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Lipid profile in adult patients with Fabry disease - Ten-year follow up

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ABSTRACT

Background: Fabry disease, an X-linked genetic condition, results from alpha-galactosidase deficiency and increased accumulation of glycosphingolipids in cardiovascular tissues. Clinical manifestation includes vasculature associated complications. Hyperlipidaemia is one of the cardiovascular risk factors however it has never been well defined in Fabry disease. Enzyme Replacement Therapy (ERT) is available but its effect on serum cholesterol is unknown. The aim of this project was to assess the influence of long-term ERT on lipid profile in a large cohort of adult patients with Fabry disease.

Methods: This was a retrospective analysis of lipid profile results. Patients with Fabry disease were on ERT for 10 years, were not treated with statins and had no severe renal impairment. All patients had lipid profile measured before ERT was commenced and 6, 12, 24, 36, 48, 60, 120 months later. Statistical analysis included ANOVA, Student *t*-test and descriptive statistics.

Results: Among 72 patients, 40 were females (median age 45; range 29–75), 32 males (median age 46; range 20–69). There was no significant difference in total cholesterol or HDL-cholesterol measured at baseline before ERT was commenced and 6, 12, 24, 36, 48, 60 and 120 months after ERT was commenced in 72 patients (ANOVA; $P = 0.673$ and $P = 0.883$, respectively). Female patients on ERT had higher mean HDL-cholesterol as compared to female patients with Fabry disease who were asymptomatic and not treated ($P \geq 0.05$). Total cholesterol between treated and non-treated female patients was comparable. Female patients on ERT have higher total cholesterol and HDL-cholesterol when compared to lipid results in male patients on ERT. Total cholesterol/HDL-cholesterol ratio was low in female and male patients on ERT over 10 years.

Conclusion: Adult patients with Fabry disease have remarkably elevated HDL-cholesterol and as a result, elevated total cholesterol. It is possible that elevated HDL-cholesterol has a cardioprotective effect in patients with this condition. Long term ERT does not have a significant impact on lipid profile in female and male population with Fabry disease.

1. Introduction

Fabry disease (OMIM 301500), an X-linked genetic condition caused by alpha-galactosidase (EC 3.2.1.22) deficiency, is associated with increased accumulation of glycosphingolipids in cardiovascular tissues and leads to organ failure and premature death [1]. Affected male patients display clinical features of the disease but female carriers manifest with symptoms later in their life. The clinical manifestations consist of vasculature associated complications, but the pathophysiology is unclear. It was shown that the Fabry disease specific vascular lesions occur as a result of vascular dysfunction with major components being endothelial dysfunction, alterations in cerebral perfusion and athero-thrombogenesis [2,3]. Although some patients with Fabry disease may suffer from stroke by involvement of larger arteries, small-vessel disease causes cerebral complications and probably contributes to complications of the kidney and the heart [4,5,6].

Undoubtedly, other cardiovascular risk factors contribute to enhanced worsening of arterial performance. Hypercholesterolaemia with a markedly raised HDL-cholesterol was observed in patients with Fabry disease [7] and was previously associated with the occurrence of cardiovascular disease [8]. Atherosclerosis was previously described in several case studies [9,10,11].

Two forms of Enzyme Replacement Therapy (ERT) are available that may arrest the disease progression and reverse symptoms [12,13]. Treatment with ERT does not prevent the occurrence of new complications, although it is possible that earlier intervention may be more beneficial in this respect. It was demonstrated in a small study that ERT does not have a significant impact on total cholesterol, HDL-cholesterol,

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LDL-cholesterol and triglycerides [7]. Therefore, the aim of this project was to assess the influence of long-term ERT on lipid profile in a large cohort of adult patients with Fabry disease.

2. Methods

2.1. Study design and ethical consideration

This was a retrospective analysis of lipid profile results. All patients have their lipid profile requested as part of their routine care when attend our Metabolic Clinic appointments every 6 months. Data is documented in their Electronic Patient Record and was reviewed as part of a wider audit project to review practise and the benefit of routinely requested biochemical tests.

2.2. Patients

All patients included in the study had confirmed diagnosis of Fabry disease and were treated with Enzyme Replacement Therapy (alpha-galactosidase 1 mg/kg fortnightly) for 5–10 years. Entry criteria included: no statin therapy, eGFR > 60 mL/min and no proteinuria. The incidence of cardiovascular events, diabetes mellitus history and smoking history were reviewed. All patients had lipid profile measured before ERT was commenced and 6, 12, 24, 36, 48, 60, 120 months later.

2.3. Biochemistry tests

Serum lipid profile, including total cholesterol, HDL-cholesterol and triglycerides, was analysed using enzymatic method on Siemens Advia 2400 automated analyser in Clinical Biochemistry Department and expressed in mmol/L. LDL-cholesterol was calculated using Friedwald equation. Total cholesterol/HDL-cholesterol was automatically calculated.

2.4. Statistical analysis

Descriptive statistics: mean ± SD and median (minimum-maximum), were used to describe continuous variables. Percentages were calculated for categorical variables.

For normally distributed variables repeated measures, analysis of variance (ANOVA) was performed for testing the significance of the main effect of therapy (pre- vs. post-measures). The overall change in total cholesterol and HDL-cholesterol was calculated using ANOVA. The test was used to determine whether there was any significant difference between the means of independent groups of variables all together.

Changes in total cholesterol and HDL-cholesterol between male and female patients were analysed using two-tailed paired *t*-test and presented as means ± SD. Statistical tests were conducted using Stats Direct statistical software. *P*-value ≤ 0.05 was considered statistically significant.

3. Results

From 120 adult patients with Fabry disease, 72 met entry criteria and were included in the study (40 (56%) females, 32 (44%) males). Median age of female patients was 45 (29–75) and of male patients was 46 (20–69). Among female patients, 23 were treated with ERT for up to 10 years and 17 were asymptomatic and not treated. All male patients were treated with ERT.

Their lipid profile included complete sets of total cholesterol and HDL-cholesterol results at 8 different time points. LDL-cholesterol and triglycerides were not measured in all patients and results were missing.

3.1. Clinical presentation

Among females, none of patients had documented previous cardiovascular event i.e. stroke-like episode, 8 had arrhythmia, including 3 had pacemaker/defibrillator fitted. One had new onset diabetes mellitus. Among males, one patient had past medical history of cardiovascular event, 12 had arrhythmia, 4 had pacemaker/defibrillator inserted. No patients were treated with statins or had significant renal impairment. Patients were non-smokers or ex-smokers.

3.2. Genotype

In the female group: six patients had mutations N215S, five P259R, two Q119X, two G183S. The remaining mutations were: PE7X, C52G, G361R, R301Q, R342X, A257P, c.1184INSTAG, c.194 + 1G.A, c.677DEL G, c.695 T > C, c.7161NST, IVS2 + 4DELAG, IVS6-1G.A, P.6183S, P.A31V, P.G271D, P.T4101, P·W277C/P, T412 N, W287X.

In the male group, two patients had mutations A257P, seven N215S, two R112C, two R301Q and the remaining mutations were: P259R, Q119X, R227X, P293S, P342P, P.6183S, P.A31V, T141I, T412 N, Y88D, c.1011-1029DEL19, c.194 + 1G > A, c.350 T > G, c.793C > T, c.350 T > G, IVS2 + 4DELAG, IVS5-2DEL2BP.

3.3. Total cholesterol and HDL-cholesterol before and after ERT

There was no significant difference in total cholesterol or HDL-cholesterol measured at baseline and 6, 12, 24, 36, 48, 60 and 120 months after ERT was commenced in 72 patients (ANOVA; $P = 0.673$ and $P = 0.883$, respectively).

3.4. Total cholesterol and HDL-cholesterol in female patients on ERT vs no ERT

Overall, female patients on ERT had higher mean HDL-cholesterol as compared to female patients with Fabry disease who were asymptomatic ($P \geq 0.05$, Table 1B). Total cholesterol between treated and non-treated female patients was comparable (Table 1A).

3.5. Total cholesterol and HDL-cholesterol in female and male patients on ERT

Female patients on ERT have slightly higher mean total cholesterol and HDL-cholesterol compared to male patients on ERT (no statistical significance; $P \geq 0.05$, Table 2A and 2B).

Table 1A
Female patients on ERT vs non ERT; total cholesterol at baseline and at 6, 12, 24, 36, 48, 60 and 120 months of ERT. Normal cut off value for total cholesterol is < 5 mmol/L.

Mean total cholesterol (± SD)	Baseline	6 months	12 months	24 months	36 months	48 months	60 months	120 months
Females no ERT ($n = 17$)	5.1 ± 1.3	5.7 ± 1.4	4.9 ± 0.8	4.97 ± 0.9	5.38 ± 1.3	5.18 ± 1.2	5.2 ± 1	5.4 ± 1
Females ERT ($n = 23$)	5.16 ± 0.7	4.9 ± 0.5	5.4 ± 1	5.1 ± 1.16	5.11 ± 1	5.12 ± 0.97	5.32 ± 1	5.33 ± 1.2