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Lipid profile evaluation and severe hypercholesterolaemia screening in the middle-aged population according to nationwide primary prevention programme in Lithuania

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ABSTRACT

Background and aims: Cardiovascular disease (CVD) is a major cause of premature death in Lithuania where abnormal lipid levels are very common among middle-aged adults. The aim of this study was to evaluate lipid profile in middle-aged Lithuanians and perform population-based severe hypercholesterolaemia (SH) screening.

Methods: This study included men aged 40–54 and women aged 50–64 years without overt CVD, participating in the Lithuanian High Cardiovascular Risk (LitHiR) primary prevention programme during the period 2009–2016. Lipidograms of 92,373 adults (58.4% women and 41.6% men) included in the database were analysed and screening for SH was performed.

Results: The mean levels of total cholesterol, LDL cholesterol (LDL-C) and triglycerides (TG) among participants were 6.08 mmol/l, 3.87 mmol/l, and 1.59 mmol/l, respectively. Any type of dyslipidaemia was present in 89.7%, and severe dyslipidaemia in 13.4% of the study population.

80.2% of adults without overt CVD had LDL-C $\geq$3 mmol/l. SH (LDL-C $\geq$6 mmol/l) was detected in 3.2% of study participants. Prevalence of SH decreased from 2.91% to 2.82% during the period 2009–2016 (p for trend = 0.003). LDL-C $\geq$6.5 mmol/l was observed in 1.5% of subjects while both LDL-C $\geq$6.5 mmol/l, and TG $\leq$ 1.7 mmol/l was found in 0.6% of subjects.

Conclusions: SH was present in 3.2% of the middle-aged population without overt CVD. Slightly decreasing prevalence of SH was observed during the period 2009–2016 in Lithuania. Likely phenotypic familial hypercholesterolaemia was observed in 1.5% of middle-aged Lithuanians. Further clinical and genetic evaluation of people with SH is needed to detect familial forms of SH.

1. Introduction

Various genetic, pathology, observational and intervention studies have established the important role of dyslipidaemia in the development of cardiovascular disease (CVD) [1]. Dyslipidaemia is a multifactorial disorder as an interplay between genetic, lifestyle and environmental factors [2]. It may have different manifestations in certain groups of patients [3]. Proper treatment of dyslipidaemia has been shown to reduce CVD risk by 30% in a 5-year period [4]. Dyslipidaemia remains poorly controlled and is a very prevalent risk factor in Lithuania through the years, whereas variations in the characteristics of individual lipidogram parameters have been observed [5]. Dyslipidaemias cover a broad spectrum of lipid disorders and a high proportion of patients have complex lipid abnormalities.

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Elevation of low-density lipoprotein cholesterol (LDL-C), known as severe hypercholesterolaemia (SH), constitutes a major risk factor for the development of atherosclerosis and receives most attention as an established treatment goal [6]. Patients with severely elevated LDL-C might have genetic disorders, such as familial hypercholesterolaemia (FH), polygenic hypercholesterolaemia (PH) and familial combined hyperlipidaemia (mixed hyperlipidaemia) (FCH) or non-genetic explanations including secondary causes of SH (e.g. nephrotic syndrome, cholestasis, untreated hypothyroidism) or lifestyle factors [7,8]. It is evident that only a small proportion of severely hypercholesterolaemic subjects will have identified FH mutations, so recognition of SH is important on a population-basis as extremely elevated LDL-C levels drive the clinical risk for these patients [8]. Analysis of serum lipid profiles could provide an initial approximate differentiation between various types of dyslipidaemia and help distinguish subjects for further evaluation for the familial forms of dyslipidaemia, as opportunistic screening in community laboratory for potential FH has been proven to be effective [9]. The importance of identifying and screening for various types of dyslipidaemia is underlined by the problem of underdiagnosing and undertreating FH, as there are over fourteen thousand people estimated to have FH in Lithuania [10]. Early diagnosis and treatment of this condition is crucial, so there is a need for systematic screening for FH worldwide [11]. Different countries have tried various approaches to find the FH patients. National genetic cascade screening programmes for FH are successfully applied in the Netherlands, Spain and Wales, while numerous other countries have advanced regional and local programmes [12].

More than ten years ago, in 2006, the Lithuanian High Cardiovascular Risk (LitHiR) primary prevention programme was started based on the unfavorable situation of cardiovascular morbidity and mortality in our country. The design of the programme is compatible with ESC/EAS Guidelines suggesting that risk factor screening, including the lipid profile, may be considered in men ≥40 and women ≥50 years of age [6]. Having a huge database of lipidograms of middle-aged Lithuanians without overt CVD, the electronic extraction approach could be used to screen the population for SH, consistent with likely phenotypic FH, and other lipid abnormalities. The aim of this study was to describe the lipid profiles of middle-aged Lithuanians without overt CVD and estimate the prevalence of severe hypercholesterolaemia in large nationwide prevention programme database.

2. Materials and methods

2.1. Study participants

This study describes the analysis of the lipid profile in a randomly selected group of 92,373 subjects included in the electronic database of the primary prevention programme during the period 2009–2016. The LitHiR programme is funded by the Ministry of Health and has obtained the Local Research Ethics Committee's approval. It includes men aged 40–54 and women aged 50–64 years without overt CVD from all regions of Lithuania. This programme is conducted in 398 out of 420 (94.8%) primary health care centres, uniformly covering the whole country. In 2016, 256,625 adults were examined in the primary health care centres, covering about 37.5% of all target population. LitHiR programme consists of subjects selected in three different ways: enlisting patients of proper age in primary health care centres, inviting patients who fit programme enrollment criteria after looking at existing medical history, and enrolling patients informed about the programme via mass media [13]. The exclusion criteria are: a) proven (clinically evident) coronary heart disease (CHD); b) proven (clinically evident) cerebrovascular disease; c) proven (clinically evident) peripheral artery disease; d) end-stage oncological disease; e) any other end-stage somatic disease. A detailed description of the Lithuanian primary prevention programme protocol is provided in the article by Laucevicius et al. [13].

2.2. Lipid measurements

Serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) were evaluated by commercially available kits using venous blood samples at the standardized laboratories in the participating centres. LDL-C levels were calculated using the Friedewald formula for individuals with TG < 4.5 mmol/l. Tests were performed in the morning and participants were recommended not to eat at least 12 h before tests. Secondary causes of dyslipidaemia were not ruled out. Less than 5% of subjects in the database are reported to use lipid-lowering medications. Participants were divided into groups according to their lipidogram parameters and different lipid profiles were distinguished. Dyslipidaemia was considered if serum TC > 5 mmol/l, or LDL-C >3 mmol/l, or HDL-C <1.0 mmol/l in men and <1.2 mmol/l in women, or TG > 1.7 mmol/l. Severe dyslipidaemia was described as TC ≥ 7.5 mmol/l, or LDL-C ≥6 mmol/l, or TG ≥ 4.5 mmol/l. Severe hypercholesterolaemia was described as LDL-C ≥6 mmol/l and severe hypertriglyceridaemia was defined as TG ≥ 4.5 mmol/l. To define the likely FH phenotype, we selected LDL-C cut-off values that align with commonly used criteria to identify possible FH – Dutch Lipid Clinic Network criteria [14]. We described the likely FH phenotype simply as LDL-C 6,5–8,49 mmol/l and LDL-C ≥8,5 mmol/l. Study data has been further analysed by dividing all subjects into appropriate groups by age, men: 40–44 years, 45–49 years, 50–54 years and women: 50–54 years, 55–59 years, 60–64 years.

2.3. Statistical analysis

Continuous variables were expressed by means and standard deviations (SD). For categorical data, frequencies (%) are reported. Mantel-Haenszel Chi-square test for trend was used to analyse the trends of prevalence for categorical variables ("*p* for trend"). To evaluate linear associations between continuous variables, ANOVA for linear trend was used ("*p* for trend"). Continuous variables were compared using the Kruskal–Wallis univariate analysis of variance (ANOVA). Categorical variables were compared with the help of the Chi-square test. All reported *p*-values are two-tailed. The level of significance was set to 0.05.

3. Results

3.1. Sample characteristics

During the period 2009–2016, a total of 92,373 middle-aged subjects (58.4% women and 41.6% men) without overt CVD were evaluated. The average age of subjects was 52.15 ± 6.21 years. The average values of lipidogram parameters of the whole study population are shown below in Table 1.

3.2. Dynamics of serum lipid profile among middle-aged Lithuanian adults from 2009 to 2016

Prevalence of any type of dyslipidaemia remained stable and high, affecting 89.7% (n = 82,893) of middle-aged adults, while the prevalence of severe dyslipidaemia decreased from 12.2% to 11.6% (*p* for trend <0.013). The trends of the prevalence of any type of dyslipidaemia and severe dyslipidaemia in thr general population