REVIEW ARTICLE

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Hyperlipidaemia in Paediatric Patients
The Role of Lipid-Lowering Therapy in Clinical Practice

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Abstract

Atherosclerosis begins in childhood with the formation of fatty streaks. Early plaques can be found in adolescence and early coronary disease can be found in young adults. It has been suggested that early treatment may lead to great benefits in later life. This article is a narrative review of the role of lipid-lowering drug therapy in paediatric practice.

Increased rates of atherosclerosis are known to occur in children with familial hypercholesterolaemia (FH), especially in homozygotes. There is evidence for the efficacy and safety of lipid-lowering therapies in children, particularly with respect to the effects of HMG-CoA reductase inhibitors (statins) on lipids and, to a limited extent, on other surrogate measures of atherosclerosis in patients with FH. Diagnosis of FH and its early treatment are recommended in all guidelines. Lipid-lowering drug therapy is recommended for the treatment of homozygous FH at all ages and from as young as 10 years of age for the treatment of heterozygous FH when there is a family history of very premature coronary heart disease (occurring at age <40 years).

Controversy exists about other possible indications. Increased rates of atherosclerosis are seen in autoimmune disorders, including type 1 diabetes mellitus, systemic lupus erythematosus and Kawasaki's disease, and in transplant recipients. All evidence in these areas is derived by extrapolation from studies in adults. These disorders can be divided into those for which percutaneous coronary intervention is performed early and/or for which

drugs used to treat the primary disorder increase the rate of atherosclerosis, and those for which this is not the case. In both cardiac transplantation and Kawasaki's disease, increased atherosclerosis can occur as a result of (i) disease-related vasculopathy; or (ii) increased restenosis secondary to interventions. Statins have a good evidence base for reducing rates of re-occlusion following coronary artery procedures, and this justifies their use in these settings. In renal transplantation, statins may have a role to play in patients with persistent dyslipidaemia and additional cardiovascular risk factors. In other disorders, such as type 1 diabetes, the disease process is atherogenic and thus statins may be justified in patients with a long history of disease (>10 years), poor control, and evidence of vascular or endothelial damage or additional cardiovascular risk factors.

There is a role for lipid-lowering therapies in children at high risk of atherosclerosis, but the evidence base outside of FH is weak. Lipid-lowering therapy should be prescribed to all children with homozygous or severe heterozygous FH. Based on adult evidence, statin therapy should be considered in patients who have undergone coronary artery procedures or received cardiac transplants, in whom their primary role is to prevent vascular re-occlusion. In diseases associated with a chronic increased atherogenic risk, such as type 1 diabetes, statins should be considered in high-risk cases where additional cardiovascular risk factors are present.

At present, the most important need is for trials to be performed in children using accepted surrogate endpoints to define whether lipid-lowering drug therapy is beneficial in this group.

The role of lipid-lowering therapy is well established in adults, in whom it is accepted that the presence of established atherosclerotic disease, its risk equivalents such as diabetes mellitus, or a calculated cardiovascular risk of >20% over the next decade are indications for the prescription of anti-atherosclerotic drug therapy.[1,2] However, such considerations are impossible to apply in children and adolescents as the risk of cardiovascular disease (CVD) never exceeds 20% in these groups simply because atherosclerosis is principally driven by age.[3] Thus, any consideration for treatment in children or adolescents relies on relative cardiovascular risk and forward projection of any risk to adulthood. There are established protocols for the investigation and diagnosis of hyperlipidaemia in children.[4] The risks of early adult disease are considered significant in a small subgroup of conditions: genetic hyperlipidaemias, autoimmune disorders and organ transplants.[5] Although the individual prevalence of these disorders is small, ranging from 1 in 500 to 1 in 1000, in sum they could add up to approximately 1% of all children/adolescents. As a result of this, the American Academy of Pediatrics has suggested that atherosclerosis modifying therapies should be considered in some circumstances.[5] The basis of these recommendations is that while absolute CVD risk may be low in each case because of low age, as these individuals proceed to adulthood their life expectancy will be grossly shortened by their genetic, autoimmune or acquired diseases and, thus, their absolute CVD risk will rapidly exceed treatment thresholds of >20% per decade in young adulthood if relative risk modifiers act uniformly on background risk factors. The recommendations are also based on the extrapolation of long-term safety and efficacy data, mostly derived from adult populations, to children and adolescents, which is controversial.[6]

This review focuses on the role of antihyperlipidaemic agents in the paediatric setting. However, it should be noted that treatment of atherosclerotic risk, especially in patients with diabetes, is multimodal and may comprise simultaneous

prescription of antithrombotics (e.g. aspirin [acetylsalicylic acid]) and antihypertensive drugs (e.g. ACE inhibitors).

1. Cardiovascular High-Risk Groups in Children

Atherosclerosis begins in childhood, with fatty streak development being obvious by age 6 years, but there are data to show that the fetus of hypercholesterolaemic mothers may show earlier changes even *in utero*.[7] Postmortem studies such as the PDAY (Pathobiological Determinants of Atherosclerosis in Youth) study show that significant disease is present in adolescents by age 20 years, with 35% of individuals having a 25% coronary artery stenosis by early adulthood.[8,9] In the PDAY study, the principal determinants of accelerated progression of atherosclerosis were obesity, smoking, hyperlipidaemia and insulin resistance. Increasing attention is being paid to the role of environmental risk factors in driving the progression of atherosclerosis. Obesity is a recognized problem throughout all age groups; however, rates of childhood obesity are increasing quickly because of changes in lifestyle, cultural precepts and decreased exercise.[10] The greater availability and aggressive marketing of foods with high saturated fat content and increasingly high carbohydrate content, allied with the use of high glycaemic index products and supplementation of processed food stuffs with high fructose corn syrup, are changing lifestyle habits. Many of these food components seem to have addictive features and all are marketed to children. Smoking rates, although reducing in adults, are also increasing in some countries in children and adolescents.[11] Similarly, rates of adrenergic drug abuse, again once confined to the adult population, are increasingly being seen in adolescent populations.[12]

2. Familial Hypertriglyceridaemias

Dyslipidaemia is known to occur in childhood and to be associated with adverse prognosis.[13,14] The treatment for type I hyperlipidaemia (familial chylomicronaemia) is well established and the principal reason for such treatment is to reduce the prevalence of pancreatitis and secondary β-cell failure-induced diabetes.[15-17] However, fibrates (fibric acid derivatives), the principal drugs used to treat hypertriglyceridaemia, show little efficacy in type I hyperlipidaemia and physicians must resort to plasmapheresis. Type V hyperlipidaemia is less common in children and there are few studies of lipid-lowering drugs in this population.[15] However, given its lesser severity and its age dependency for expression of the phenotype, it is likely that type V hyperlipidaemia would respond to fibrate, omega-3 fatty acid and/or niacin therapy. In familial combined hyperlipidaemia[18] or remnant hyperlipidaemias, unequivocal diagnosis of affected individuals is dependent on environmental interactions, making these conditions difficult to diagnose prior to adulthood.[19,20] There is no consensus on whether children with familial combined hyperlipidaemia or remnant hyperlipidaemias should be treated prior to adulthood, even in families where the diagnosis can be established.

3. Familial Hypercholesterolaemia

In contrast to hypertriglyceridaemia, hypercholesterolaemia in children is both well defined and has some evidence base for treatment. Children with familial hypercholesterolaemia (FH) have an earlier onset of endothelial dysfunction, coronary calcification and other markers of atherosclerosis than children with family histories of CVD but without FH.[21-25] Indeed, children with homozygous FH can develop symptomatic coronary heart disease (CHD) prior to teenage life, and some children with severe heterozygous FH develop CHD in their early adult lives.[26] The Simon Broome Register collaboration showed that relative risk in individuals with untreated FH was increased 100-fold in men and 200-fold in women aged 20–40 years, and 50% had a CHD event prior to the age of 50 years.[27] After allele dose, the principal determinant of risk in individuals with FH is the age of onset of CVD in the family, not the plasma low-density lipoprotein cholesterol (LDL-C) concentration.[26] Treatment of

adult heterozygous FH reduces mortality by 80%,[28] while studies of individuals with homozygous FH show that a mixture of maximal drug therapy allied to apheresis can reduce coronary artery disease progression.[29] There is evidence supporting the use of lipid-lowering drugs in children with FH, based on both lipid and surrogate endpoints (see section 9). Thus, many guidelines recommend that children of families with a history of FH be screened for diagnostic purposes between the ages of 6 and 10 years and that treatment with lipid-lowering drugs is started in the highest risk individuals.[1,2,30,31] The latter category is usually stated as comprising children with homozygous FH and children from families in which the age of onset of CHD is <40 years, although many clinicians are more conservative with respect to the latter group and treat if the age of onset of CHD is <30 years in affected men and <40 years in affected women.[32]

4. Cardiovascular Disease in Diabetes Mellitus

Although treatment of genetic hyperlipidaemias in childhood is well established, CVD risk is also increased in other patient groups. Type 1 diabetes has an age of onset of 5–15 years and is driven by autoimmune destruction of pancreatic β cells. The disorder is increasing in prevalence for reasons that remain unclear. Type 1 diabetes is associated with a number of factors that drive progression of atherosclerosis, including impaired renal function, hypertension, dysglycaemia, inflammation and autoimmunity.[33,34] Many studies have shown increased carotid intima media thickness in children with type 1 diabetes and a small but significant incidence of early-onset CHD.[33] Based on data from adults, it is estimated that the risk of CVD is increased by 10- to 40-fold in individuals with type 1 diabetes.[35,36] Although the risk of CVD is increased, there are no trials of the effects of statins or other lipid-lowering drugs on surrogate or clinical endpoints in type 1 diabetes. Data from epidemiological studies suggest that the risk of CVD in type 1 diabetes is driven more by poor glycaemic control, hypertension and nephropathy than by lipids.[37] Thus, the role of statin therapy is secondary and may be limited to patients with a young age of onset of disease, more than 10 years' duration of disease, poor control and evidence of target organ damage or additional cardiovascular risk factors (e.g. smoking). Fibrates may have additional beneficial effects on microvascular disease[38] but there are no data as yet to support their use in childhood diabetes.

The world epidemic of obesity is not only further driving the rate of progression of type 1 diabetes but is also leading to the earlier diagnosis of type 2 diabetes. Cases of type 2 diabetes used to be rare in childhood and were often associated with the presence of genetic mutations associated with the development of maturity-onset diabetes of the young.[39] These days, cases of diabetes simply associated with environmental and familial risk factors allied with gross obesity are routinely seen in subjects aged 10–20 years. The evidence base for treatment of lipids in adults with type 2 diabetes is extensive but is limited by trial recruitment criteria of age >40 years and a >5-year (usually 10-year) history of diabetes; these make for difficulties extrapolating the data to children. However, such trials show convincing benefits for statin therapy[40] and a possible role for fibrates based on effects on a secondary endpoint.[41] Obesity is associated with a greater severity of renal failure, and, if significant proteinuria is present, renal disease is associated with accelerated rates of atherosclerotic disease; however, there are suggestions that fibrates may reduce rates of microvascular disease.[41] There may be a role for statins in the treatment of rare individuals with young-onset type 2 diabetes prior to adulthood.

5. Cardiovascular Risk in Organ Transplantation

The American Academy of Pediatrics guidelines[5] recommend early treatment of hyperlipidaemia after organ transplantation in all age groups. Increased cardiovascular risks are often seen after renal and cardiac transplantation, even in children.[42-44] Moderate-dose statins reduce

coronary artery transplant vasculopathy in patients with cardiac transplants[45] and are safe in children.[46] Both transplantation and its treatment with ciclosporin (cyclosporine), more than other immunosuppressants, are associated with increased rates of transplant vasculopathy and atherosclerosis.[47] Additional risks are found with the use of prednisolone, which causes mixed hyperlipidaemia and is diabetogenic. Statins have been shown to reduce atherosclerosis after cardiac transplantation in adults, but the effects following renal transplantation are less clear.[48,49] Recently, in the AURORA (A study to evaluate the Use of Rosuvastatin in subjects On Regular haemodialysis: an Assessment of survival and cardiovascular events) study of patients with chronic renal failure, rosuvastatin had no effect on cardiovascular endpoints,[50] while earlier data from the 4D (Die Deutsche Diabetes Dialyse) study in patients with diabetes on dialysis had shown minimal benefits with atorvastatin.[51] However, both these studies excluded patients with renal transplants, demonstrating only that statins had little cardiovascular benefit in patients with well established, end-stage renal disease. Studies in renal transplant populations are far more limited and are open to criticism on the grounds that they used a low efficacy, weak statin. In the SOLAR (Study Of Lescol in Acute Rejection) trial, fluvastatin had no effect on rejection events,[52] while in the ALERT (Assessment of LEscol in Renal Transplantation) study of patients with renal transplants, a 35% reduction in cardiovascular events was seen.[53,54] The SHARP (Study of Heart And Renal Protection) study of adult renal impairment associated with use of a combination of simvastatin and ezetimibe includes a subgroup of renal transplant patients,[55] but given the results of other studies in established renal disease and the controversial results with simvastatin/ezetimibe therapy in aortic stenosis,[56,57] this study, when completed, may not clarify the role of lipid lowering in this group.

Thus, current data suggest that statin therapy has a role in cardiac transplantation because transplant vasculopathy leads directly to coronary atherosclerosis in this condition. The data in renal transplantation are less clear and statins should remain a second-line therapy for those with persistent hyperlipidaemia, recurrent rejection episodes and in whom corticosteroid-minimization and/or switch of immunosuppressants to agents that cause less dyslipidemia are not possible.[58]

6. Cardiovascular Risk in Autoimmune Disease

An additional population at high cardiovascular risk is patients with autoimmune diseases. Increased risks are seen in patients with psoriasis and ankylosing spondylitis, and the risks are even greater in patients with rheumatoid arthritis or, in particular, systemic lupus erythematosus (SLE), where the risk is increased 8- to 16-fold.[59,60] Autoimmune diseases are generally rare in childhood with the exception of diabetes and Kawasaki's disease. The onset of Kawasaki's disease is in the teenage years and the disorder is associated with dyslipidaemia and other cardiovascular risk factors that persist after statin therapy.[61,62] Kawasaki's disease is also associated with development of aneurysms and thus an increased risk of atheroembolic events. There is no evidence that lipid-lowering drugs have any effect on aneurysmal disease. One small study has shown a reduction in the rate of aortic aneurysm growth in the elderly,[63] but there are no endpoint studies of statins in patients with this condition. In children, one study has shown improvement in inflammatory markers and endothelial function in Kawasaki's disease after statin therapy.[62] Lipid-lowering therapy is recommended by the American Academy of Pediatrics[5] on the basis of lack of early immunoglobulin therapy, early age of onset of disease, and severity and location of aneurysms. The nearest analogues to the generalized aneurysmal disease of Kawasaki's disease are the localized thrombosis in the atrial appendage and with mural thrombosis in atrial fibrillation and the aneurysm-related thrombosis seen in late stage peripheral arterial disease. There are no specific large-scale studies of lipid-lowering in atrial fibrillation but some smaller-scale studies and registries suggest a reduction in cardiovascular events.[64,65] The case for statin treatment in

peripheral arterial disease is well established but may apply more to occlusive lesions than aneurysmal disease. Studies in aortic aneurysmal disease are few and not conclusive.[66] However, studies of antithrombotic drugs, including aspirin (acetylsalicylic acid), warfarin and, lately, the combination of aspirin and clopidogrel, suggest that these strategies may have greater benefits in atherothrombotic disease than previously supposed and merit further investigation.[67]

7. Cardiovascular Risk in HIV Disease

Children with HIV infection have increased rates of atherosclerosis due to both the primary viral infection but also secondary to the dyslipidaemic and lipodystrophic changes associated with the therapies used to treat this condition.[68-70] There are no data on how cardiovascular risk in these populations should be addressed beyond control of the infectious disease and its associated inflammation, together with general lifestyle measures.

8. Lifestyle Measures

Few large-scale, randomized controlled trial data exist specifically on the efficacy of lifestyle measures in children/adolescents with familial hyperlipidaemias beyond general consensus interventions, such as prevention of initiation of smoking and avoidance of gross obesity.[14,71] Lifestyle therapies are more effective for the treatment of obesity than for other cardiovascular high-risk conditions, and small-scale studies show benefits from both exercise and calorie reduction.[14,72] Diets have relatively little effect on cholesterol.[72,73] They are used as general recommendations in FH and immunological conditions but are considered adjunctive therapies with limited potential to modify disease progression in the short term.[14] Their limited utility in polygenic hyperlipidaemia in children is based on the limited progression of disease at young ages as cholesterol levels are moderately elevated in childhood and increase to adult levels in puberty only in response to testosterone production. Risks are thus increased more in male children than in females and only from puberty. However, epidemiological studies suggest that small changes in cholesterol made earlier in life can translate into large changes in lifetime risk, and dietary therapy may therefore be sufficient in all except the most extreme risk groups.[74] The role of supplements[75] and nutriceuticals such as phytosterols in children is also unclear, although small-scale studies suggest some beneficial effects on lipids similar to those seen in adults.[76,77]

9. Efficacy of Drug Therapy

The vast majority of therapeutic trials have targeted surrogate measures, particularly lipid levels.[14] There are no outcome studies in this area of paediatrics. The longest established therapies, used originally on the basis of anecdotal evidence, are the bile acid sequestrants. Their efficacy in children is similar to that in adults and it is stated that their tolerability is also similar to that in adults, with a 20–30% discontinuation rate.[78] However, there are no studies documenting the rate of intolerance of bile acid sequestrants in actual clinical practice, and experience suggests that the actual rate of non-adherence in all age groups is considerably higher. Fibrates have been used extensively in children and adolescents over the years and again show similar efficacy to adults, with better tolerability than bile acid sequestrants but lesser efficacy in reducing LDL-C levels.[76,79] Niacin has also previously been used extensively in adolescents and has similar lipid-lowering efficacy to bile acid sequestrants and fibrates.[80] However, these drugs (i.e. bile acid sequestrants, fibrates and niacin) are now little used with the possible exception of the new bile acid sequestrant colesevelam, the efficacy of which in adolescents has never been formally assessed, but which does have a better tolerability profile in adults than earlier bile acid sequestrants.[81] Ezetimibe has been shown to reduce LDL-C levels by 20% in children with homozygous FH.[82]

The preferred drugs for treating hyperlipidaemia in adolescents are statins. After many years of use in adults following anecdotal reports and later in response to changes in patent extension

following specific studies in adolescents, statins have been used in approximately 1000 children and adolescents with heterozygous FH for periods of up to 2 years.[83,84] Initial studies showed that the efficacy of these drugs in 12- to 16-year-olds was similar to that in adults.[85-89] Extensive data exist for lovastatin[85] and simvastatin[86] in 2-year studies, for atorvastatin over 6 months[87] and, most recently, for low to moderate doses of rosuvastatin for up to 1 year in the PLUTO (Paediatric Lipid redUction Trial of rOsuvastatin) study.[88] Additional evidence for the beneficial effects of statins in children with FH was demonstrated when pravastatin reduced the rate of progression of carotid intima media thickness in 193 children over 2 years.[89] Statins are less efficacious in homozygous FH as they are dependent on the presence of functional hepatic LDL receptors for their action.[90] Statins are effective in only 30% of patients with homozygous FH, and their efficacy is generally reduced by 30–50%. Thus, increased emphasis is placed on the use of intestinally acting agents such as bile acid sequestrants and ezetimibe in patients with homozygous FH.[26] In contrast to colestyramine, which binds ezetimibe, the combination of ezetimibe and colesevelam is additive[91] and can be used effectively in homozygous FH, usually in combination with apheresis until the definitive treatment of hepatic transplantation can be performed.

10. Safety of Drug Therapy

The safety profile of lipid-lowering therapy is well established in adults. Adverse effect frequencies range from 20–30% for colestyramine to about 2–3% for statins or ezetimibe. Fewer data exist in children. In studies involving approximately 1000 children and adolescents aged 10–18 years receiving statins at lower doses for a period of 6 months to 2 years, no adverse effects or significant increases in hepatic transaminase or creatine kinase levels were seen.[83,84] Similarly, specific studies of effects on sex steroids and Tanner development stage progression in children and adolescents receiving statins revealed no significant differences over a 2-year period.[83,84] Studies of bile acid sequestrants, fibrates, niacin and ezetimibe show similar safety profiles to those in adults but are generally smaller in scale and of shorter duration and have been conducted in patients with either heterozygous or homozygous FH. All these studies are short term; similar to other drug classes, there is a lack of long-term, systematically collected safety data for all lipid-lowering drugs in paediatric practice.

11. Perspective

The increasing burden of cardiovascular risk factors associated with atherosclerosis in adolescence and the explosion in the obesity rate has led to an increased focus on early treatment, particularly as even limited interventions at younger ages can translate into large reductions in lifetime CVD risk.[5] This is especially relevant as the prevalence of type 2 diabetes in younger populations increases. Similarly, as screening becomes established for FH, affected individuals are being regularly identified at younger ages and consideration must be given as to how to treat these individuals.[30,31] While there is no debate about the need, prior to definitive treatment by liver transplantation, for lipid-lowering treatment in homozygous FH given its extremely poor prognosis, there is still debate as to how cases of heterozygous FH ought to be treated.[14] A case can be made for treatment of those patients with a severe family history of CVD but controversy exists about more typical cases.[14] Many favour dietetic measures until adulthood when statin therapy is instituted, while others suggest earlier drug treatment to prevent atherosclerosis becoming established. There are some efficacy and safety data for lipid-lowering drugs in this group of patients. Additional indications are suggested for patients with autoimmune-related disorders (e.g. type 1 diabetes, SLE), in whom rates of CVD are increased by the underlying condition, the variation in immune function and some of the drugs used as immunosuppressants. The evidence for lipid-lowering therapy in patients with these disorders is limited (where available), based on adult studies and dependent on the known accelerated rates of atherosclerosis in autoimmune

disease. Lipid-lowering drugs may attenuate transplant vasculopathy and may also decrease the high rates of cardiovascular events in these patients. In both these groups, the relative risks of CVD are greatly increased, and lipid-lowering therapy is consequently used for preventive purposes. However, it could be argued that more stable and effective lipid-neutral immunosuppressant regimens could substantially reduce rates of atherosclerosis[92] by directly targeting the inflammatory process, as has been demonstrated on a limited scale with statins in rheumatoid arthritis,[93] and that formal endpoint studies of statins are required prior to therapy becoming common practice. Similarly, in inflammatory atherothrombotic disease for which there is little evidence for the benefits of lipid-lowering therapy, immunomodulatory and antithrombotic therapies may be more effective.

Rates of prescribing in children in the US are increasing by 15% per year and prescriptions for hypoglycaemic and antihypertensive drugs are increasing, as could be predicted from the known benefits of these agents on microvascular complications, which precede macrovascular complications.[94] In contrast, rates of prescribing of lipid-lowering agents are stable or decreasing because of the greater controversy over how to use these agents, the exact risks of atherosclerotic macrovascular disease in children and the rate at which it may progress.[6] The perils of extrapolating evidence from epidemiological studies or subgroup analyses are well known. For example, statins have been unsuccessful in formal endpoint clinical trials in aortic stenosis, advanced cardiac failure or renal disease despite early indications of potential benefit. Thus, only well constructed surrogate endpoint studies in paediatric populations will finally clarify the conditions under which lipid-lowering agents will be beneficial.

12. Conclusions

There is a role for lipid-lowering therapies in children at high risk of atherosclerosis, but the evidence base outside of FH is weak. Lipid-lowering therapy should be prescribed to all children with homozygous or severe heterozygous FH. Based on adult evidence, statin therapy should be considered in patients who have undergone coronary artery procedures or received cardiac transplants, in whom their primary role is to prevent vascular re-occlusion. In renal transplant patients, statins may have a role to play in patients with persistent dyslipidaemia, in whom additional risk factors for transplant-associated atherosclerosis are present. In diseases associated with a chronic increased atherogenic risk, such as type 1 diabetes or SLE, statins should be considered in high-risk cases where additional cardiovascular risk factors are present. At present, the most important need is for trials to be conducted in children using accepted surrogate endpoints to define whether lipid-lowering drug therapy is as beneficial in these groups as in adults.

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