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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.

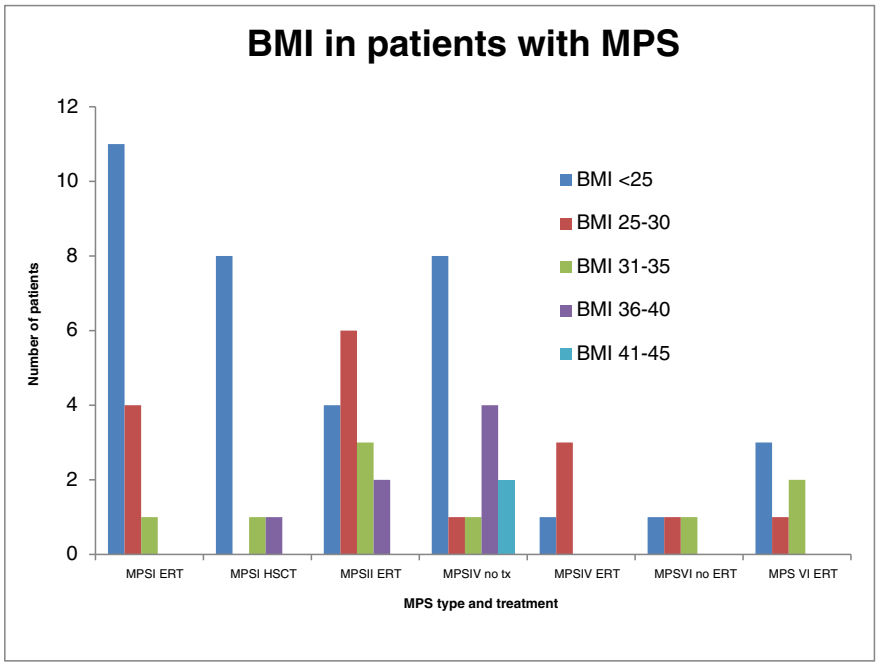

Fig. 1. Distribution of BMI (kg/m^2) in patients with MPS disorders.

3. Results

3.1. Basic characteristics

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%). Patients' characteristics were summarized in Table 1.

3.2. BMI vs insulin resistance

BMI above 25 kg/m^2 in all MPS types indicated that most patients were overweight. Among MPS I patients 3 were obese (BMI above 30 kg/m^2). Among 16 MPS II patients, 3 had BMI > 30 kg/m^2 and 2 had BMI > 35 kg/m^2. Among 24 MPS IV patients 4 of them had BMI > 35 kg/m^2, 1 had BMI > 30 kg/m^2 and 2 had BMI > 40 kg/m^2. Among 10 MPS VI patients, 3 had BMI > 30 kg/m^2 (Table 1 and Fig. 1).

Glucose tolerance test (GTT) results were available for 11 MPS I patients post-HSCT and HbA1c results were available for patients with MPS I, II, IV and VI and was below 42 mmol/mol (Table 1). Only one patient post-HSCT had diabetes and it was likely to have been associated with steroids treatment. In 3 cases, insulin was analysed during GTT and showed no insulin resistance despite raised BMI (insulin was < 600 pmol/L at 2 h).

3.3. Lipid profile

The mean values of total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides were calculated for five individual MPS types. Patients were grouped respectively of the treatment option; ERT, HSCT or none (Table 2). *P* value was calculated accordingly. There was no statistically significant difference in lipid profile between MPS I patients on ERT and post-HSCT. There was no statistically significant difference between patients with MPS IV on ERT and those who were not treated. Statistical difference between lipids in MPS VI patients on ERT and those who did not have any therapy was unremarkable (Table 2). Mean total cholesterol and mean LDL-cholesterol for individual MPS types are lower compared to targets for primary prevention (< 5 mmol/L and < 2 mmol/L, respectively).

Table 2
Lipids in various MPS types.

MPS type	Treatment (n)		Total cholesterol (< 5 mmol/L)		Triglycerides (< 1.7 mmol/L)		HDL-cholesterol (< 1.2 mmol/L)		LDL-cholesterol (< 3 mmol/L)		Lipoprotein (a) (< 30 mg/dL
MPS I	ERT	HSCT	4.6 ± 0.87	4.68 ± 0.95	0.63 ± 0.24	1.5 ± 1.02	1.6 ± 0.44	1.4 ± 0.49	2.4 ± 0.77	2.3 ± 1.1	
	n = 16	*n* = 12	*p* = 0.85		*p* = 0.07		*p* = 0.31		*p* = 0.77		
MPS II	ERT		4.32 ± 0.82		1.24 ± 0.8		1.36 ± 0.26		2.56 ± 0.85		
	n = 16										
MPS III	No treatment		4.125 ± 0.99		1.4 ± 0.85		0.74 ± 0.34		2.7 ± 0.85		
	n = 4										
MPS IV	ERT	No treatment	4.6 ± 0.34	4.69 ± 0.9	1.11 ± 0.29	1.17 ± 0.65	1.7 ± 0.4	1.55 ± 0.5	2.38 ± 0.21	2.57 ± 0.69	15.12 ± 13.05 Median 11.6 Range (2.2–33.4)
	n = 5	*n* = 19									*n* = 6
			p = 0.83		*p* = 0.86		*p* = 0.5		*p* = 0.59		
MPS VI	ERT	None	3.97 ± 1.3	3.6 ± 0.53	0.8 ± 0.3	0.97 ± 0.25	1.25 ± 0.42	1.11 ± 0.34	1.95 ± 0.77	2.07 ± 0.32	
	n = 7	*n* = 3	*p* = 0.04		*p* = 0.54		*p* = 0.14		*p* = 0.14		

Mean ± SD. Lipids expressed in mmol/L; HSCT - Haematopoietic Stem Cell Transplant; ERT - Enzyme Replacement Therapy.

3.3.1. Lipids in a child vs adult MPS I post-HSCT

In one patient with MPS I post-HSCT lipid profile was measured at the age of 13 and later at the age of 18 years, after the transition to the Adult Inherited Metabolic Disorders. Overall, there was no significant discrepancy in lipid profile with total cholesterol of 3.8 vs 4.2 mmol/L, HDL-cholesterol 1.43 vs 1.2 mmol/L, LDL-cholesterol 2.1 vs 1.7 mmol/L. Triglycerides were higher at 2.9 mmol/L at the age of 18 as compared to 0.6 mmol/L at the age of 13 years. Total cholesterol/HDL-cholesterol ratio was 2.68 at 13 years vs 3.5 at 18 years.

3.3.2. Lipids in patients with MPS II pre- and post-ERT

In two patients with MPS II non-fasting lipid profile was available before they were commenced on ERT and during ERT. In one patient pre- and during ERT, total cholesterol was 5.5 vs 4.9 mmol/L, HDL-cholesterol was 2.06 vs 1.75 mmol/L and total cholesterol/HDL-cholesterol was 2.7 vs 2.8.

In another patient pre- and during ERT, total cholesterol was 3.9 vs 4.2 mmol/L, HDL-cholesterol 1.53 vs 1.49 mmol/L and total cholesterol/HDL cholesterol ratio was 2.5 vs 2.8 respectively. In both cases lipid profile pre- and during ERT were similar.

3.3.3. Lipids in a patient with MPS VI pre- and post-ERT

In one patient with MPS VI lipid profile was measured pre- and during ERT. Total cholesterol was 4 vs 5.9 mmol/L, HDL-cholesterol was 1.43 vs 1.33 mmol/L and total cholesterol/HDL-cholesterol ratio was 2.8 vs 4.4, pre- and during ERT respectively.

3.3.4. Lipoprotein (a)

Lipoprotein (a) was available for 6 MPS IV patients and was not significantly raised (Table 2). In one patient lipoprotein (a) was measured before ERT was commenced and 9 weeks into the ERT. Both results were not dissimilar: 3.4 and 4.7 mg/dL respectively.

4. Discussion

This study presents the largest set of lipid profile results in adult patients with five different types of MPSs. Overall we found that MPS disorders are not associated with hypercholesterolaemia or diabetes mellitus despite raised BMI.

The analysis showed that total cholesterol and LDL-cholesterol in our MPS patients were not raised above the target (< 5 mmol/L) outlined for non-MPS patients and mean LDL-cholesterol was within the target (< 3 mmol/L) for healthy non-MPS population [29]. Lipoprotein (a), a marker of increased cardiovascular disease, was not raised before or during ERT in six patients with MPS IV. These results were contrary to previously described findings by Hendriksz who found out that lipoprotein (a) is raised in MPS IV patients obtaining ERT and suggestive of the overall increased cardiovascular risk [30]. Our findings would be consistent with the previously documented lack of atherosclerotic plaque in histopathological examination of MPS specimens [17,18,19,20]. It is highly suggestive that serum lipids do not yield a significant effect on atherosclerosis in arteries and indirectly on cardiovascular risk in this group of patients.

One of possible explanations of low serum cholesterol is the presence of accumulating unesterified cholesterol in the cell bodies of neurons and glia in brain. In view of the absence of increases in total cholesterol, possible shifts in the distribution of the cholesterol rather than absolute increases have been suggested [31]. To support this hypothesis, some studies examined cholesterol storage in neuronal cell bodies versus axons in culture which appeared to show elevated perikaryal cholesterol but decreased axonal cholesterol [32]. This accumulation occurs as cholesterol granules in cell bodies of neurons and glia and has been reported in a wide spectrum of lysosomal diseases, including Niemann-Pick C disease [33,34], GM1 and GM2 gangliosidosis, α-mannosidosis [35] as well as MPS I, II, IIIA, and VI diseases [36,37,38].

In our study we did not observe any association between concentration of serum cholesterol and high BMI in MPS patients. We showed that MPS patients in general have a higher BMI. A study by Marcelino et al. showed that not only low weight and low height were found in MPS patients but 25% of the BMI scores were classified as obese [39]. High proportion of patients with intellectual disabilities has been shown to be overweight and obese [40]. High BMI in our MPS cohort, in particular MPS IV, might be due to loss of motor function, resulting in a lack of physical activity. A higher BMI might also be explained by the use of psychotropic medication (e.g., risperidone), which is frequently used for MPS III patients to control behavioural disturbances [41,42].

Patients with MPS are characterized by a higher degree of adiposity as evidenced by relatively high values of the parameters relating to global adiposity and the cross-sectional area of arm adipose tissue. They also display a lower level of musculature development in comparison to their non-MPS population [43]. Reduced adiposity due to dysfunctional or absent adipocytes can result in severe insulin resistance [44]. In our cohort of patients we did not observe diabetes apart from one case of MPS I post-HSCT. In our study, glucose and insulin tolerance test results measured in three patients showed normal response that was in keeping with an experimental study results [44]. MPS I mice had normal fasting plasma insulin levels. Furthermore, MPS I mice had normal responses to both glucose and insulin tolerance tests. Therefore, it appeared that MPS I mice suffer from depletion and/or a failure of triglyceride deposition in adipocytes and not dysfunctional adipocytes. Reduced adiposity could be due to reduced caloric intake or lipid malabsorption [44]. Another experimental study on mice with lysosomal storage diseases, including MPS I, MPS IIIB, MPS VII, Niemann-Pick types A and B, and neuronal ceroid lipofuscinosis, observed decrease of adiposity in mice with these conditions [45].

Insulin resistance, however, has been found in patients with other lysosomal storage diseases such as Gaucher disease type 1 [46]. It has been hypothesised that GM3 ganglioside levels, that are increased in tissues of patients with Gaucher disease [47], are known to modify insulin receptor signalling substantially. In the absence of GM3 ganglioside, insulin receptor autophosphorylation is enhanced leading to increased insulin sensitivity [48]. In contrast, increased GM3 ganglioside levels impair insulin receptor signalling [49]. This increased level of GM3 ganglioside may explain the insulin resistance found in patients with Gaucher disease type 1. Importantly, it has been previously suggested that GM3 and GM2 are involved in GAGs accumulation and therefore in inhibiting the activity of additional lysosomal hydrolases in MPS disorders [38]. Therefore, we may hypothesised that GM3 may also be involved in insulin resistance in patients with MPS.

In our study patients with MPS I obtained HSCT or ERT and mean fasting cholesterol was no different between these two groups. These results were comparable to the outcomes of previous studies [19,50] which showed that mean fasting triglycerides, LDL-cholesterol, HDL-cholesterol and total cholesterol in the MPS cohort were no different between those who had received HSCT and those who did not. These studies, however, compare lipids post-HSCT versus non-HSCT patients and not versus ERT as an alternative therapy.

The progression of coronary artery narrowing and occlusion from myointimal proliferation in rapidly progressing MPS I appears to be reduced after successful HSCT [19]. It plays a significant role in prolonged survival in these patients [51,52]. An increased risk of premature cardiovascular disease is a long-term effect of HSCT however the study by Tichelli et al. showed that coronary arteriopathy rather than the anticipated atherosclerostic changes are observed in MPS patients after HSCT [53]. Atherosclerotic changes may be observed in adult MPS patients post-HSCT much later in their life [53]. Regression of pathological changes in coronary arteries has been shown in one case with MPS IH 14 years after HSCT [19].

Additionally, serum cholesterol was not different in our patients with MPS II, IV and VI who obtained ERT versus patients of these three

MPS types who were treatment naïve. ERT, as an alternative treatment method, has been previously shown to be associated with the rapid increase in cholesterol in liver that was observed in experimental study on mice [45]. It was suggested that conversion of GAGs and/or membrane to lipids, reduced lipids catabolism and an increased influx of cholesterol are possible mechanisms of the lipid storage in liver of mice on ERT [45].

One of the limitations of this study was the small number of results in some MPS types. In particular among patients with MPS III, the available lipid profile results were limited. Most of our patients with MPS III have learning disabilities and therefore have no capacity to consent for routine blood tests. Due to the results necessarily being divided into small groups according to MPS type, the limited data available preclude definitive statements.

In conclusion, our findings strongly suggest that 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 adult MPS patients. Lipid profile should not be considered in the overall assessment of cardiovascular risk in MPS disorders. Predominantly low serum cholesterol concentration does not merit routine repetition of lipid profile in this cohort of patients who, in addition, do not require life-long treatment with statins. This saves the cost and inconvenience to the patients of repeated testing.

Whether long-term cardiovascular risk is dependent on lipid profile, diabetes, obesity or GAGs deposition within the organ system remains unanswered. Further research is needed to explore potential causes of increased cardiovascular risk in these patients, with the measurement of carotid intimal thickness as a potential surrogate marker of coronary artery disease.

Conflict of interest

KS received travel grants from Genzyme, Shire and Amicus. No conflict of interest for this publication.

FS received honoraria and travel grants from Genzyme, Biomarin and SHIRE. No conflict of interest for this publication.

CH is a Consultant for Actelion, Biomarin, Chiesi Inventiva, Sanofi, Genzyme and Shire and is owner director of FYMCA Medical Ltd. No conflict of interest for this paper.

Contributions

KS analysed all data and prepared the first draft of the manuscript.

FS extracted data for her MPS patients.

CH was the initiator of this project and contributed to the final version of the manuscript.

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