6th Hellenic Congress in Athens, of the Hellenic Atherosclerosis Society, on the 04-06 December 2014

Novel Pharmacologic Treatments of Familial Hypercholesterolaemia

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Familial hypercholesterolaemia (FH) is the most common inherited monogenic lipid disorder. It is caused by mutations of genes related to low density lipoprotein (LDL) receptors, apolipoprotein B or proprotein convertase subtilisin/kexin type 9 (PCSK9). Homozygous FH (HoFH; 1/400,000 births) is treated by LDL apheresis. Recently lomitapide has been used for the treatment of HoFH as a monotherapy or in addition to LDL apheresis. Heterozygous FH (HeFH), 1/250-1/200 births, is associated with an increased cardiovascular disease (CVD) risk. The main treatment for HeFH has been high doses of high intensity statins plus ezetimibe. However, this is not usually enough to attain LDL-C targets, especially in those with overt CVD or equivalents (LDL-C goal of <70 mg/dl). Data from the Atherosclerosis Risk in Communities study showed that loss of function mutations of PCSK9 were associated with a 28% lower LDL-C level and an 88% reduction in the risk of CVD in blacks, while in whites these numbers were 15% and 47%, respectively. This led to the development of technology to block PCSK9 with monoclonal human antibodies (e.g. evolocumab and alirocumab). These antibodies have been shown in phase II and III trials to be safe and to produce reductions in LDL-C levels by around 60% either as monotherapy or on top of optimal therapy with statins and ezetimibe. These antibodies are administered subcutaneously every 2 weeks with an automatic device. Anti-PCSK9 antibodies are expected to be licensed soon (? in 2015) and are considered by many as "the statins of the 21st century".

Triglycerides, Genes and Vascular Risk

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Hypertriglyceridaemia may occur partly due to genetic variation. About 30 genes may be involved. There are also rare mutations (e.g. in apolipoprotein C2, A5 and E, as well as lipoprotein lipase) that can contribute to hypertriglyceridaemia. The genome-wide association studies (GWAS) suggest links with cardiovascular disease (CVD). These genetic abnormalities are aggravated, or "expressed", by the presence of lifestyle factors (e.g. excess alcohol intake, obesity, metabolic syndrome and smoking), administration of drugs (e.g. steroids, diuretics, beta-blockers, colesevelam, tamoxifen or estrogens) and occurrence of diseases (e.g. hypothyroidism, liver disease, diabetes or kidney disease).

We need to agree on the definition of hypertriglyceridaemia. Values vary according to different guidelines. We also need to establish whether we can use fasting and/or post-prandial levels in routine clinical practice and how genetic abnormalities affect these levels. It is difficult to be sure if hypertriglyceridaemia (fasting and/or post-prandial) predicts vascular risk independently or if this association occurs because of links with other factors [e.g. obesity, decreased high density lipoprotein (HDL) levels, insulin resistance, remnant particles, small dense low density lipoprotein (LDL) and adverse haemostatic effects]. Markedly elevated triglyceride levels are associated with an increased risk of acute pancreatitis. Treatment is a priority in such situations. In the presence of hypertriglyceridaemia, using non-HDL-cholesterol levels as the treatment target is preferable to LDL-cholesterol levels.

Growth Hormone Sensitivity and Development of Non-alcoholic Fatty Liver Disease

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Non-alcoholic fatty liver disease (NAFLD) is a complication of the metabolic syndrome (MetS). However, not all patients with MetS develop NAFLD. This susceptibility could be due to variable sensitivity to hormones that regulate hepatic lipid content. Growth Hormone (GH) in the liver induces triacylglyceride uptake and also induces hepatic lipogenesis. These activities are counteracted by enhanced hepatic very low density lipoprotein (VLDL) secretion leading to lower lipid accumulation. Patients with NAFLD have lower plasma GH levels than controls. Furthermore, adult GH deficiency is associated with NAFLD and patients resemble the MetS and 29% of children with GH deficiency developed NAFLD after cessation of GH therapy. Reduced steatosis is observed in GH transgenic mice and after GH replacement therapy in adults with GH deficiency. The protective action of GH on liver steatosis has also been highlighted in genetic studies showing the hepatic inactivation of the GH receptor, its associated kinase, JAK2 or its downstream signaling intermediary STAT5b, all lead to hepatic steatosis. Due to the disruption of hepatic IGF-1 production, the negative feedback regulation on GH secretion is disrupted and these mice exhibit elevated circulating levels of GH and consequently increased peripheral lipolysis. Our recent studies identified a negative feedback inhibition of GH actions in the cell through SOCS2 protein. Our findings show that deletion of SOCS2 leads to enhanced cellular sensitivity to GH and this has protective effect on diet-induced fatty liver. The decreased fatty liver in the GH sensitive mice was explained by increased hepatic release of VLDL.

Challenges for Familial Hypercholesterolaemia Screening Program in the MENA Region

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The INTERHEART study found that the mean age of the first presentation of acute myocardial infarction (AMI) was 10 years younger in the Middle East countries compared with the other regions of the world. These findings were attributed to the early onset of cardiovascular diseases (CVD) risk factors, the two most prevalent being smoking and hypercholesterolaemia.

Familial Hypercholesterolaemia (FH) is an inherited autosomal dominant disorder caused by mutations mainly in the low density lipoprotein (LDL) receptor, apolipoprotein B (apo B) and proprotein convertase subtilisin/kexin type 9 (PCSK9) genes, that result in the decreased clearance of LDL particles from the circulation, significant increase of plasma LDL cholesterol and the manifestation of severe atherosclerosis and CVD. FH prevalence in the Middle East and North Africa (MENA) region is unknown. The expected FH cases in the MENA region according to the population size and the prevalence of 1:500 estimation is around 764437 cases. There are approximately 57 reported FH cases in the MENA region (i.e. representing only 0.01% of FH prevalence), thus FH remains significantly underreported compared with countries like the Netherlands (71% reported FH cases). Several factors could contribute to the under-diagnosis and under-treatment of FH cases in the MENA region. These include the lack of FH screening programs and established lipid clinic networks as well as the limited presence of established centers for molecular diagnosis and LDL-apheresis therapy.

All these challenges need to be addressed in order to improve the gap for identification and treatment of FH in the MENA region.

The Role of LDL Apheresis in the Management of Familial Hypercholesterolaemia

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Familial hypercholesterolaemia (FH) is an autosomal co-dominant disorder characterized by a marked elevation of serum low-density lipoprotein cholesterol (LDL-C) concentration, which in turn is associated with a greatly increased risk of premature cardiovascular disease. Early diagnosis and life-long treatment is essential for patients with FH in order to reduce the risk of developing cardiovascular diseases early in life, increase life expectancy and improve quality of life. Internationally statins are recommended as the first line of treatment for patients with this condition. However, homozygous FH patients with persistently elevated LDL-C levels are usually resistant to multiple-drug therapy. LDL apheresis is an efficacious method to decrease LDL-C concentrations in patients with severe FH who are refractory or intolerant to lipid-lowering medications, or if there is progressive cardiovascular disease despite maximal drug therapy as a means to prevent the onset or progression of cardiovascular events in this high risk population.

LDL apheresis is an invasive procedure that selectively removes LDL-C and other atherogenic lipoproteins from the plasma via an extracorporeal circulation device. The most recently developed method enables lipoproteins to be adsorbed directly from whole blood using polyacrylate columns.

New drugs, especially microsomal triglyceride transfer protein (MTP) inhibitors, anti-sense oligonucleotides to apoB mRNA and, most recently, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serum protease (PCSK9) might have an effect on the use of LDL apheresis.

Important Strategies for Cardiometabolic Disease Management in the MENA Region

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The prevalence and incidence of obesity, hypertension, diabetes mellitus and dyslipidaemia in the Middle East and North African (MENA) countries has increased significantly. This has led to a substantial increase in morbidity and mortality from cardio- and cerebro-vascular events. Proper strategies that depend on prevention, early detection, adequate management and easy access to health care should be established to manage these cardiometabolic diseases. A well-designed national survey in each country is required to achieve this goal and as well as gathering relevant specific data on the prevalence burden and cost of these diseases, collaboration between all parties involved with these conditions, improved awareness and education of the population and facilitate access to health care. These steps will not be achievable without a proper national program with a clear plan for implementation, monitoring and evaluation of these cardiometabolic diseases.

Primary health care should play the main role in the implementation of these strategies as well as in the management of these conditions with appropriate support from secondary and tertiary health services. This lecture highlights the importance and possible implementation of these strategies and the role of concerned societies such as the Oman Society of Lipid and Atherosclerosis (OSLA) in this regard.

Prevalence of Metabolic Syndrome in the MENA Region How can we do Better?

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Metabolic syndrome (MetS) is a disorder of energy utilization and storage. It is a multiplex risk factor that arises from insulin resistance accompanying abnormal adipose deposition and function. It is a risk factor for coronary heart disease, as well as for diabetes, fatty liver and several cancers. Some studies have shown the prevalence of MetS in the USA to be up to 34% of the adult population and increasing with age.

MetS prevalence is also high in the Middle East and North Africa (MENA) region. In this context, MetS prevalence in United Arab Emirates (UAE) is 23%, in Kingdom of Saudi Arabia (KSA) 39%, in Oman 21%, in Jordan 36% and in Qatar 28%. In addition, the analysis of the Gulf Registry of Acute Coronary Events (Gulf RACE), showed the overall prevalence of MetS in patients with acute coronary syndrome is 46% in six Middle Eastern countrie, with higher prevalence in females. This is associated with higher recurrent ischemia and development of chronic heart failure compared with patients without the syndrome. Data support that the prevalence of all MetS components, i.e. insulin resistance, central obesity, hypertension and dyslipidaemia, are very high in the region. These data support that more aggressive and holistic strategies need to be implemented to treat MetS.

Atherogenic Dyslipidaemia and the Metabolic Syndrome: the Role of Incretin-Based Therapies

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Higher plasma triglyceride (TG) levels and decreased high-density lipoproteins (HDL) concentrations are usually accompanied by the presence of small, dense low-density lipoproteins (LDL) in the so-called “atherogenic dyslipidaemia” that is associated with abdominal obesity and insulin resistance and represents one of the components of the metabolic syndrome. Atherogenic dyslipidaemia is closely associated with endothelial dysfunction as well as with enhanced oxidative stress. Both atherogenic dyslipidaemia and oxidative stress are key mechanisms linked to the development and progression of atherosclerosis. The accumulation of LDL particles within the vascular wall represents the most prominent feature of atherogenesis and small, dense LDL particles are particularly atherogenic in comparison with larger, more buoyant subspecies because of their longer residence in the bloodstream, preferential penetration through the endothelial barrier and greater oxidative susceptibility. Enhanced oxidative stress and oxidative modifications are considered as the initial steps for LDL conversion into more atherogenic particles. The magnitude and independence of the association of small, dense LDL with cardiovascular risk has been reviewed and discussed in the first European Panel Statement on LDL subclasses. Lipid lowering agents are able to favourably modulate the distinct components of atherogenic dyslipidaemia; in addition, interesting data are coming from the use of incretin-based therapies in patients with type-2 diabetes. These novel anti-diabetic agents are able to decrease TG levels as well as to increase HDL-cholesterol concentrations. Preliminary data suggest that incretin-based therapies may also reduce levels of small, dense LDL in patients with type-2 diabetes and the metabolic syndrome.

Dysfunctional HDL: Clinical Relevance and Potential Therapeutic Target in Cardiovascular Disease

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The plasma levels of high-density lipoprotein (HDL) cholesterol are inversely correlated with the risk of cardiovascular disease (CVD). HDL particles differ in their lipid and protein composition, as well as in particle size and density. HDL protects against atherosclerosis primarily by inducing reverse cholesterol transport. HDL also exhibits antioxidant, anti-inflammatory, antithrombotic and anti-apoptotic effects. An important role in the HDL antiatherogenic activities is lipoprotein-associated phospholipase A_2 (Lp-PLA_2), which is independently associated with lower risk for cardiac death in CVD patients. The cardioprotective role of HDL is further supported by studies using reconstituted HDL particles (rHDL). These studies demonstrated that infusion of rHDL in animal models and humans leads to acute changes in atherosclerotic plaques. Changes in HDL protein composition attributable to infection, oxidative stress, inflammation or diabetes, are associated with decreased HDL antiatherogenic potency (acute phase HDL or dysfunctional HDL). Dysfunctional HDL has been identified in diabetic and CVD subjects. Raising HDL-cholesterol using specific cholesteryl ester transfer protein (CETP) inhibitors (torcetrapib and dalcetrapib) is not associated with an improvement in clinical outcomes. Furthermore, Mendelian randomisation studies do not support the causal association of low HDL with atherosclerosis. These findings raise serious concerns regarding the cardioprotective role of HDL. Thus, several unresolved questions remain to be answered before we reach any definite conclusion for the causal role of HDL in CVD.