Small Dense LDL Cholesterol Particles, Apolipoprotein B & the Effect of Low Saturated Fat Low Carbohydrate Diets

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BACKGROUND

Diet is one of the major environmental factors that affect the serum lipids and lipoproteins. Among dietary components that elevate serum lipids, saturated fats and cholesterol content are considered important. It is an established fact that saturated fats increase the total plasma cholesterol, low density lipoprotein (LDL) cholesterol and the risk of coronary artery disease. However, the influence of carbohydrates, which is a major calorie source for individuals on low saturated fat diets, on serum lipids and lipoproteins still deserves further investigation. Currently dietary guidelines for reducing the risk of cardiovascular diseases emphasize the replacement of saturated fat with carbohydrates, so that the total fat intake does not exceed 30% of energy intake. Low saturated fat, high carbohydrate diets improve the total plasma cholesterol concentration, but can also cause an increase in plasma triglycerides concentration, increase small dense LDL particles, and increased in apolipoproteinB (ApoB) levels. Many studies had reported that these clusters of non traditional risk factors are strongly related with development of coronary artery disease (CAD). Thus, these increases in plasma triglycerides (TG), ApoB, small dense LDL particles and reduced high density lipoprotein 2b(HDL2b) dilute the favorable improvement achieved in total plasma and LDL cholesterol with low saturated fat, high carbohydrate diets.[1,2,3,4]

Introduction

Atherosclerosis is one of the most common causes of death in western societies. Therefore, reducing the risk factors, such as elevated plasma total and LDL cholesterol, and recently added apolipoproteinB, small dense LDL-C particles and triglycerides levels and raising HDL-C, is a major public health goal. Since, the pioneer work of Hegsted and Keys et al demonstrated that changes in dietary fat and cholesterol are associated with changes in plasma total cholesterol, dietary modifications have become the foundation of the therapeutic approach for the prevention of cardiovascular diseases. However, the debate on the type of diet, ultimately reducing the coronary risk, is still unsettled. The replacement of total and saturated fat with high carbohydrates has been at the centerpiece of recommendations to reduce heart disease, but the degree of risk reduction to be expected has received little attention. The effect on blood lipids of replacing saturated fat with carbohydrates has been evaluated in numerous controlled feeding studies.[5, 6, 7] With these dietary changes, serum total cholesterol, LDL cholesterol decline and high-density lipoprotein HDL cholesterol also decreases and triglycerides levels are elevated[5,7,8,9.] Thus, the ratio of total cholesterol over HDL cholesterol is minimally affected by replacing saturated fat with carbohydrates, suggesting that there is little if any benefit expected. Moreover, available evidence suggests that in the setting of high serum triglycerides, there is an overall rise in serum ApoB and small LDL particle levels. These increases in ApoB and small LDL-C particles magnify the coronary risk by five folds.[10,11,12] Consequently, this implies that low saturated fat, high carbohydrate diets should not be the only dietary modification recommended in the prevention of coronary artery disease. In the present case study, we achieved a marked reduction in ApoB, triglycerides and small LDL-C particle concentrations with a low saturated fat diet that was also low in carbohydrates.

Dietary Intakes

The diet used in the present case report was composed of portions consisting 50% of vegetables, grains and 50 % lean meat and plant proteins. All dietary portions consumed by the patients were low in saturated fats and low in carbohydrates. Patients were instructed to eat small portions of food and to eat five times per day. Daily calorie consumption was 1400-1800 kcal. The daily calorie consumption measurement was based on the detailed food history. All foods containing sugar, starch, and saturated fats were avoided (see tab 1). The type of diet used with these patients is a routinely recommended diet in our clinical practice.

Tab 1Composition of Diets in terms of types of food

Food to avoid		***Food to eat***	
1. Beans	9. Potatoes	1.Beef (Less than 5% fat)	9.Bean Sprouts
2. Peas	10. Fried Food	2.Poultry (no Skin)	10.Broccoli
3. Corn	11. All breads	3. Pork (lean)	11.Cabbage
4. Beats	12. All Pasta	4.Tofu	12.Edamame
5 Juices	13. Ice creams	5.Nuts	13.Green Beans
6. Fruits	14. Chips	6.Avocado	14.Spinach
7. Dairy Products	15. Rice	7.Low Fat Yogurt (with no sugar or salt)	15.Tomatoes
8. Crackers	16. Cookies	8.Asparagus	16.Turnips

Salt Consumption (less than 2000mg/d)

Case Presentation

Patients A, B, C with a mean age of 34 years and BMI 28 came in for cardiac evaluation. They did not have any symptoms of PND, Orthopnea, palpitations, leg edema, claudications, syncope, chest pain or chest tightness and also has no history of smoking and alcohol intake.

Patients did have a past medical history of hypercholestremia for which they were not on any treatment. Only patient A has a significant family history of coronary artery disease.

On physical examination all patients were comfortable, alert, not in distress and oriented to 3 spheres. Mean systolic and diastolic pressure ranges from 110-130 mm hg and 80-82 mm hg respectively with an average heart rate of 64 bpm, respiration rate 14 and were afebrile. HEENT: Normal conjunctivae, normal oral mucosa. Neck: no elevated JVP. Chest: Clear to auscultation bilaterally. Heart: S1, S2 normal with no added sounds. Abdomen: Soft, non tender, normal bowel sounds. EKG of all three patients shows normal sinus rhythm, within normal limits with a mean heart rate of 80 beats per minute. The baseline advanced lipid panel results from three patients are shown in table 2

Tab 2. Baseline Values for Patient A, B, C

	Patient A	Patient B	Patient C
1.Age(years)	43	33	34
2.Blood Pressure (mm/hg)	120/70	110/70	120/80
3.BMI	23	31	30
4.Total cholesterol(mg/dl)	189	168	208
5. LDL Cholesterol(mg/dl)	109	113	124
6. HDL Cholesterol (mg/dl)	34	36	41
7. Triglycerides(mg/dl)	231	97	214
8. Apo-B(mg/dl)	109	91	128
9. LDL IIIa+b (%)	50	40.9	43.6
10.LDL IV (%)	3.3	2.8	2.8
11. HDL 2b (%)	9	11	8
12. LPLAC(ng/ml)	121	116	133
13. QLDL IIIa+b (mg/dl)	46.7	39.3	57.7
14.QLDL IVb (mg/dl)	3.8	3.3	0.8
15. Metabolic Syndrome score	2	2	2

Criteria of Metabolic Syndrome by third report of National cholesterol education program (NCEP)

- ***Abdominal obesity: waist circumference > 35 inches in women or 40 inches in men***
- ***B MI ≥30***
- ***Triglycerides > 150 mg%***
- ***HDL-cholesterol < 50 mg% in women or < 40 mg% in men***
- ***Blood pressure > 130/85 mm Hg***
- ***Fasting plasma glucose > 110 mg%***

The results showed that all 3 patients had a disarranged lipid panel and had a metabolic syndrome score of 2. Patients were extensively counseled about the importance of metabolic syndrome. All patients underwent a Berkeley Heart Lab advanced lipid profile testing. As the patients were young and did not want medications as their primary therapeutic intervention, they were started on a low carbohydrate, low fat diet for six months without reducing the daily calorie consumption.

Follow-up at 6 Months

The results from patients A, B, C are shown in Table 3. As expected we observe a reduction in total plasma and LDL cholesterol and reversal of LDL/HDL ratio which is consistent with results from previous studies done on low saturated fat diets. Remarkably, in addition to this, we also notice a significant drop in TG, ApoB100, and small LDL particle concentrations. Moreover, inspite of the small

sample size (n=3), the drop achieved in small dense particles; LDLIIIa+b(13.6 ± 9.4 %), QLDLIIIa+b(10.9 ± 6.0 mg/dl), was of statistically significance (P=.012, P=.038) respectively and a near statistical significant drop (P=.078) for ApoB levels. A substantial increase in HDL2b percentage was also noted. Mean BMI at follow up visit was 26.

Tab 3. Follow Up Values for Patient A, B, C

Lipid Parameters	***Patient A***	***%Δ***	***Patient B***	***%Δ***	***Patient C***	***%Δ***
1.Total cholesterol(mg/dl)	134	-29%	173	-3%	165	-20%
2. LDL Cholesterol(mg/dl)	81	-25%	113	0%	105	-15%
3. HDL Cholesterol (mg/dl)	36	5.9%	43	19%	45	10%
4. Triglycerides(mg/dl)	86	-62%	84	-13%	77	-64%
5. Apo-B(mg/dl)	67	-38%	77	-15%	81	-36%
6. LDL IIIa+b (%)	24.3	-51%	9.2	-77%	6.2	-85%
7.LDL IV (%)	2.5	-2.4%	0.9	-67%	0.5	-82%
8. HDL 2b (%)	9	0%	11	0%	12	50%
9. LPLAC(ng/ml)	100	-17%	118	1.7%	142	6.7%
10. QLDL IIIa+b (mg/dl)	17.7	-62%	9.2	-76%	5.9	-52%
11.QLDL IVb (mg/dl	2.2	-42%	0.9	-72%	0.6	-25%

Discussion

For every ApoB, there is one LDL particle, and LDL particle number does not necessarily correspond to the total LDL cholesterol levels. Thus, ApoB is a better representation of the LDL particle number. Total plasma Apo B concentration, as opposed to LDL apolipoprotein B, also accounts for the number of triglycerides rich lipoproteins (VLDL and IDL). Recent data suggests that these two lipoprotein sub fractions play an important role in CAD. Therefore, plasma ApoB concentration could be considered as a crude marker of plasma atherogenic particles. On the other hand, small dense LDL particle's atherogenic potential has been recognized in several studies and along with ApoB can predict the risk for cardiovascular diseases. These small dense LDL particles have greater susceptibility to oxidation and their reduced affinity for LDL receptor has been linked as a mechanism for their atherogenic potential. Therefore, above described role of ApoB, small LDL particle size and TG as potential risk factors for CAD and outcomes achieved in the present case report, points out that adopting a low saturated fat, high carbohydrate diet as primary dietary prevention will not address the issue of CAD adequately; There is a need to be more proactive. Thus, more aggressive strategy in terms of low saturated fat, low carbohydrate diets should be adopted.

Multiple lines of evidence suggest that a low saturated fat, high carbohydrate diet induces the formation of triglycerides rich lipoproteins (TRL)[17,18,19] TRL is a heterogenous group of chylomicrons (rich in ApoB48) VLDL(ApoB100) and cholesterol remmants. These sub fractions are high in cholesterol and have been implicated in atherosclerosis. In contrast to this, the debate concerning the effectiveness of high carbohydrate diets as a mean to reduce CHD is largely ignored in view of the fact that exercise offsets the harmful effects of such dietary intervention.[13,14,15,16]Numerous studies are done in this respect but the outcomes achieved in these studies are inconsistent and opposing.[13,14,15,16] In line with this thinking,

studies which had reported a favorable improvement in TG were based on the explanation that exercise decreases hepatic TG secreation and might increase the lipoprotein lipase activity. However, the reduced energy intake reported in the same studies might have attributed to this effect. Moreover, several studies had reported that low fat, high carbohydrate diet increases de novo synthesis of free fatty acid. This increase in fatty acids may contribute to the increase in hepatic TG synthesis and VLDL secreation which will ultimately increase the formation of small dense LDL particles, thus accelerating the atherosclerosis in arterial walls. It is also note worthy that low satuarted fat, high carbohydrate diets result in overall reduction of high density lipoproteins (HDL) cholesterol. Additionally, such dietary recommendations raise fasting insulin levels, as well as decrease sensitivity to insulin, especially in individuals who are overweight and a have sedentary lifestyle. Also, Quebec[10,11] cardiovascular risk increases twenty fold with an increase in fasting insulin, ApoB and small dense LDL particles. In another study, it was reported that there is a high prevalence of small dense LDL particles in conjunction with low saturated fat, high carbohydrate diets.Interestingly, in the same study it was observed that diets low in fat and high in carbohydrates can significantly alter the composition of stable LDL subclass pattern A.[20,21]

It is now increasingly recoginized that the consumption of total fat per se is less related to higher risk of coronary artery disease than previously thought and also it is increasingly appreciated that different types of fats have different health effects.[22,23] Taking 14 years follow up data from the Nurses Health Study, Hu et al [23]conducted a detailed perspective analysis and found a weak positive association between saturated fat intake and risk of CHD, indicating that different classes of saturated fatty acids have different effects on plasma lipid and lipoprotein levels. On the other hand, consumption of polysaturated fatty acids was observed with a lower risk of coronary heart diseases. In this context, many observational and epidemiological studies also state that replacing polyunsaturated fat with carbohydrates will increase the coronary risk .Interestingly, the same study demonstrated that subsitution of five percent of energy from monosaturated fats and five percent from polyunsaturated fats with isocaloric carbohydrates can increase the relative risk of CHD by 26% and 58% respectively.[23] Therefore, indicating that the low fat, high carbohydrate diet campaign has been based on little evidence and has not been able to address the issue of coronary artery disease adequately.

In summary, although evidence of the replacement of total or saturated fat by carbohydrates is more limited, but the results obtained in the present case report,observation made from previous studies, as well as the role of small dense LDL particles, apolipoproteinB and triglycerides in atherosclerosis, inhibits the replacement of fats with high amounts of refined carbohydrates and sugar. However, the present case study is limited by its small sample size and reterospective design. Also there was no control group.Moreover, patients were not kept in controlled enviroment, so we can montior the amount of food they consumed. Nevertheless, the shift in LDL particle size and decreases in ApoB and triglycerides achieved in the present case report further suggest that recommended low fat/ high carbohydrate diets are based on little evidence , thus challenging their widely recommended use.

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