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## EDITORIAL

INTER-PROFESSIONAL TEAMWORK CHALLENGES IN THE EMERGENCY ROOM AND CRITICAL CARE UNIT

## BRIEF REPORT

FAMILIAL HYPERCHOLESTEROLEMIA. PERSPECTIVES ON FH REGISTRY SYSTEMS

## RESEARCH ARTICLES

ORGANIZATION AND MANAGEMENT OF INTENSIVE CARE UNIT, CORRELATION OF TEAM CLIMATE WITH JOB SATISFACTION OF THE NURSES IN THE ICU

COST-EFFECTIVE SURGICAL MANAGEMENT OF LIVER DISEASE IN AN UNIVERSITY HOSPITAL: A RETROSPECTIVE STUDY

NUTRITIONAL PREFERENCES OF PRESCHOOL CHILDREN FOR BREAKFAST

DETERMINATION OF FEVER MANAGEMENT AND RATIONAL DRUG USE OF MOTHERS WITH CHILDREN UNDER SIX YEARS OLD

RELIGIOSITY AND CORONARY HEART DISEASE IN GREEK ADULTS

## SYSTEMIC REVIEW

MANAGEMENT OF ACUTE PANCREATITIS IN THE EMERGENCY DEPARTMENT

INVASIVE TECHNIQUES FOR THE REMOVAL OF NECROTIC TISSUE IN CHRONIC WOUNDS, A SYSTEMATIC REVIEW

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## BRIEF REPORT

## FAMILIAL HYPERCHOLESTEROLEMIA. PERSPECTIVES ON FH REGISTRY SYSTEMS

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**Abstract**

Familial Hypercholesterolemia (FH) is a genetic cause of premature Cardiovascular Disease (CVD) which is the leading cause of morbidity and mortality worldwide. In Greece, it is estimated that 90% of patients remain undiagnosed. Patients with FH are at high risk for cardiovascular events, peripheral arterial disease, stroke and death at a young age. Therefore, early detection of these is important for the implementation of appropriate preventive measures. Patient medical records are a powerful tool for recording and monitoring the disease and promoting clinical practices, thus helping to improve outcomes and reduce the cost of healthcare. Simultaneously with the registers, patient-centered management, multidisciplinary teamwork, involvement of primary care physicians, patient networks and support teams are required. Of most importance is the Greek online register system of people with familial hypercholesterolemia, by the Hellenic Atherosclerosis Society in collaboration with major hospital centers and the Hellenic College of Atherosclerosis Treatment registration system in the community. The purpose is to find people who are suffering from FH, to diagnose, to educate them and to put them under treatment and follow-up. In conclusion, effective care of patients with dyslipidemia requires: a) detailed evaluation of medical history, b) clinical and laboratory tests, and c) patient education programs regarding lifestyle changes and disease management. The above strategies of care will help reduce time and cost of medical treatment, obtain better clinical outcome and improve patients' quality of life.

**Key words:** Familial hypercholesterolemia, perspectives, registry systems.

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## INTRODUCTION

Familial hypercholesterolemia (FH) is the most common form of genetic disorder that is inherited with the autosomal dominant character. In the USA, in many countries of Northern Europe, but also in Greece, it is estimated that 1 in 250 people have FH, ie about 40,000 patients. The vast majority of them, which reach 90%, remain undiagnosed.<sup>1-3</sup>

Familial hypercholesterolemia is mainly caused by mutations in the Low Density Lipoprotein (LDL) receptor gene, 30 mutations have been detected in the Greek population. But there are other genes that encode proteins involved in the metabolism of LDL particles, the mutations of which may lead to the clinical picture of FH.<sup>4</sup>

Nowadays, dyslipidemias are classified based on their genetic mutations. Scientific groups and organizations have established criteria for the diagnosis of FH, with the most prevalent criteria being the Simon Broome UK and Criteria according to the Dutch Lipid Clinic Network program.<sup>5-8</sup>

The main characteristic clinical sign of FH is the appearance of xanthomas in the tendons. In addition it is the cornea or arch of the cornea and the xanthelasmas on the skin of the eyelids.<sup>9</sup> The reason that makes its timely diagnosis necessary is the effects on the cardiovascular system, such as myocardial infarction, stroke, valvular diseases and / or death. 1/3 of cases of ischemic heart disease are attributed to elevated cholesterol levels.<sup>10</sup>

Other effects are silent atherosclerosis, thickening of the carotid artery wall.<sup>11,12</sup>

A variety of treatments such as hypolipidemic drugs, combination therapy, treatment with genetic methods, have been proposed to treat familial hypercholesterolemia. Dietary intervention can rarely correct primary dyslipidemias.<sup>13</sup>

FH screening has been shown to work, as studies show that early diagnosis results in a reduction in complications leading to a reduction in morbidity and mortality from the disease.<sup>13</sup>

A systematic review of financial evaluations for the detection and treatment of familial hypercholesterolemia has shown that screening of relatives with suspected FH is highly cost-effective.<sup>14</sup>

The current European high levels of undiagnosed people with

FH and associated morbidity and mortality mean that the adoption of ongoing services will bring significant benefits to quality of life and survival.

A similar study in Poland shows that screening for FH is very cost-effective. The cost-effectiveness strategies of the disease screening strategy are complementary and the use of a combination of them is recommended.<sup>15</sup>

Other research on the same topic regarding genetic testing for FH in the US has shown that it is more effective if started before the age of 40 in first-degree relatives and before the age of 15 in second-degree relatives.<sup>14</sup>

Researches on familial hypercholesterolemia conclude that potentially millions of children and adults worldwide are unaware that they are ill. Respectively, in Greece the true prevalence of FH is unknown. An equally serious problem is the non-registration of patients that is why an attempt is being made in several countries for electronic registration.

All studies suggest that the electronic FH registry causes the detection of many new cases and referral to lipid clinics. Therefore, the FH register raises the general awareness but also the awareness of the doctors about the prevalence of FH and its related complications, which will improve the management of FH in the long run. The registers help to record, so that the statistics for the prevalence of the disease, help in the diagnosis and prevention.<sup>16</sup>

## FAMILY HYPERCLOSTERENEMIA

The disease that is the most common genetic disorder is clinically differentiated depending on the severity, in homozygous and heterozygous and LDL levels, 2 to 4 times higher than expected. In 1938, the Norwegian physician Carl Müller was the first to associate clinical signs, xanthomas - xanthelasmas, high plasma cholesterol levels, hereditary predisposition, and myocardial infarction within a clinical entity. In addition, the heterozygous and homozygous form was described by Khachadurian before the genes responsible for the disease were identified.<sup>17</sup>

Later, in 1986, the LDL receptor was identified as responsible for autosomal dominant Dominant Hypercholesterolemia (ADH). This was followed by the discovery of many LDL recep-

tor mutations, and in 1985 Brown and Goldstein confirmed their role in LDL receptor lipid metabolism. ADH has been considered a monogenic disease for many years. However, when more genotypes of patients with ADH were encoded, individuals with the same phenotype of familial hypercholesterolemia but without mutation in the LDL receptor were found.<sup>17-19</sup> In 2001, the autosomal recessive hypercholesterolemia gene was expressed. All these discoveries have led to the confirmation of the view on the polygenic etiology of familial hypercholesterolemia.<sup>17,20,21</sup>

### EPIDEMIOLOGICAL BACKGROUND

Few epidemiological studies have evaluated lipid levels in Greece. According to the results of the ATTICA study in which 3042 adults participated, without any clinical signs of cardiovascular disease and living in Attica, 46% of men and 40% of women had abnormally high levels of total cholesterol. In addition, men had higher levels of total cholesterol compared to women. Of those with abnormally high total cholesterol, 40% of men and 30% of women said they did not know it. Also 15% of men and 14% of women had total cholesterol levels greater than 240 mg / dl. In addition, in the age group over 50, 49% of men and 52% of women had abnormally high total cholesterol levels. Finally, 21% of men and 7% of women had very low HDL levels. In relation to gender, it was found that men had higher levels of triglycerides compared to women. About 28% of men and 13% of women had high triglyceride levels.<sup>22</sup>

Another study by a Mediterranean country, specifically in Portugal, reported that the incidence of elevated total cholesterol levels in the elderly was 57%, while in Spain in another study the incidence reached 68%.<sup>23,24</sup>

In a prevalence study of dyslipidemia conducted in Cyprus in the two years 2005-2007 in a sample of 1000 people, it was found that 53.1% of the study population had abnormally high levels of total cholesterol, LDL > 130 mg / dl had 68.5% while low HDL had 29.9% with lower conditions, 40 mg / dl for men and 50 mg / dL for women. Triglycerides were found to be pathologically elevated by 21.5%.

In some populations such as French-Canadians, Christian Lebanese, South Africans, Tunisians, Icelanders the incidence of

familial hypercholesterolemia (FH) is particularly high due to the presence of a "fundamental mutation". The presence of "fundamental mutation" occurs when a subpopulation results from the migration of a small number of individuals carrying the mutation and the consequent increase in that population.<sup>25</sup>

In a retrospective study conducted in the USA. in the years 1999-2012 on the impact of FH with the Dutch criteria system, showed that the impact is 1 in 250 adults.<sup>3</sup>

In a study conducted by Pavlatou et al, 2021, which evaluated and analyzed data from 1578 people, from a record of the Hellenic College of Atherosclerosis Treatment, present important data for familial hypercholesterolemia in Greece. In particular, the study population concerns Greeks living in the prefecture of Attica. According to the diagnostic criteria for familial hypercholesterolemia used by the Simon Broome organization in Great Britain in the sample of the present study, it was found that 8 people are sick, 13 are with a probable diagnosis while 1557 people are not sick. Thus, in the present study, out of 1578 people, 8 people have certain disease, making the incidence 1: 198.

Similarly, the Hellenic Atherosclerosis Society has started registering patients in health structures, the frequency is estimated to be 1 in 250 people with familial hypercholesterolemia (FH), ie about 40,000 patients.

The increased prevalence of the disease confirms the need to find patients to reduce the risk of death from cardiovascular events, which is its first silent manifestation at a young age.<sup>14,26</sup>

### DIAGNOSTIC CRITERIA

The first attempt to classify lipids and lipoproteins was made by John Gofman in 1949, followed by Donald Fredrickson in 1965. Fredrickson classified dyslipidemias according to peripheral blood lipid levels. Today, dyslipidemias are classified based on their genetic mutations. Mutations cause diseases such as familial hypercholesterolemia, familial abnormality of apolipoprotein B-100, familial combined hyperlipidemia, etc.<sup>17</sup>

Scientific teams and organizations have established criteria for the diagnosis of familial hypercholesterolemia, with the most prevalent criteria being Simon Broome Great Britain and Criteria according to the Dutch Lipid Clinic Network program.<sup>27,28</sup>

## CLINICAL POINTS

The main characteristic clinical sign of familial hypercholesterolemia is the appearance of xanthomas, which are evaluated regardless of whether they concern the patient or his suffering relatives and make the diagnosis of familial hypercholesterolemia with more certainty. Xanthomas are composed of fibrous connective tissue and foam cells with abundant fat droplets in their cytoplasm. The arch or corneal arch is an off-white arc of fat deposition on the cornea, often in the form of a ring. Xanthelasma appear on the skin of the eyelids.<sup>9</sup>

## FH REGISTER

The purpose of creating electronic registers is to collect data to facilitate the design of clinical services, information on best practices and research. In March 2015, within the framework of the 83rd EAS Conference, a meeting of the "FH Patient Advocacy Group" (FHSC) was held in Glasgow in cooperation with the European Union (AES). Sixty participants from 32 countries from Europe, South and North America, Asia and Africa took part with the common goal of discussing the FH problem. Initially, presentations, extensive discussions, exchange of experiences and knowledge between organizations and countries took place. Obstacles were then mentioned for the optimal management of FH, in raising the awareness of the public and the health team, mainly at the level of primary care. The consequences of the subdiagnostic and subcharacteristic treatment of FH were also discussed, as well as the promotion of a uniform standard of care based on studies.

Patient organizations were seen as an effective tool for raising FH awareness, as well as promoting education and influencing public health policies. Contacts and exchange of experiences between organizations from different regions and countries can support their common goals, helping new start-ups to consolidate and expand. However, problems facing these organizations are lack of funding and institutional support. A key action they decided to encourage is to raise the awareness of the general population, patients, healthcare providers and policy makers. Actions such as social campaigns, newsletters, social media dissemination, websites, forums, could be helpful in

understanding the implications of the problem. In addition, training plays an important role in the identification and proper management of FH.

Other aspects raised during the conference included the general lack of strategies for the availability and accessibility of treatments, especially new treatments, and the lack of financial support for patients on chronic medications. Another problem that was highlighted was the need for real and effective contact and cooperation between patients, health team and clinics in order to have a comprehensive model of their care. Finally, it was reported that as an inherited disease, genetic testing may increase patients' awareness and compliance with treatment.<sup>29</sup>

## CZECH REPUBLIC

A register was set up in the Czech Republic in 1998 to prevent premature deaths in patients with FH. Since then it has developed into a network of 63 centers covering the whole country. The recording checks the diagnosis and treatment of patients with FH, as well as DNA collection for genetic analysis. Currently, the database includes data on more than 6,100 patients. The FH that causes the mutation has been detected in more than 2,100 patients so far. The organization's website provides patients, relatives and the general public with reliable and up-to-date information on FH's disease and treatment options.<sup>30</sup>

## SPAIN

It is estimated that more than 100,000 people have FH in Spain. Since lipid-lowering therapy became available to patients free of charge in 2004, enrollment has been favored. More than 20,000 people were diagnosed with FH, representing about 20% of the population. Of these, more than 60% were diagnosed based on clinical criteria. In recent years, different strategies have been implemented to detect FH, including genetic diagnosis. This has led to the genetic identification of more than 7,000 people with FH.<sup>31</sup>

The Hellenic College of Atherosclerosis Treatment has started recording patients in the community in order to investigate the frequency and impact of the disease on Greeks. 14 sectors of the Greek Territory were separated, while Attica was divided into 8 sectors. According to the press release 28-12-

2012 ELSTAT, Piraeus, census of 2011 requires a sample of 7668 people. In a first publication with a sample of Greeks living in the prefecture of Attica, a closed-ended question form was recorded using the method of personal interview. Data from 1578 people were evaluated and analyzed, of which 8 people are ill, making the incidence frequency 1: 198.

At the same time, the Hellenic Atherosclerosis Society, which has started registering patients in health structures, the frequency is estimated to be 1 in 250 people with familial hypercholesterolemia (FH), ie about 40,000 patients. An important observation is that the vast majority, which reaches 90%, remain undiagnosed. The increased prevalence of the disease confirms the need to find patients to reduce the risk of death from cardiovascular events, which is its first silent manifestation at a young age.

## CONCLUSIONS

Familial hypercholesterolemia is a major public health problem as it is common in the general population and its presence carries risks of cardiovascular events or even death. Primary health care should include the creation of a program to inform and control the public, as well as the implementation of measures in case of need from an early age. The information is provided by groups of health personnel and concerns the normal values of lipids, cholesterol and other factors, the control age and intervals, the ways of managing hyperlipidemia. In addition, the needs of people with diabetes hypothyroidism and other comorbidities, healthy lifestyle information, exercise and the Mediterranean diet.

Skilled nurses along with other health professionals can play an important role in preventing and treating the disease in primary health care. This is because, they are for a long time next to the patient and the family and have the opportunity to intervene and make patients comply with medical instructions.

The effort to create a Greek online register of people with familial hypercholesterolemia, by the Hellenic Atherosclerosis Society in collaboration with major hospital centers and the Hellenic College of Atherosclerosis Treatment in the community is very important. The main purpose of this attempt is to find people who are suffering from FH, to diagnose, to educate

them and to put them under treatment and follow-up.<sup>32,33</sup>

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