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The factors affecting lipid profile in adult patients with Mucopolysaccharidosis

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ABSTRACT

Background: Mucopolysaccharidoses (MPS) are a group of rare inherited disorders characterized by abnormal accumulation of glycosaminoglycans (GAGs) within the myocytes and coronary arteries. Little is known about hyperlipidaemia as a potential cardiovascular risk factor in these patients. Baseline cholesterol data in adults are scarce. Therefore, the aim of this study was to analyse factors affecting lipid profile in different types of MPSs to determine if abnormalities in lipid profile contribute to the overall risk of cardiovascular disease.

Methods: Adult patients (above the age of 16) with MPS type I, II, III, IV and VI attending clinics in two Inherited Metabolic Disorders centres were included. Their lipid profile, lipoprotein (a), HbA1c, Glucose Tolerance Test (GTT), BMI and treatment type were extracted. Analysis included descriptive statistics and Student *t*-test.

Results: Eighty two patients with five MPS types (I, II, III, IV and VI) were included in the study; 29 were females (35%) and 53 were males (65%). BMI above 25 kg/m^2 in all MPS types indicated that some patients were overweight for their height. Only one patient post-HSCT had diabetes. In 3 cases insulin was analysed during GTT and showed no insulin resistance despite raised BMI. Mean total cholesterol and LDL-cholesterol were below 5 mmol/L and 3 mmol/L, respectively, in five individual MPS types. Lipoprotein (a) was available for 6 MPS IV patients and was not significantly raised.

Conclusions: MPS disorders are not associated with significant hypercholesterolaemia or diabetes mellitus despite increased BMI. Total cholesterol and LDL-cholesterol were within the targets for primary prevention for non-MPS population. Lipoprotein (a) is not a useful marker of cardiovascular disease in a small group of adult MPS IV patients irrespectively of treatment option. Whether long-term cardiovascular risk is dependent on lipid profile, diabetes, obesity or GAGs deposition within the organ system remains unanswered.

1. Introduction

Mucopolysaccharidoses (MPS) are a group of rare (incidence 1:25 000) inherited disorders characterized by abnormal accumulation of glycosaminoglycans (GAGs) such as dermatan, keratan, heparin and chondroitin sulfates. Alterations in GAGs metabolism has been shown to be involved in pathological processes, including anatomic and functional abnormalities, such as myxomatous mitral valves [1,2] aortic aneurysm [3], and atherosclerotic vasculature [4]. Cardiac valves (predominantly mitral and aortic) are thickened and become significantly regurgitant or stenotic. As a consequence, diffuse coronary artery stenosis, myocardial dysfunction and aortic root dilation often occur [5,6,7]. Dermatan-sulfated GAGs are a prominent component of normal cardiac valve tissue [8] that is a common feature of MPS I, II and VI and remains the main cause of cardiac valve disease [9,10,11,12] in these MPS types. The mechanisms by which the accumulated heparan-sulfated GAGs and attendant vascular interstitial cells affect the vasculature of the great vessels and coronary arteries in MPS I, II, and III remains unclear. It has been hypothesised that GAGs induce inflammation by activating the Toll-like receptor 4 pathway, leading to upregulation of degradative proteases [13].

Importantly, GAGs deposition within the epicardial coronary arteries initiates myointimal proliferation that contributes to severe and diffuse narrowing of these vessels [14,15]. The progressive coronary artery occlusion is a feature of Hurler syndrome [14] but coronary involvement in “non-Hurler” MPS is still not well understood. Both the presence and absence of coronary disease was alternatively reported in non-Hurler MPS types, including attenuated MPS I [6,9,15,16] however very little is known about the incidence or severity of coronary artery involvement in these conditions. Initially reported histological abnorm-

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Table 1
Baseline characteristics.

MPS type	MPS I					MPS II	MPS III	MPS IV		MPS VI	
Treatment type	ERT	HSCT				ERT	No treatment	No treatment	ERT	No treatment	ERT
n	16 (9 females,7 males)	12 (3 females, 9 males)				16 males	4 (2 females, 2 males)	19 (8 females, 11 males)	5 (2 females, 3 males)	3 (2 males, 1 female)	7 (4 females, 3 males)
Age (years) mean ± SD	32.6 ± 10.3	24.6 ± 5.8				27.8 ± 11.6	27.5 ± 4	32.3 ± 11	29.6 ± 8.7	26.3 ± 2.1	34.3 ± 17.4
HbA1c mean ± SD (< 42 mmol/mol)	34.5 ± 8.8 (n = 6) 1 patient post-HSCT: HbA1c 47.5 mmol/mol confirms diabetes mellitus					31.75 ± 3.7 (n = 5)	n/a	34.8 ± 2 (n = 6)		33.5 ± 2.6 (n = 4)	
Glucose tolerance test (GTT: fasting < 7, 2 h < 11 mmol/L)		Fasting glucose: mean 4.36 mmol/L 2-h glucose: mean 6.17 mmol/L (n = 11)									
GTT & insulin (2.3–26 pmol/L) (n = 3)		F. glucose (mmol/L)	Insulin (pmol/L)	2-h glucose	Insulin (pmol/L)						
		3.9	64.3	7.1	170						
		4.6	41.3	6.1	521						
		4.5			583						
BMI (kg/m^2) mean ± SD (< 25 kg/m^2)	23.7 ± 3.5	23.65 ± 6.3				28 ± 4.7	n/a	28.5 ± 8	24.3 ± 3.23	26.6 ± 5.2	24.6 ± 7.6

alities of the MPS aorta included increased thickness of the aortic intima from the presence of GAG and atherosclerotic plaque, foam cells and macrophages [14]. Subsequent histopathological post-mortem examination of MPS specimens showed GAGs storage and myointimal proliferation in wall vessels but no atheromatous plaque formation [17,18,19,20].

Estimating the risk of coronary artery disease in patients with MPS disease is vital because coronary artery disease can increase morbidity and mortality. The presence of significant coronary narrowing is an important risk factor for individuals undergoing surgical correction of skeletal manifestations of the disease [21]. While complications related to coronary artery stenosis are being recognized as potentially fatal manifestations of MPS [18,22,23], there are currently no validated biomarkers of cardiovascular or coronary artery disease in these patients. It is important to predict the coronary artery risk in MPS conditions that is not currently possible based purely on the knowledge about the effect of GAGs pathophysiology on vasculature.

Haematopoietic stem cell transplantation (HSCT) and enzyme replacement therapy (ERT) have changed the previously life-limiting natural history of the MPSs and improved their survival well into adulthood. Although the positive effect of HSCT and ERT on ventricular function, with no effect on cardiac valve pathology, has been previously recognized [24,25,26,27], little is known about hyperlipidaemia as a potential cardiovascular risk factor in this cohort of patient. Baseline cholesterol data in adults are scarce, reported only for MPS I [28] where it was found to be normal.

Therefore, the aim of this study was to analyse factors affecting lipid profile in different types of MPSs to determine if abnormalities in lipid profile contribute to the overall risk of cardiovascular disease.

2. Methods

2.1. Study design and ethical consideration

It was a retrospective audit of our clinical practice. All patients have their blood tests (lipid profile, HbA1c, GTT) requested as part of their routine care when attend our Metabolic Clinics appointments every 6 months. We follow the protocol developed in collaboration with adult endocrinology team. It was implemented as our clinical guidelines after input from the paediatric metabolic and endocrinology teams who previously cared for the majority of these patients.

2.2. Patients and clinical examination

Adult patients (above the age of 16) with MPS type I, II, III, IV and VI attending Metabolic Clinics at two Inherited Metabolic Disorders specialist centres were included in the study. Age, gender, MPS type, Body Mass Index (BMI; kg/m^2) and treatment type; enzyme replacement therapy (ERT) or haematopoietic stem cell transplantation (HSCT) were extracted. None of patients sustained any cardiovascular event or surgery within 12 months when lipids where measured.

2.3. Biochemistry tests

Serum lipid profile included total cholesterol, HDL-cholesterol and triglycerides were 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. Lipoprotein (a) measured using immunoassay method (mg/dL). Glucose Tolerance Test was used to screen for increased glucose intolerance or diabetes. The measurement of HbA1c (mmol/mol) using chromatography assay was used to screen for diabetes.

2.4. Statistical analysis

Descriptive statistics mean (SD) and median (range) were used to describe patients' demographic and clinical characteristics for continuous variables. Percentages were calculated for categorical variables. Student t-test was used to estimate the statistical significance of a difference in lipids between two groups.

The results were presented as means with ± SD. Statistical tests were conducted using Analyse-it (v4.00.1). A p-value ≤ 0.05 was considered statistically significant.

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