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HYPERLIPIDEMIA: TREATMENT MODALITY AND BUSTING MYTHS OF DIETARY APPROACH.

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ABSTRACT

The patients of Hyperlipidemia constitute abnormality in raised serum concentrations of LDL and total average Cholesterol as well as rise of TGs. Thus these patients have a higher risk of accentuating atherosclerotic changes at early age, while drug therapy to decrease the raised serum levels of average cholesterol, TGs, LDL and VLDL must be necessitated properly. Hyperlipidemia is a major cause of atherosclerosis and atherosclerosis-induced conditions, such as CAD. The incidence and absolute number of annual events will likely increase over the next decade because of the epidemic of obesity and the aging. Dyslipidemia including Hyperlipidemia (hypercholesterolemia) and low levels of HDL-C are major causes of increased atherogenic risk; both genetic disorders and lifestyle (sedentary behavior and diets high in calories, saturated fat, and cholesterol) contribute to the dyslipidemia seen in countries around the world. For many individuals, alterations in lifestyle have a far greater potential for reducing vascular disease risk and at a lower cost than drug therapy. When pharmacotherapy is indicated, providers can choose from multiple agents with proven efficacy. Thus the lifestyle modification including the dietary module approach and strict implementation of desired pharmacotherapy as either

monotherapy as single drug or as combination therapy which comprises of two or more drugs necessitated with appropriate psychological reinforcement counseling for smoking cessation and restriction of alcohol. As exercise leads to increase in HDL cholesterol and decrease in TGs level while dietary approaches eventually lead to decrease in TGs levels, LDL cholesterol, total serum cholesterol. Thus it seems directly to synergize role of exercise with dietary module approach. **Conclusion**: The pharmacotherapy must be combined with dietary approach and necessary lifestyle modifications must be implemented for good outcomes.

KEYWORDS: LDL-c: low density lipoprotein-cholesterol, HDL-c: high density lipoprotein cholesterol, TGs: triglycerides, VLDL-c: very low density lipoprotein cholesterol, CVS: cardio vascular system, BP: blood pressure, CAD: coronary artery disease, SFAs: saturated fatty acids, PUFAs: polyunsaturated fatty acids.

INTRODUCTION

The increase in plasma lipids, constituents of plasma lipoproteins including reduced HDL, LDL and VLDL, TGs, Cholesterol esters and phospholipids are attributable to Hyperlipidemia.[1,2] The cardiovascular diseases and ultimate progression of atherosclerosis corresponds to Hyperlipidemia which is correlated to rise in oxidative stress resulting in development of oxygen free radicals, which progress to modifications in LDL, thus results into initiation of cascade.[1]

The patients of Hyperlipidemia constitute abnormality in raised serum concentrations of LDL and total average Cholesterol as well as rise of TGs. Thus these patients have a higher risk of accentuating atherosclerotic changes at early age, while drug therapy to decrease the raised serum levels of average cholesterol, TGs, LDL and VLDL must be necessitated properly.[3,4] Now depending upon the individual patient the pharmacotherapy of Hyperlipidemia is constituted, whilst option available is either single drug therapy comprising Statins or Fibrates which is sometimes inadequate, therefore combination therapy of Fibrates plus Statins is prescribed.[5]

In United States and in most western countries, CAD is one of the major cause of death and serum cholesterol is a major risk factor.[6,7]

The pharmacotherapy and dietary approach will lead to decrease in LDL and total serum cholesterol eventually leading to decrease risk of cardiovascular morbidity and mortality and

first line therapy includes dietary approach.[8,9,10] The increment of dietary fibre in diet will lead to safe approach for reduction in cholesterol.[11] The role of psychological counseling: The cardiovascular risks well established must be addressed to the patients with concern and reinforcement to improve lipid profiles by alteration of dietary module.[12] The systematically reviewed 19 RCTs demonstrated that the dietary approach resulted in decrease of total cholesterol by only 3-6%, as dietary modules were not appropriately followed.[13] The advice inculcated by dietician as compared either self help, or physician consultation regarding advice was found to be more successful in short to medium term.[14]

The last three decades have revealed that half of decrease in CVS mortality has directly been because of alteration in dietary modules and other lifestyle modifications, primarily by decrease in cholesterol levels, BP and cessation of smoking. But the risk factors which offset this trend include: Type 2 DM and obesity.[15,16]

The ageing factor also contributed to CVD episodes.

SYMPTOMS OF HYPERLIPIDEMIA: Broadly the patients of Hyperlipidemia does not exhibit obvious symptoms, but the routine blood investigations may reveal the abnormal levels in lipid profile or until the patient reaches the end point of Ischaemic stroke or myocardial infarction. However patients with Hyperlipidemia as familial trait may develop Xanthomas, which are deposited under eyes and skin as cholesterol. Also patients with elevated levels of TGs may exert various pimples like lesions at different sites of their body.[17]

DIAGNOSIS: The diagnosis of Hyperlipidemia can be made via lipid profile screen comprising of blood investigations for Total serum cholesterol, LDL-c, HDL-c, TGs.

The American heart association's have requisite their physicians to determine total and HDL-c.[18]

COMPLICATIONS OF HYPERLIPIDEMIA

- **CAD**: The persistent raised level of lipid profile has been correlated to development of coronary atherosclerosis.[19]

- **Atherosclerosis**: It is defined as the pathological process comprising of accumulation of calcium. Cholesterol and lipids and development of fibrous plaques within the lumen of medium and large arteries.[20]
- **Myocardial Infarction**: It is a pathological condition which results when oxygen and blood supplied to one or more coronary artery has been occluded. The occlusion may result from the rupture of atherosclerotic plaque. Also various studies have demonstrated that 1/4th of MI survivors were known/unknown patients of Hyperlipidemia.[21]
- **Ischaemic stroke**: The fourth leading cause of death. It results due to occlusion of artery by blood clot or rupture of atherosclerotic plaque that breaks in a small artery within the brain. According to various clinical trials that the decrease in LDL and total serum cholesterol by 15 percent significantly decrease risk of first stroke.[22]

The Role of dietary factors is very much necessitated to influence the lipid concentrations. The dietary modifications include alteration of constituents of nutrients, specified food intake, proprietary use of food additives and dietary appropriate approach towards diet.

DIETARY APPROACH: The lipid levels are affected by low carbohydrates and low fat diet. The desired limited intake of red meat, poultry, eggs, dairy products while increased intake whole grains, vegetables, tree nuts, fish, wine may be included. The diet rich in Mediterranean food which comprises of monosaturated fats and decreased consumption of saturated fats is desired.[23] The comparison of two forms of diet rich in Mediterranean food when compared with diet consisting of low fat food, the Mediterranean diet leads to lowering of total to HDL cholesterol levels which is quite more than low fat diet.[24]

ROLE OF EXERCISE SYNERGIZED WITH DIET: As exercise leads to increase in HDL cholesterol and decrease in TGs level while dietary approaches eventually lead to decrease in TGs levels, LDL cholesterol, total serum cholesterol. Thus it seems directly to synergize role of exercise with dietary module approach. In the documented two reviewed literature includes (a) Diet low in saturated fats combined with exercise, (b) Nutritional components taken as supplements (viz. plant sterols, oat bran, fish oil etc.) combined with diet. The result of latter plan demonstrates the reduction of LDL-c by 8-30% and TGs by 12-39% while increasing HDL-c by 2-8%. The former plan suggested that saturated fat diet when combined with exercise reduces LDL by 7-15% and TG by 4-18%, while increasing HDL by 5-14%. Thus exercise may be synergized with diet.[25]

The pharmacotherapy using Statins and target BP achievement leads to greater residual during management in patients having higher baseline risk, which augments early intervention.[26,27]

Dietary approach hallmarks

- The healthy diet plan when followed no nutritional supplements are required.
- The dietary approach leads to alteration of risk of CVS morbidity and mortality and also other chronic disorders such as cancer.
- The energy intake must be limited to as desired to maintain ideal body weight.

  The dietary approach affects via three levels: specific diet, specific food and specific nutrients.

Fatty acids: The risk for development of CAD is reduced by 2-3 percent when 1 percent of total energy intake from SFAs has been replaced by PUFAs. But the same has not been demonstrated for replacement with MUFAs and carbohydrates. The SFAs consumption must be decreased to 10% of total energy intake by replacement with PUFAs.[28]

The PUFAS are broadly classified into two categories: (a) omega 3 FAs which are mainly derived from fats and fish oils. Further the omega 3 FAs are classified into docosahexanoic acid and eicosapentanoic acid. However they do not alter total serum cholesterol levels and although debatable to conclude that whether they exert a favorable effect on patient of CAD.[29,30]

Vitamins: As per various RCTs, an 11% reduction in risk for CVS mortality has been observed with vitamin D3 supplementation, but this does not apply for vitamin D2 supplementation.[31]

Fibre: The 7g/day increased intake of total dietary fibre is correlated with 9% reduced risk of CAD, as demonstrated by meta analysis of prospective cohort studies.[32]

FOOD GROUPS AND DIETARY FOODS

Nuts: The documentation of daily intake of 30 g of nuts results in decrease of ~ 30% CAD, according to Meta analysis of prospective cohort studies.[33]

Functional foods: The phytosterols constitutes stanols and plant sterols are found to be effective in reducing LDL by ~ 10%, when appropriately consumed for 2 g/day. Also the greater reduction in cholesterol must be obtained with higher doses of phytosterols.[34]

Alcoholic beverages: The myth has been busted after the Mendellian randomization which includes analyses from 59 epidemiological studies excluding the beneficial effects of alcohol consumption in moderate quantity, demonstrating the lower risks of CVS outcomes in abstainers.[35]

Aerated non alcoholic drinks and beverages including soft drinks: The regular consumption of sweetened sugar beverages were associated 35% CAD chances in woman, whereas artificially sweetened beverages were not correlated with evidence of CAD. According to WHO, the maximum dietary intake of 10% of energy from mono and disaccharides which includes sugar present in fruits and juices and added sugars.[36]

Vegetables and fruits: The additional intake of one serving of vegetables and fruits per day has documented with 4% reduction in CAD, according to a Meta analysis report.[37]

PHARMACOTHERAPY OF DYSLIPIDEMIA: The drug category includes: proprotein convertase subtilisin/kexin type 9 (PCS K9), bile acid sequestrants, HMG Co-A reductase inhibitors, Fibrates, the selective cholesterol absorption inhibitors.

The Statins (Atorvastatin, Fluvastatin, Lovastatin, Pitavastatin, Pravastatin, Rosuvastatin, Simvastatin) reduce LDL thus reducing CVS mortality and morbidity as well as decrease in incidence of CAD.[38,39]

The pharmacotherapy consisting of Statins decreases TGs and the results of Meta analyses demonstrates the lower risk of developing pancreatitis.[40]

Thus they are considered to be the first line drugs for patients of dyslipidemia.

The increased glycated hemoglobin and increased blood sugar levels are dose dependent and may occur with Statin pharmacotherapy and may accentuate weight gain, but benefits outweigh the risks.

However for selected patient's combination therapy with **selective cholesterol absorption inhibitors** (Ezetimibe) to decrease LDL with maximal tolerated dose of a Statin.

Another combination therapy includes use of **Niacin and Fibrates** (Fenofibrate, Clofibrate, Ciprofibrate, Gemfibrozil, Bezafibrate) for reducing levels of TGs and increasing HDL, while omega 3 FAs(2-4 g/day) are used for TGs lowering effects.[41]

Further in relation to prevention of pancreatitis (TGs > 900 mg/dl), the levels of TGs must be dealt with not only drugs but also with dietary modifications including restriction of alcohols, pharmacotherapy of DM, estrogen therapy withdrawal.

Also regarding recent modality of pharmacotherapy with **PCSK9 inhibitors** from established data of phase I-III trials demonstrates the decrease of LDL upto 60 percent either as monotherapy or as combination therapy with maximal tolerated Statin dose.

The combination pharmacotherapy: The evidence of beneficial effects of Statins with Ezetimibe clinically according to one RCT has been well stressed upon.[42] The combination therapy of Statins with Niacin increase LDL while decrease TG. However flushing is the main adverse effect of Niacin, which may hinder compliance. Further the clinical benefit is withheld for this combination drug therapy.[43]

Fibrates especially Fenofibrate (145 mg) may act as useful drug for lowering LDL, when used along with Statin. The Fibrates must be taken in morning and Statins in evening to minimize the peak concentrations which may lead to myopathy.

CONCLUSION

Hyperlipidemia is an serious emerging concern all over the world and despite of sudden cardiac deaths and CVD relationship well established, absolute dietary module approach consisting of a healthy nutritious diet synergized with exercise, as it leads to beneficial effects on metabolic parameters viz. lipid profile, simultaneously effective pharmacotherapy with good compliance necessitated with psychological reinforcement counseling to give up alcohol and smoking cessation must be implemented, also need to treat other co-morbid conditions viz diabetes mellitus, cancers, stroke, hypertension at same time for prevention of complications because of atherosclerosis and Hyperlipidemia to reduce morbidity and mortality from Hyperlipidemia.

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