Significance of dyslipidaemia in patients with heart failure of unexplained aetiology

Mirostaw Skwarek, Zofia T. Bilif ska, Łukasz Mazurkiewicz, Jacek Grzybowski, Mariusz Kruk, Paweł Kurjata, Wal erian Piotrowski, Witold Rużyło

1 1st Department of Coronary Artery Disease, The Cardinal Stefan Wyszyński Institute of Cardiology, Warsaw, Poland
2 Laboratory of Biostatistics, Department of Epidemiology, Prevention of CVD and Health Promotion, The Cardinal Stefan Wyszyński Institute of Cardiology, Warsaw, Poland

Abstract

Background: Dyslipidaemia has been studied in the prognosis of heart failure (HF). Little is known about the role of dyslipidaemia in the aetiopathogenesis of dilated cardiomyopathy (DCM).

Aim: To assess (1) serum lipid levels in DCM considering the severity of heart failure; (2) the association between DCM and lipid abnormalities; (3) prognostic significance of lipids in DCM.

Methods: The study group consisted of 100 patients with angiographically proven DCM [mean age 42 years, 80% males, 65% in NYHA class III-IV, mean left ventricular ejection fraction (LVEF) 32%], whose fasting serum lipids had been assessed during diagnosis between 1992 and 2001. Patients’ lipid levels were compared with those observed in healthy controls (n=100), age-, gender-, and BMI-matched and related to findings reported in population samples from WHO Pol-MONICA studies from: 1993 (n=526), 1997/1998 (n=526) and 2001 (n=1364). Three (3%) patients received lipid-lowering drugs. Transplant-free survival was assessed in the study group. In the statistical analysis, nonparametric Wilcoxon test and uni- and multivariate logistic and Cox regression analyses were used.

Results: Serum total cholesterol (TC), LDL (LDL-C) and HDL cholesterol (HDL-C) tended to be lower (differences NS) in NYHA class III-IV patients vs. class I-II (TC: 196.9±45.5 vs. 207.9±47.1 mg/dl, LDL-C 126.2±37.5 vs. 128.5±42.7 mg/dl, HDL-C 44.2±11.3 vs. 44.7±13.7 mg/dl, respectively), and triglycerides (TG) were lower in advanced HF vs. NYHA class I-II (135.9±51 vs. 170.3±63.4 mg/dl, p=0.004). In DCM patients HDL-C was lower than in controls (44.1±12.1 vs. 54.3±17.6 mg/dl, p <0.001), and TG level was higher (147.9±58.1 vs. 114.1±61.6 mg/dl, p <0.001). HDL-C and TG levels in controls were similar to those observed in population samples. Multivariate analysis with age, low HDL (defined as <40 mg/dl for males, and <50 mg/dl for females), and hyperTG (TG ≥150 mg/dl) showed that both low HDL-C (OR=2.31; 95% CI 1.2-4.457, p=0.0122), and hyperTG (OR=1.978, 95% CI 1.029-3.799, p=0.0407) were independently associated with DCM. Low HDL-C level occurred more frequently in female DCM patients vs. males (65 vs. 33.8%, p=0.022). There was a trend towards more frequent occurrence of hyperTG in male patients vs. females (42.5 vs. 20%, p=0.11). The mean follow-up time was 7.32±4.7 years. In Cox univariate analysis low TC tended to be a prognostic factor (p=0.067), but in Cox multivariate analysis only NYHA class (HR=1.7, 95% CI 1.136-2.541; p=0.01) and LVEF (HR=0.963, 95% CI 0.932-0.996; p=0.027) turned out to be independent predictors of poor outcome.

Conclusion: Dyslipidaemia might play a role in the aetiopathogenesis of DCM. Low TC is not an independent prognostic factor in DCM.

Key words: heart failure, dilated cardiomyopathy, aetiopathogenesis, prognosis, dyslipidaemia, lipids

Kardiol Pol 2008; 66: 515-522

Introduction

Dilated cardiomyopathy (DCM) is defined by the presence of left ventricular dilatation and left ventricular systolic dysfunction in the absence of abnormal loading conditions (hypertension, valve disease) or coronary artery disease sufficient to cause global systolic impairment [1]. It is estimated that at least 25% of patients have evidence of familial DCM with a predominantly autosomal dominant pattern of inheritance. Other cases of DCM are defined as sporadic. Factors such as viral infection, immunological disturbances, as well as toxic factors including alcohol abuse, and the administration of cardiotoxic drugs, are among the most important causes leading to development of the sporadic form of the disease.

Until recently, the role of lipid abnormalities during the course of heart failure was evaluated only in the context of predictive value [2-4]. There are very few data regarding the contribution of lipid metabolism disturbances to DCM...
The aims of the study were: 1) to evaluate serum lipid concentrations in patients with DCM in relation to the severity of heart failure; 2) to search for a correlation between lipid metabolism disturbances and DCM; 3) to evaluate the predictive value of lipid parameters in patients with DCM.

Methods

The study involved 100 patients with DCM referred to the Department of General Cardiology or the 1st Department of Coronary Artery Disease, Institute of Cardiology in Warsaw between 1992 and 2001 who underwent clinical examination, evaluation of functional status according to NYHA classification, ECG study, two-dimensional echocardiography with Doppler, and cardiac catheterisation with coronary angiography, as well as complete serum lipid analysis.

Diagnosis of DCM was established based on WHO criteria that included severe LV systolic dysfunction (LV dilatation exceeding 117% of normal value corrected for age and body surface area) and LV ejection fraction (LVEF) ≤45% measured in angiography, without significant coronary artery disease (>50% lumen diameter reduction of one of the main coronary arteries), hypertension, or acquired or congenital heart disease. Patients with diabetes mellitus and systemic disorders were also excluded [6, 7].

Fasting concentrations of lipids measured during the first diagnostic hospitalisation in the Institute of Cardiology were analysed. Total cholesterol (TC), HDL cholesterol (HDL-C) and triglyceride (TG) concentrations were measured using standard laboratory techniques. Plasma LDL cholesterol (LDL-C) concentration was calculated according to the Friedewald's formula (LDL-C = TC – HDL-C – 0.2 × TG). Dyslipidaemia was defined as TC concentration ≥200 mg/dl or LDL-C level ≥130 mg/dl or TG concentration ≥150 mg/dl or low HDL-C level (<40 mg/dl for men and <50 mg/dl for women). Lipid concentrations in patients with DCM were related to clinical data including functional NYHA class.

A control group of healthy individuals that did not differ with respect to age, gender or body mass index was recruited from the Pol-MONICA population probe studied in 2001. To approximate assessment of the changes in lipid levels throughout the decade, the results of lipidogram examination in three Polish populations studied in 1993, 1997/1998 and 2001 as part of the Pol-MONICA trial were also analysed [8-10].

Patient survival was evaluated in the DCM group. All follow-up visits had been completed by March 31, 2007. End-points of the follow-up were death or heart transplantation.

Statistical analysis

The methods of descriptive statistics, mean, standard deviation and rate of the analysed qualitative variables were used to describe data. The χ² and exact Fisher’s test were used to compare the prevalence of the given parameters in the DCM and control groups. The non-parametric Wilcoxon test was used to compare the means of continuous variables. To analyse the relationship between prevalence of DCM and lipid abnormalities, uni- and multivariate logistic regression method was employed. In patients with DCM, survival rate was estimated by means of Kaplan-Meier method. The following binary cut-off points of the analysed lipid parameters were adopted: TC concentration ≥200 mg/dl vs. <200 mg/dl, LDL-C level ≥130 mg/dl vs. <130 mg/dl, TG ≥150 mg/dl vs. <150 mg/dl, and low concentration of HDL-C vs. normal HDL-C level. The correlation between the selected lipid parameters and the incidence of follow-up end-points was examined using Cox’s proportional hazard ratios model (HR). A p value <0.05 was considered statistically significant. Statistical analysis was carried out using SAS ver. 8.2 statistical package.

Results

Study population

Clinical characteristics of DCM patients are presented in Table I. Mean age of patients was 42 years and 80% of them were males of reproductive age. Mean disease duration was 22.4 months. Thirty-five percent of patients were found in functional NYHA class I or II and 65% of patients presented with severe heart failure. Echocardiographic as well as haemodynamic parameters indicated severe heart failure in the majority of study patients. Thirty six percent of them had LVEF in the range between 30 and 45%.

Table I shows mean age, male gender and body mass index of the control group as well.
Comparison of lipid levels in relation to heart failure severity

Total cholesterol and its fractions were non-significantly lower in patients found in functional NYHA class III or IV than in class I or II (TC: 196.9±45.5 vs. 207.9±47.1 mg/dl, LDL-C: 126.2±37.5 vs. 128.5±42.7 mg/dl, HDL-C: 44.2±11.3 vs. 44.7±13.7 mg/dl, respectively). Values of TG levels were significantly lower in advanced DCM group (135.9±51 vs. 170.3±63.4 mg/dl in NYHA class I or II, p=0.004) (Figure 1).

A weak negative correlation between LDL-C level and TG concentration for the whole examined group was found (r=–0.232, p=0.02). In 18 (18%) patients, HDL-C level <40 mg/dl and TG concentration ≥150 mg/dl were found.

Comparison of lipid levels in DCM patients vs. control group and probes of Polish population studied in 1993, 1997/1998 and 2001

Levels of TC and LDL-C in patients with DCM were similar to those measured in the control group (TC: 200.2±46.9 vs. 197.9±42.9 mg/dl, LDL-C: 127.1±39.6 vs. 120.7±37.8 mg/dl) (Figure 2).

HDL-C concentration was significantly lower in DCM patients than in the control group (44.1±12.1 vs. 54.3±17.6 mg/dl, p <0.001) while TG level was markedly higher (147.9±58.1 vs. 114.1±61.6 mg/dl, p <0.001) (Figure 3). Levels of HDL-C and TG in the control group were comparable to those in the population probes.

General prevalence of dyslipidaemia was 84% in patients with DCM and 61% in the control group (p=0.0003).

Prevalence of DCM vs. lipid abnormalities

Prevalence of DCM was shown to be associated with abnormal lipid levels (Table II). In the univariate analysis, prevalence of DCM was found to be 2.3-fold higher in patients with low HDL-C level than in individuals with normal HDL concentration (p=0.0069). Similarly, prevalence of DCM was 2.3 times higher in patients with high TG levels (hyperTG) than in patients with normal TG concentrations (p=0.092). Co-existence of low HDL-C level and hyperTG were not found to be correlated with the prevalence of DCM (p=0.16).
To assess which of the factors were independently associated with DCM prevalence, multivariate analysis involving 3 variables, i.e. age, low HDL-C concentration and hyperTG, was performed. Both lipid parameters were found to be independently correlated with the prevalence of DCM. Odds ratio for low HDL-C level was 2.313 (p=0.0122) and 1.978 for hyperTG (p=0.0407) (Table III).

Clinical characteristics of DCM patients in relation to dyslipidaemia

Patients with dyslipidaemia were older (mean age 48.7±9.8 vs. 47.2±16.1 years, p=0.032), and prevalence of dyslipidaemia was comparable in both genders. The distribution of lipid abnormalities in DCM patients with respect to gender is presented in Figure 4. Low HDL-C level was more frequently seen in women than in men. The incidence of hypercholesterolaemia and hypertriglyceridaemia was non-significantly higher in men. No statistically significant differences with respect to other clinical variables were found.

Predictive value of lipids in DCM

Mean follow-up duration was 7.32±4.7 years. Within this period, 44 patients died due to progressive heart failure and 14 underwent heart transplantation. Survival analysis by means of Kaplan-Meier method in the DCM group with or without lipid abnormalities with respect to individual lipid parameters was carried out. No significant differences in survival were found. Table IV shows the results of univariate Cox analysis of the relative risk of death or heart transplantation in the study group of 100 patients. Significant predictive factors were high functional NYHA class (p=0.001), low LVEF (p=0.03) and increased LV end-diastolic dimension (LVEDD) (p=0.045). A trend towards unfavourable impact on survival was also noted for low TC (p=0.067) and HDL-C level (p=0.195).

In the Cox multivariate analysis of the parameters that were previously found predictive in the univariate analysis (NYHA, LVEDD, LVEF), the independent diagnostic factors were higher NYHA functional class (HR=1.7, 95% CI 1.136-2.541; p=0.01 for an increase by one class) and LVEF reduction (HR=0.963, 95% CI 0.932-0.996; p=0.027 for a drop by 1%). In the multivariate analysis also involving lipid parameters (NYHA, LVEDD, LVEF, TC, HDL-C) the independent predictive factors were only higher functional NYHA class (HR=1.78, 95% CI 1.112-2.524; p=0.014) and LVEF reduction (HR=0.962, 95% CI 0.930-0.995; p=0.024).

Discussion

The present study showed that DCM patients had significantly lower HDL-C level and markedly higher TG concentrations than healthy subjects of the Pol-MONICA.
Significance of dyslipidaemia in patients with heart failure of unexplained aetiology

Levels of HDL-C and TG in the control group were comparable to the population probes examined in 1993, 1997/1998 and 2001. Levels of TC and LDL-C in DCM patients did not differ significantly from the control group. Although we observed a trend toward lower TC and its fractions’ level in patients with advanced heart failure, only TG levels were significantly lower in patients being found in functional NYHA classes III to IV.

There are very few published data on the role of lipid abnormalities in the prevalence of DCM. So far only Sampietro et al. have studied lipid levels in patients found in NYHA functional classes I to II in comparison to healthy controls recruited from laboratory personnel, who underwent complete clinical and laboratory examinations [5]. Our results are consistent with their findings on lower levels of HDL-C and higher TG concentrations in DCM patients compared to the control group. Moreover, Sampietro et al. noted that levels of HDL-C categorised as <40 mg/dl and >40 mg/dl but not hyperTG were strongly and independently correlated with the prevalence of DCM, measured by means of prevalence odds ratio (POR) (p <0.0005) [5]. Age of patients and serum concentration of intercellular adhesion molecule (ICAM)-1 were also revealed to be independent predictive factors of DCM development [5]. We found (in younger patients at the mean age of 42 years) that either low level of HDL-C or increased TG concentration was independently associated with the prevalence of DCM. Sampietro et al. [5] also examined Apo AI and AII apolipoprotein levels, which were markedly lower in DCM patients than in the control group. It has been suggested that apolipoprotein AI and AII levels may contribute to low HDL-C concentration in the early stage of DCM.

Vredevoe et al. evaluated lipid abnormalities in patients with advanced heart failure, comparing lipid levels in patients with heart failure of ischaemic aetiology and idiopathic DCM. They noted lower TC and LDL-C levels in 109 patients with DCM vs. 113 patients with ischaemic heart failure [11].

Analysing the prevalence of lipid metabolism disturbances with respect to gender in DCM patients, we found that women had low HDL-C level more frequently than men (65 vs. 33.8% in men, p=0.022), while hyperTG was seen slightly more often (not significantly) among male than female patients (p=0.11). There are no published data available on the distribution of lipid disturbances in DCM patients according to their age.

There is no clear answer to the question of how lipid abnormalities might lead to DCM development. Hypercholesterolaemia causes impairment of flow-dependent vessel dilatation even in patients with normal coronary arteries [12]. Additionally, an increased LDL-C level changes vasomotor properties via inhibition of endothelium-dependent vessel wall relaxation [13]. Hypertriglyceridaemia either isolated or accompanied by hypercholesterolaemia impairs endothelium-induced vessel relaxation as well [14, 15].

Most data were collected on the role of HDL-C in normal endothelial function preservation [16, 17]. Molecules of HDL-C influence key control mechanisms regulating microcirculation [18, 19]. In DCM patients abnormalities of coronary perfusion are seen either at rest or in a response to pharmacologic or metabolic stress [20]. More and more studies showing enhanced endothelial activation in patients with heart failure of unknown aetiology have been published [21-28]. Similarly, in the report by Prochorec-Sobieszek et al. inflammatory endothelial activation was seen in a half of examined patients [29]. Prolonged endothelial activation eventually leads to its dysfunction [30]. Neglia et al. found severely depressed myocardial blood flow (MBF) measured with PET after dipyridamole to be an independent risk factor of death or progressive heart failure in patients with idiopathic myocardial dysfunction [20]. HDL and apolipoprotein A-I bind and neutralise lipopolysaccharide and bacterial endotoxin, thereby preventing the release of TNF-α, inhibit complement activation and mitigate cytokine-induced expression of the endothelial adhesion molecules. This leads to a decrease of endothelial activation and, in this way attenuates endothelial dysfunction [18, 31-33].

Contrary to the favourable impact of low TC level on prognosis in patients with coronary artery disease, decreased concentration of TC is associated with higher mortality in patients with heart failure. Richartz et al. [4] showed low TC levels to be related to increased mortality in 45 patients undergoing LV mechanical device implantation. Moreover, Horwich et al. in a retrospective analysis of 1134 advanced heart failure patients noted that subjects with the lowest quintile of TC level (<129 mg/dl) presented two-fold higher relative risk of death in comparison to individuals who had cholesterol concentration found in the highest quintile [2]. In two studies [2, 3], low TC level was an unfavourable prognostic factor, independently of heart failure aetiology (either ischaemic or idiopathic). In the previously mentioned study reported by Vredevoe et al., lower TC, its fractions and TG in patients with advanced heart failure (functional NYHA class III or IV) were predictive factors of poor outcome only in patients with idiopathic DCM (at the mean age of 47 years, females: 37%) but not in subjects with ischaemic aetiology (at the mean age of 56 years, women: 11%). Unfavourable impact of TC level on survival depends on age, being significant in the 5th decade of life and negligible in older subjects [34]. Christ et al. in a study with DCM patients only that involved 422 subjects at the mean age of 50 years, including 19% women and 67% individuals in functional NYHA class I or II, found using univariate analysis that decreased TC, HDL-C and apolipoprotein A1 levels were weak predictors of unfavourable outcome. However, in multivariate analysis decreased cholesterol levels did not...
independently predict adverse prognosis in DCM [35]. Similarly, in our study, which involved younger patients (at the mean age of 42 years including 20% women and 65% patients in NYHA class III or IV) the univariate analysis revealed only a trend towards reduction of survival in patients with low TC concentration (p=0.067). The multivariate model however provided evidence for a significant impact on prognosis only of classical clinical parameters such as lower LVEF and higher functional NYHA class. These findings are consistent with the previous reports [36-38].

Study limitations

This is a retrospective study that involves a group of patients examined between 1992 and 2001. Lipid-lowering drugs were taken by only three patients with diagnosed dyslipidaemia. No impact of smoking on lipid levels was evaluated. No differences with respect to the prevalence of menopause were assessed, although examined and control groups were matched for age. Moreover, effects of therapy on both lipid abnormalities and survival were not investigated.

In conclusion, our data suggest that lipid abnormalities, particularly low HDL cholesterol and high triglyceride concentrations, may contribute to the development of DCM. Lipid parameters are not independent prognostic factors in this young group of DCM patients.

References

13. Lewis TV, Dart AM, Chin-Dusting JP. Endothelium-dependent relaxation by acetylcholine is impaired in hyperglycemic humans with normal levels of plasma LDL cholesterol. J Am Coll Cardiol 1999; 33: 805-12.


Znaczenie dyslipidemii u chorych z niewydolnością serca nieznanego pochodzenia

Mirostawiń Skwarek1, Zofia T. Bińńska2, Łukasz Mazurkiewicz1, Jacek Grzybowski1, Mariusz Kruk1, Paweł Kurjata1, Waleria Piotrowski2, Witold Rużyło1

1 I Klinika Choroby Wieńcowej, Instytut Kardiologii im. Prymasa Tysiąclecia Stefana Kardynała Wyszyńskiego, Warszawa
2 Pracownia Biostatystyki, Zakład Epidemiologii i Prewencji Chorób Układu Krążenia i Promocji Zdrowia, Instytut Kardiologii im. Prymasa Tysiąclecia Stefana Kardynała Wyszyńskiego, Warszawa

Streszczenie

Wstęp: Do niedawna oceniano znaczenie zaburzeń lipidowych w niewydolności serca jedynie pod kątem rokowniczym. Bardzo mało jest danych na temat znaczenia zaburzeń lipidowych w powstawaniu kardiomiopatii rozstrzępnionej (ang. dilated cardiomyopathy, DCM).

Cel: 1) ocena poziomów lipidów w surowicy chorych z DCM z uwzględnieniem zaawansowania niewydolności serca; 2) ocena związku występowania zaburzeń lipidowych z DCM; 3) ocena znaczenia rokowniczego parametrów lipidowych u chorych z DCM.

Metodyka: Grupę badaną stanowiło 100 chorych z DCM [średni wiek 42 lata, 80% mężczyzn, 60% w III–IV klasie wg NYHA, średnia frakcja wyrzutowa lewej komory (LVEF) 32%] z prawidłowymi tętnicami wieńcowymi w koronarografii, u których oznaczono lipidogram, badanych w latach 1992–2001. Wyniki badań lipidogramu chorych z DCM porównano z wynikami zdrowych osób (n=100), dobranych pod względem wieku, płci i wskaźnika masy ciała, a także odniesiono do próbek populacyjnych z badań WHO Pol-MONICA z lat 1993 (n=526), 1997/1998 (n=526) i 2001 (n=1364). Trzech (3%) chorych otrzymywało leczenie hipolipemizujące. W grupie badanej oceniono przeżycie bez przeszczepu. W analizie statystycznej stosowano test nieparametryczny Wilcoxona, regresję logistyczną jednowarstwową oraz model hazardów proporcjonalnych Coksa.

 Wyniki: Poziomy cholesterolu całkowitego (TC) oraz jego frakcji: LDL (LDL-C) i HDL (HDL-C) były nieznacznie niższe u chorych w klasie III–IV wg NYHA niż u chorych w klasie I–II (TC: 196,9±45,5 vs 207,9±47,1 mg/dl, LDL-C: 126,2±37,5 vs 128,5±42,7 mg/dl, HDL-C: 44,2±11,3 vs 44,7±13,7 mg/dl, odpowiednio), a trójglicerydów (TG) istotnie niższe w zaawansowanej DCM niż w I–II klasie wg NYHA (135,9±51 vs 170,3±63,4 mg/dl, p=0,004). U chorych z DCM poziom HDL-C był istotnie niższy niż u osób zdrowych (44,1±12,1 vs 54,3±17,6 mg/dl, odpowiednio, p<0,001), a poziom TG istotnie wyższy (147,9±58,1 vs 114,1±61,6 mg/dl odpowiednio, p<0,001). Poziomy HDL-C i TG w grupie kontrolnej były podobne jak w próbkach populacyjnych. W analizie wielowarstwowej z uwzględnieniem wieku, niskiego poziomu HDL-C (zdefiniowanego jako <40 mg/dl dla mężczyzn i <50 mg/dl dla kobiet) i hipertrójglicerydemii (hyperTG, TG ≥150 mg/dl) wykazano, że zarówno niski poziom HDL-C (OR=2,31, 95% CI 1,2–4,457, p=0,0122), jak i hyperTG (OR=1,978, 95% CI 1,029–3,799, p=0,0407) mają niezależny związek z występowaniem DCM. Niski poziom HDL-C występował znacznie częściej u kobiet z DCM niż u mężczyzn (65 vs 33,8%, p=0,022), stwierdzono tendencję do częstszego występowania hyperTG u mężczyzn niż u kobiet (42,5 vs 20%, p=0,11). Średni okres obserwacji w grupie badanej wynosił 7,32±4,7 roku. W analizie jednoczynnikowej Coksa stwierdzono tendencję do gorszego przeżycia u chorych z niskim poziomem TC (p=0,067), natomiast w analizie wielowarstwowej Coksa istotne rokowniczo okazały się klasa wg NYHA (HR=1,7, 95% CI 1,136–2,541; p=0,01) oraz LVEF (HR=0,963, 95% CI 0,932–0,996; p=0,027).

Wnioski: Dyslipidemia może odgrywać rolę w powstawaniu DCM. Niski poziom TC nie jest niezależnym czynnikiem rokowniczym w DCM.

Słowa kluczowe: niewydolność serca, kardiomiopatia rozstrzępniona, etiopatogeneza, rokowanie, dyslipidemia, lipidy

Kardiol Pol 2008; 66: 515-522

Adres do korespondencji:
doc. dr hab. n. med. Zofia Bińńska, I Klinika Choroby Wieńcowej, Instytut Kardiologii, ul. Alpejska 42, 04-628 Warszawa, tel.: +48 22 343 41 50, e-mail: zbilinska@ikard.pl