SOME THOUGHTS ABOUT HIGH CHOLESTEROL IN CHILDREN AND ADOLESCENTS

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Lipids and their various components such as cholesterol, fatty acids, and lipoproteins are essential for our well being by providing nutrient calories and by serving as important building blocks for various life processes. Lipids are essential for the cell membrane; for the sheath that surrounds nerves; as the basic molecule for synthesizing and secreting steroids by the adrenal, gonads and placenta; as important participants in the immune recognition of foreign invaders and the mediation of inflammation via T-lymphocytes. No discussion of the problems of excess cholesterol, its relationship to atherosclerotic heart disease and its treatment can take place without some simple review of the metabolism of lipoproteins and of cholesterol.

Most of our lipoproteins enter via the diet and undergo a series of enzymatic degradations via lipoprotein lipase, hepatic lipase and other enzymes that ultimately result in their ability to be used as nutrient substrates or to be taken up by the cells in the liver and in the periphery. Cholesterol uptake is mostly mediated via the LDL receptor which recognizes LDL with its aproprotein. This enables generation of free cholesterol within the cell which acts to suppress further cholesterol synthesis and to decrease LDL receptors. Therefore, a drug such as a statin which interferes with a key step in cholesterol synthesis, will result in a decrease of intercellular cholesterol and up regulation in LDL receptors with an increase in the clearance of cholesterol from the blood. This simple scheme won the Nobel Prize for Drs. Goldstein and Brown and is the entire basis for the use of statins which are rapidly emerging as the primary treatment for increased cholesterol throughout the world. The HDL cholesterol, so called "good" cholesterol, can be taken up for synthesis of bile acids within the liver and by the adrenal glands, testes, ovaries and placenta for steroid synthesis.

Abnormalities in the concentrations of cholesterol and other lipid moieties can only arise by increased production, decreased removal or combination of these two things. These entities can either be genetically determined via defective steps in the enzymes or receptors or by diseases which interfere with lipid metabolism. Amongst these, the most preventable cause is hypothyroidism and diabetes. Always consider secondary causes of dyslipidemia before embarking on treatment regimes for the primary genetic hyperlipidemias.

In the past, these genetic dyslipidemias were characterized by their flotation characteristics in the so called Friedrickson Classification. However, this classification is falling out of favor as we learn more about the genetic basis of each of the major abnormalities. Among these abnormalities, the most common is heterozygous familial hypercholesterolemia (HeFH). Cholesterol is intimately involved in the formation of plaques along the major arteries, including the aorta and coronary arteries. However, recent information indicates that in addition to obstruction, there are inflammatory processes that determine the fate of the plaque. Therefore, inflammatory markers such as C-Reactive Protein, IL6 and others are important in the consideration of whether an individual is at greater risk for the future development of coronary vascular disease (CVD). These considerations formed the basis for the importance of screening for childhood hypercholesterolemia and for its treatment. Heterozygous familial hypercholesterolemia (HeFH) occurs in 1 in 500 people, can be readily modified by therapeutic approaches to limit cholesterol intake, to limit its absorption, to increase its excretion or to decrease its synthesis and thereby increase its uptake from the circulation. These considerations form the basis of all known drugs currently used in the hyperlipidemias. They are of such great importance that they have been widely investigated to provide guidelines for treatment primarily in adults (Adult Treatment Panel III – ATPIII). These guidelines were most recently updated in 2004 and their pediatric counterparts discussed in 2007.

I present data on the management of the lipid disorders in childhood based on these guidelines as modified for Pediatrics and based on two approaches. The first is a population approach, in which lifestyle changes of diet and exercise are targeted to reduce cholesterol. These guidelines clash with the current eating habits of adolescents in many developed and developing countries. A second approach is the individual approach, based on risk profiles including a family

history of myocardial infarction earlier than age 50-55, and the presence of elevated cholesterol. They are modified by obesity, presence of diabetes, hypertension, smoking and the presence of other inflammatory markers. Although not all authorities agree, most are coming to accept that the use of statins should be a first line treatment for children at high risk for developing coronary vascular disease and that ongoing studies should define the long-term safety. However, a meta analysis of studies that have been relatively short term and as long as two years in duration, clearly demonstrate the efficacy and safety of these drugs. Moreover, there is now evidence of a reduction in the intima media thickness (IMT) of the carotid artery via ultrasound or CT examinations and it's reversal by the use of statins in adolescents with HeFH. The criteria for intervention in children remain somewhat more lenient than those in adults with demonstrated coronary vascular events but, nevertheless, have undergone reduction in the absolute levels of cholesterol at which one should intervene and in the targets for acceptable ranges.

I conclude the presentation with two case studies that are illustrative and hope to answer questions during a spirited discussion. To facilitate this discussion I provide the full set of the slides used in the presentation, and seven key references which, should provide ample basic and practical knowledge for the management of lipid disorders in childhood.

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