all the studies that indicate large increases in fasting TG levels on higher carbohydrate diets typically last a few weeks or less.

During the next 8 months of this study the subjects continued to consume the same high-carbohydrate, low-fat (15% of energy) diet. However, during this phase the researchers no longer tried to control how much their subjects ate or what they weighed. During this phase, the subjects' calorie intake was ad libitum. Their average fasting TG levels gradually returned to its baseline level. Not surprisingly, in this 8 month period, the subjects lost another 4.5 pounds consuming a self-selected VLF diet (ad libitum). It is likely that if people were taught to consume a VLF diet, which consisted largely of natural plant foods, they would lose excess body fat without any need to count calories. In addition, in most subjects, the overall blood profile would improve and their risk of CHD would fall dramatically over time.

Every study published by the Stanford group and others, which has shown detrimental effects of high-carbohydrate relative to high unsaturated fat diets on blood lipids, has required their subjects to consume the same energy level and/or maintain the same body weight on both high-fat and high-carbohydrate diets. It is because a diet with more fat is generally more calorie dense and lower in fiber than a higher carbohydrate diet that it would be expected to lead most people to consume more calories than they would ad libitum on a diet lower in fat.[31] It appears that the NCEP ATP III should have been much more concerned about the type of high-carbohydrate foods consumed than the percent of energy coming from carbohydrate and fat.

It seems likely then that it is only when research subjects are required (by researchers) to eat past satiety on a very-high-carbohydrate diet, to prevent weight loss, that potentially adverse metabolic changes result in most people. Higher fasting TG levels, higher postprandial TG and RLP concern the ATP III but a comprehensive review of the literature shows the presumably adverse changes in blood lipids when people first switch to a high carbohydrate diet are mostly transient unless the high-carbohydrate diet is very high in sugar and has little fiber.[32] It should be noted that a high-carbohydrate diet that is high in sugar and refined white flour and has a high calorie density may not lead to a reduced ad libitum energy intake. Such a diet may not promote weight loss and may have detrimental metabolic effects in many people.[33] However, a diet consisting of less processed and refined high-carbohydrate foods is likely to increase satiety, aid weight loss, reduce insulin resistance and improve blood lipids.[34] [35]

Do High-Carbohydrate Diets Lower HDL-C Levels and Increase CHD Risk?

The ATP III was also concerned about the often reported drop in HDL-C levels that frequently accompany the rise in fasting TG levels in most people who initially switch to a diet much higher in carbohydrate and much lower in fat. However, just as is the case with higher fasting TG, there is reason to suspect the ATP III's concern about higher carbohydrate diets promoting atherosclerosis because of lower levels of HDL-C is unwarranted if one examines the big picture. It should be noted that while higher HDL-C levels are typically associated with a reduced risk of atherosclerotic disease, this is not always the case. In some patients who have a mutation in the hepatic lipase gene and also in those who have the apo E3/E4 genotype, HDL-C are often in the normal range or even elevated and yet these patients are still at higher risk of CHD.[36] What impact changes in dietary fat and carbohydrate intake have on reverse cholesterol transport in patients with these genetic abnormalities requires more study.

The drop in HDL-C level and the rise in fasting TG level are typically observed in short-term studies where the high-carbohydrate and high-unsaturated fat diets are fed isoenergetically.[37] [38] However, most research suggest that both fasting TG and HDL-C levels often return close to baseline levels if the higher carbohydrate diet is fed ad libitum and for a long enough time for the body to physiologically adapt to the higher carbohydrate intake. A big part of that adaption is the loss of excess body fat and improved insulin sensitivity.

Two studies examined the metabolic effects of a VLF diet (15% fat) compared to a moderate-fat (30% of energy) diet but in these studies the VLF diet was fed either isocalorically with the higher fat diet or ad libitum. In both studies, when the VLF diets were fed at the same calorie level as the higher fat diets, the VLF diets produced the same potentially adverse metabolic effects typically associated with the metabolic syndrome (increased fasting TG and decreased HDL-C). However, these adverse metabolic changes largely disappeared when the research subjects were allowed to eat the VLF diets ad libitum.[39] [40]

Data from the National Weight Control Registry, which has examined people who have successfully lost weight and kept it off long-term, clearly shows that most do so with a low-fat diet and regular exercise. Indeed, over 90% of those who successfully lost weight and kept it off consumed a diet with less than 30% fat calories.[41] This is consistent with the conclusions of a recent review of popular diets. They conclude, "Diets that are high in carbohydrate and low to moderate in fat tend to be lower in energy. The lowest energy intakes were observed for those on a vegetarian diet. The diet quality as measured by the HEI

(Healthy Eating Index) was highest for the high carbohydrate groups and lowest for the low carbohydrate groups. The BMIs were significantly lower for men and women on the high carbohydrate diet: the highest BMIs were noted for those on a low carbohydrate diet."[42]

In the real world, a more vegetarian diet that is lower in fat and has more fiber will usually lead to reduction in ad libitum energy intake. Over time this lower energy intake leads to a lower BMI.[43] Weight loss nearly always lowers both fasting and postprandial TG levels and raises HDL-C. However, the studies the ATP III uses to justify recommending a diet with more unsaturated fat all controlled energy intake and body weight of their subjects. Therefore, the experimental design of these studies prevented perhaps the major metabolic advantage of higher carbohydrate diets from occurring. In addition, all of the studies associating adverse metabolic changes with a lower fat diet were also of very short duration, typically lasting no more than a few weeks. This may not be long enough for people accustomed to a high-fat diet to metabolically adjust to a VLF, high carbohydrate intake. Therefore, the recommendation of the ATP III for people with the metabolic syndrome to consume a higher fat diet (35% en) appears to be based on short-term studies with a design flaw that leaves their results with little relevance for most patient living in the real world.

Blood Lipids Changes Due to Genetic and Diet May Not Be Comparable

Another problem with the new ATP III guidelines is the assumption that differences in blood lipids that arise from short-term changes in diet mean the same thing as differences observed between people in Framingham, Massachusetts. In Framingham most people consume a similar diet so differences in fasting TG levels or HDL-C levels are probably largely due to differences in genetic factors and differences in body weight, activity level, smoking, etc. In addition, the differences in blood lipids that result from dietary changes are often transient whereas the differences in blood lipids between people in Framingham tend to remain fairly stable over time. A 20-year old man with a low HDL-C level is quite likely to end up as a 30 or 50 year old man with low HDL-C level. Research shows that differences in blood lipids between people in a cultural fairly homogeneous population tend to track each other over time. However, changes in blood lipids that result from a change in diet are sometimes transient.

Data from Framingham and other epidemiological studies have shown an increased risk of CAD was correlated with a lower HDL-C level and often with a higher fasting TG level. Few people doubt that higher fasting TG and lower HDL-C are usually associated with an increased risk of CAD in people eating a typical high-fat Western diet. Nor does there appear to be much doubt that higher levels of postprandial RLP are associated with a more rapid progression of atherosclerosis in people eating high-fat, Western-style diets. However, there are no studies to show that higher levels of fasting TG and postprandial RLP and lower HDL-C resulting from switching to a diet higher in carbohydrate and lower in fat actually promotes atherosclerosis. The ATP III apparently believes that changes observed in blood lipids during short-term clinical trials are detrimental. However, there is no solid clinical research that demonstrates that such lipid changes really do promote atherosclerosis and increase the risk of CAD in people who adhere to high-carbohydrate diets for a prolonged period of time.

Another problem with the idea that high-carbohydrate diets promote changes in blood lipids that increase the risk of CAD is that it seems to conflict with most epidemiological cross-cultural observations. Population studies of people consuming high-carbohydrate diets have shown that CAD is far less common in those populations than it is in America and other countries where diets high in animal products and fat are the norm.[44] However, in these populations not only is the consumption of carbohydrate higher but the intake of SFA and cholesterol are much lower and fiber intake is often much higher than they are in Americans. There may also be differences in activity and other lifestyle factors that could account for at least some of the differences in CAD risk between Americans and the high-carbohydrate diet consuming populations.

A Lower HDL-C Resulting From A High-Carbohydrate Diet May Not Be Dangerous

The ATP III apparently believe that the drop in HDL-C seen in short-term studies when dietary carbohydrate displaces fat isocalorically means there is an increased the risk of CAD in the long-run. There are several reasons to believe this is not the case. First, there is growing evidence that the drop in HDL-C that results from restricting dietary fat intake does not lead to a permanently lower HDL-C. This is because replacing high-fat foods with high-carbohydrate foods usually reduces ad libitum energy intake. A lower energy intake leads to weight loss and a lower body weight. A lower body weight usually leads to an increase in HDL-C. For example, a study by Thuesen in Europe found that when a group of hypercholesterolemic men were placed on an ad libitum VLF, near vegetarian diet for 3 months their energy intake decreased and they lost about 16.5 lbs. On this VLF, high-carbohydrate diet, their LDL-C levels dropped from 236 to 139 mg/dl (-41%) and their fasting TG dropped from 170 to 145 mg/dl (or -15%) but their average HDL-C was essentially unchanged (36 to 37 mg/dL or +3%).[45] This same study followed these men for another 9 months. Those who continued to consume a VLF diet for another 9 months saw their HDL-C levels continue to increase.

It should be noted that fasting plasma TG levels also fell on average in the Thuesen study which is the opposite of what the Stanford group has repeatedly observed in short-term studies where both the high-fat and high-carbohydrate diets were fed isocalorically over a very short time frame. The results of the Thuesen study clearly demonstrate that when a VLF, high fiber, near vegetarian diet is fed ad libitum to patients at high risk of CAD (many of whom would be identified as having the metabolic syndrome by the ATP III criteria), the changes in their blood lipids are usually favorable over the long-term. Indeed, other studies have shown that in many patients a VLF, near vegetarian diet leads to regression of atherosclerotic plaque.[46] By contrast, this same showed that those subjects in the control group who were instructed to follow what the NCEP now calls a "Heart Healthy Diet" experienced progression of their atherosclerotic lesions even though most were also taking "statin" drugs to help lower their blood lipids.

Another reason to question concerns about a drop in HDL-C when dietary carbohydrate replaces monounsaturated fat is that research has shown that the fractional clearance rate of cholesterol is much faster on VLF diets than it is on diets higher in fat.[47] This means that it is likely that the amount of cholesterol transported back to the liver from the arteries is not impaired on a high-carbohydrate diet even if the HDL-C level does drop. In animals studies, reverse cholesterol transport was not impaired despite a much lower HDL-C on a high-carbohydrate diet compared to a high-fat diet.[48]

In addition to assisting reverse cholesterol transport, HDL particles may help protect against atherosclerotic disease in other ways. For example, HDL particles contain proteins that can potentially reduce the oxidative modification of LDL particles. This is important because these oxidized LDL particles are believed to play the primary role in the initiation and growth of atherosclerotic plaques. Oxidized LDL particles attached macrophages to the artery wall. These macrophages release chemicals that trigger local inflammation within the artery wall. The examination of HDL particles taken from CAD patients with normal HDL-C levels has shown that their HDL particles do block the oxidation of LDL particles. Indeed, these HDL particles were actually shown to promote LDL oxidation and create a proinflammatory state.[49] This same research group fed mice a high-fat atherogenic diet and found that they developed pro-inflammatory HDL particles. By contrast when these same mice were fed a low fat, high-fiber chow diet their HDL particles prevented the formation of pro-inflammatory, oxidized LDL particles.[50]

So while HDL-C levels do often fall initially when most people first adopt a VLF diet, it is not clear that this lower HDL-C level necessarily increases the risk of CAD. Furthermore, in most patients, the adoption of a high-fiber, VLF, more vegetarian diet will result in weight loss. Over the long-run weight loss will eventually result in HDL-C levels returning to close baseline levels in most patients and even higher levels in many patients who lose and keep off a lot of body fat. Epidemiological evidence does suggest that HDL-C may be somewhat lower in human populations who consume very high carbohydrate diets. However, these same human populations have also been shown to have a very low incidence of CAD. So while the ATP III recommendation for an HDL-C below 40 as a risk factor seems appropriate for people consuming a typical high-fat atherogenic American diet it is questionable whether this same target is warranted for individuals who adopt a VLF more vegetarian diet that is high in fiber.

Insulin Resistance and C-Reactive Protein Level

C-reactive protein (CRP) is a nonspecific marker of chronic low level inflammation in the body. Growing research suggests inflammatory processes are involved in atherosclerotic plaque formation, progression, rupture and in thrombosis.[51] Inflammatory cytokines trigger the release of an enzyme (sphingomylinase) from both macrophages and arterial endothelial cells into the intracellular space. This enzyme has been shown to cause the aggregation and fusion of LDL particles inside the artery wall, leading to the formation of a growing pool of cholesterol-rich lipid. Increasing evidence suggests this may be the primary mechanism leading to the formation of the necrotic lipid core of atherosclerotic plaques.[52] The release of sphinogomylinase has been shown to increase in mice models of systemic inflammation.[53] This suggests that it is because CRP is a good marker of low-level systemic inflammation that it is a good predictor of atherosclerotic plaque growth. Plaques with growing necrotic lipid cores are more likely to rupture and trigger a MI or thrombotic stroke.

Not surprisingly, there is growing evidence that higher levels of CRP are associated with an increased risk of morbidity and mortality from CHD.[54] [55] CRP levels have been shown to correlate positively with insulin resistance, the metabolic syndrome, obesity and increased abdominal fat stores.[56] While the new CRP guidelines put more emphasis on losing excess body fat, the TLC Diet recommended by the ATP III specifically increases the fat content of the diet to 35% of calories for those with the metabolic syndrome. The TLC Diet recommended for patients with the metabolic syndrome is inconsistent with research showing the most effective diet for successful long-term weight control is one very low in fat. People who have been successful at losing a lot of weight and keeping it off most often consume a diet quite low in fat and do a lot more exercise than the TLC recommends.[57 58 59]

A recent study of 83 obese women showed that the loss of 7.9 kg over 12 weeks on a VLF (15% en) diet resulted in a mean 26% drop in CRP levels. The drop in CRP level was proportional the amount of weight lost.[60] While the ATP III's primary focus is on lowering LDL-C levels there is growing evidence that excessive abdominal fat can increase the risk of CVD in many ways. Greater amounts of abdominal fat promote inflammation and coagulation but inhibit fibrinolysis.[61] A VLF, low energy density diet, that is high in fiber, is probably best for reducing ad libitum energy intake. Therefore, it seems likely that such a VLF is also preferable to a diet with a higher fat content for treating overweight or obese patients with the metabolic syndrome. Unfortunately, the ATP III guidelines specifically recommend a diet higher in fat (35% en) for patients identified with the metabolic syndrome.

The ATP III focus primarily on blood lipid changes observed in short-term clinical trials has led to dietary recommendations that may prove counterproductive for achieving the reduction of other CVD risk factors such as excess body fat stores and elevated levels of CRP.

Bottom Line: Clinical Trials Show Regression on Very-Low-Fat Diets

If high-carbohydrate diets are more atherogenic than diets higher in fat, what are we to make of several studies that have reported that VLF, near-vegetarian diets cause regression of atherosclerosis in most patients who already have advanced coronary artery disease?[62 63 64 65] By contrast, there are no comparable studies showing a regression of atherosclerotic plaques with a diet higher in fat.

If diets higher in carbohydrate do result in a more atherogenic lipoprotein profile (as the ATP III apparently believes), how can we reconcile such a belief with the results of a 12-year study that found that a VLF, near vegetarian diet greatly reduced deaths from CAD? This study also showed that a VLF also markedly reduced overall mortality in older subjects (all of whom had had a previous heart attack) compared to the control group who maintained a typical high-fat American diet?[66] Obviously a more vegetarian, high-carbohydrate diet is much less atherogenic than a typical American diet, which is much higher in saturated fat, hydrogenated fat and cholesterol. It seems clear that a VLF, near vegetarian diet composed largely of natural, minimally processed plant foods is both safe and efficacious for the prevention and treatment of atherosclerosis and its sequelae.

Should SFA Be Replaced With Carbohydrate or Unsaturated Fat?

In healthy people, the benefits of lowering serum cholesterol by reducing dietary fat and increasing dietary carbohydrate have been well documented in terms of preventing CAD.[67] There really can be no rationale debate about whether replacing dietary saturated fatty acids (SFA) with carbohydrate will help to prevent CAD in the average American. Perhaps there are some people in America that would do better healthwise on a diet higher in unsaturated fat and lower in carbohydrate. However, this has not been demonstrated clinically with hard end points like MI, stroke and total mortality. Even if there are some patients who would do better on a high -unsaturated fat diet compared to a high-carbohydrate diet there is no cost effective diagnostic test(s) to determine who these patients are.

It is hard to understand the reluctance of the NCEP to recommend replacing foods high in SFA and cholesterol with foods high in carbohydrate and fiber. There is overwhelming scientific data to support such a recommendation as a safe and effective public health policy for all Americans who need to reduce their risk for CAD. Extreme reductions in dietary fat and cholesterol coupled with a marked increase in dietary carbohydrate and fiber has been proven to reverse atherosclerosis in clinical trials. Switching to a VLF, more vegetarian diet from a typical American diet has also been shown to reduce the overall risk of dying for patients with pre-existing advanced CAD. Those who would advocate replacing SFA with unsaturated fatty acids (UFA) should be aware that there is no such proof that diets higher in UFA reverses CAD. Therefore, it seem a leap of faith, rather than science to believe replacing SFA with UFA prevents CAD more effectively than consuming more fruits, vegetables, beans and whole grains instead of the monounsaturated oils.

But Wouldn't Replacing SFA With UFA Also Prevent CAD?

No one knows for sure at this point, although changes in blood lipids certainly do suggest that this would be the case. Replacing SFA with UFA does lower serum total cholesterol (TC) and LDL-C levels about as much as replacing SFA with carbohydrate. Replacing saturated fat with monounsaturated fat does not lower HDL-C levels and may lower fasting TG levels. However, there is concern that diets higher in monounsaturated fat may increase the tendency of blood to clot due to higher levels of clotting factor VII.[68] [69] The authors of a Danish study conclude, "A low-fat, high-fiber diet may not only reduce the atherogenic but also the thrombogenic tendency of an individual compared with a diet corresponding to the average Danish diet".[70] If a diet higher in carbohydrate and fiber and lower in total fat reduces the risk of thrombosis, it may be particularly beneficial for patients with advanced atherosclerotic lesions because most MIs are caused in part by thrombosis and impaired fibrinolysis.

Perhaps the ATP III believe that even if a diet higher in monounsaturated fat doesn't reduce thrombosis it may still improve blood lipids and this should help reverse atherosclerotic lesions. However, no one has shown that a diet high in MUFA would actually cause regression of atherosclerotic lesions. Indeed, in one monkey study, a diet high in MUFA did improve TC and other blood lipid levels compared to a diet high in SFA. The change in blood lipids in the monkeys was in the same direction as seen in humans fed similar diets. However, despite what appeared to be "improved blood lipids", atherosclerosis progressed to a similar degree in the monkeys fed the high-MUFA diet as those fed the high-SFA diet.[71] So at least in animal models, "improving blood lipids" does not necessarily slow the progression of atherosclerosis. The results of this study call into question the wisdom of assuming that changes in blood lipids in response to dietary changes mean the same thing as differences in blood lipids observed between individuals who are all consuming a similar diet. In this latter case, the differences in blood lipids would be largely due to genetic factors.

Conclusions

The results of most clinical trials have shown that ad libitum energy intake falls and body fat stores diminish when people are switched from a typical modern diet to a diet with a lower fat content. This is consistent with observational data from human populations that generally show that cultural groups that consume diets higher in fat generally have greater average BMIs than cultural groups consuming diets low in fat and high in fiber. Studies of human cultures typically find a low prevalence of obesity and also a low prevalence of CHD and Type 2 DM where a VLF intake is the norm.[72] More recently, carefully controlled studies have consistently shown that the primary mechanism by which reducing dietary fat leads to weight loss is the resulting decrease in ED of the lower fat diet.[73]

Because of the extremely high energy density of refined oils and most high-fat foods (e.g. nuts, nut butters, seeds) it is far more difficult to plan a diet with a low energy density if these foods are not more limited. A diet with 35% fat compared to a diet with only 10% fat would tend to be more energy dense and this would make weight loss without hunger more difficult. The metabolic syndrome is caused largely by excessive ad libitum energy intake over time coupled with a sedentary lifestyle. From this reviewer's perspective it makes much more sense to recommend a diet very low in fat for people with this syndrome. As has been shown in this review, the presumably adverse metabolic effects the ATP III seems so concerned about with diets higher in carbohydrate and lower in fat are likely to prove transient in the real world.

The presumably adverse impact of high-carbohydrate diets on blood lipids is limited primarily to short-term clinical trials in which the research subjects' calorie intake is artificially manipulated (i.e., controlled by researchers). The high-carbohydrate study diet is composed largely of sugar and other refined carbohydrates with little or no fiber. This is the Stanford model the ATP III bases their recommendation on for higher fat intake for those with the metabolic syndrome. However, by requiring research subjects to consume the same energy intake and maintain the same body weight on both high-fat and low-fat diets, these studies have shown metabolic changes that are reason for concern particularly for those with the metabolic syndrome. It is clear that people with the metabolic syndrome really need to lose excess body fat and participate in regular exercise. These reduce insulin resistance and the adverse metabolic changes that can increase CVD risk factors and promote the development of Type 2 DM. People with the metabolic syndrome do not require more dietary fat because increased dietary fat tends to promote weight gain over time.

At least some members of the ATP III are well aware of these arguments. The flawed experimental design of studies comparing high-fat and high-carbohydrate diets was explained in a letter to the editor, the Stanford Group, University of Texas Southwestern Medical Center group, and the University of California, Berkeley group.[74] [75] [76] Nevertheless, the ATP III still choose to promote a diet higher in fat for people with the metabolic syndrome.

Research in the future should compare a high-carbohydrate diet consisting largely of natural foods that are high in fiber like fruits, vegetables, whole grains, and beans with a similar diet to which olive oil had been added. Both diets would need to be fed ad libitum (rather than imposing artificial controls on their research subjects' energy intake). If such a study were done, it would likely find that a VLF, high-fiber diet does not produce the adverse changes in blood lipids the ATP III is so concerned about. In part, the favorable effects of the VLF diet compared to one higher in fat would be due to a reduction in energy intake and weight loss. Indeed, any changes in blood lipids that such a diet caused must be viewed as favorable simply because a VLF, near vegetarian diet has been proven to reverse atherosclerosis. This is something diets higher in fat have not been shown to do. Why does the ATP III want physicians and dietitians to abandon the only dietary approach ever proven to atherosclerotic disease in human subjects? For the ATP III to recommend a TLC Diet with higher dietary fat content for people with the metabolic syndrome does not make sense because increased dietary fat tends to promote weight gain. Such dietary advice is based on short-term studies with a questionable experimental design that makes their findings largely irrelevant to the real world.

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