The prevalence and clinical impact of obesity in adults with Marfan syndrome

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BACKGROUND: Patients with Marfan syndrome characteristically have an asthenic body habitus and are considered to be exempt from the obesity epidemic.

OBJECTIVE: To examine the prevalence and clinical impact of obesity in a cohort of adults with Marfan syndrome.

METHODS: Fifty outpatients (30 female) with a mean ($\pm$ SD) age of 38 ± 13 years were studied. Demographic variables including previously identified risk factors for aortic dissection were recorded. Body mass index (BMI) was determined and patients were classified as normal (BMI less than 25 kg/m^2), overweight (BMI 25 kg/m^2 to 29.9 kg/m^2) or obese (BMI 30 kg/m^2 or greater). Other cardiovascular risk factors were examined. An adverse clinical outcome was defined as either the attainment of surgical criteria for aortic root replacement or the presence of aortic dissection.

RESULTS: A family history of aortic dissection was present in 13 (26%) patients. In 23 (46%) patients, there was no known family history of Marfan syndrome. Mean BMI was $25.4 \pm 7.4 \text{ kg/m}^2$, with 18 (36%) patients having an elevated BMI. Positive smoking status was present in 15 (30%), hypertension in 13 (26%) and hyperlipidemia in 19 (38%) patients. Adverse clinical outcome was present in 27 (54%) patients. Logistic regression analysis revealed only index case (OR 44; $P < 0.001$) and higher BMI (OR 1.2; $P = 0.04$) to be significantly and independently associated with increased risk of adverse clinical outcome.

CONCLUSIONS: Obesity is common in adults with Marfan syndrome and is associated with an increased risk of aortic complications.

Key Words: Aorta; Marfan; Obesity

La prévalence et les répercussions cliniques de l'obésité chez des adultes ayant le syndrome de Marfan

HISTORIQUE : Les patients ayant le syndrome de Marfan ont un phénotype corporel asthénique caractéristique et sont considérés comme épargnés par l'épidémie d'obésité.

OBJECTIF : Examiner la prévalence et les répercussions cliniques d'obésité dans une cohorte d'adultes ayant le syndrome de Marfan.

MÉTHODOLOGIE : Cinquante patients ambulatoires (30 femmes), d'un âge moyen ($\pm$ ÉT) de 38 ± 13 ans, ont fait l'objet de l'étude. Les chercheurs ont enregistré les variables démographiques, y compris les facteurs de risque déjà établis de dissection aortique. Ils ont déterminé l'indice de masse corporelle (IMC) et ont classé les patients comme normaux (IMC inférieur à 25 kg/m^2), faisant de l'embonpoint (IMC de 25 kg/m^2 à $29,9 \text{ kg/m}^2$) ou obèses (IMC de 30 kg/m^2 ou plus). Ils ont examiné d'autres facteurs de risque cardiovasculaire. Une issue clinique négative était définie comme l'atteinte des critères chirurgicaux de remplacement de l'anneau aortique ou la présence d'une dissection aortique.

RÉSULTATS : Les auteurs ont constaté des antécédents familiaux de dissection aortique chez 13 patients (26 %). Vingt-trois patients (46 %) ne présentaient aucuns antécédents familiaux connus de syndrome de Marfan. L'IMC moyen était de $25,4 \pm 7,4 \text{ kg/m}^2$, 18 patients (36 %) ayant un IMC élevé. Les auteurs ont remarqué un tabagisme chez 15 patients (30 %), de l'hypertension chez 13 patients (26 %) et de l'hyperlipidémie chez 19 patients (38 %). Ils ont observé une issue clinique néfaste chez 27 patients (54 %). L'analyse de régression logistique a révélé que seuls le cas de référence (RRR 44; $P < 0,001$) et d'IMC plus élevé (RRR 1,2; $P = 0,04$) s'associaient de manière significative et indépendants à un risque accru d'issue clinique négative.

CONCLUSIONS : L'obésité est courante chez les adultes ayant le syndrome de Marfan et s'associe à un risque accru de complications aortiques.

Despite improvement in survival noted throughout the past few decades (1), patients with Marfan syndrome remain at risk for premature death secondary to the cardiovascular complications of aortic dilation and dissection (2). Risk factors for such complications remain poorly defined, thereby impeding attempts at risk stratification for the individual patient. Family history of aortic dissection (3) and spontaneous genetic mutations (4) have been identified as risk factors but, currently, no potentially modifiable risk factors have been elucidated.

The underlying biomechanical abnormalities in Marfan syndrome have been well described. Patients with Marfan syndrome have reduced aortic distensibility, which becomes progressively more abnormal with increasing age (5). These biomechanical abnormalities precede the vascular complication of aortic dilation and dissection, and may reflect both endothelial and vascular smooth muscle cell abnormalities of the aortic wall (6-8).

The current obesity epidemic has been the subject of much lay and scientific attention. Obesity, hyperlipidemia, smoking and hypertension have been established as clear risk factors for atherosclerotic arterial disease (9). These risk factors predispose to impaired vascular endothelial function, thereby increasing the risk of vascular complications including coronary arterial obstructive disease and stroke (10). Marfan syndrome is characteristically associated with an asthenic body habitus; as a result, these patients have been considered to be exempt from the current obesity epidemic.

We sought to determine the prevalence of obesity and overweight in an adult cohort of patients with Marfan syndrome, to assess the prevalence of other cardiovascular risk factors among this patient group – namely smoking, hyperlipidemia, diabetes and hypertension – and to determine what, if any, clinical impact such risk factors had on outcome in this patient cohort.

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TABLE 1
Characteristics of the patients (n=50) and their association with the presence of an adverse clinical outcome*

Variable	Value	Univariate		Multivariate	
		OR (95% CI)	P	OR (95% CI)	P
Sex, male:female (% female)	20:30 (60)	1.9 (0.58–6.0)	0.30		
Age at diagnosis, years, median (range)	21 (<1–50)	1.0 (0.98–1.1)	0.27		
Current age or age at death, years, mean $\pm$ SD	38 $\pm$ 13	1.04 (0.99–1.09)	0.14		
Index case, n (%)	23 (46)	30.0 (5.6–162)	<0.001	44 (7.0–281)	<0.001
Family history of aortic dissection, n (%)	13 (26)	0.38 (0.10–1.4)	0.15		
Body mass index, kg/m ² , mean $\pm$ SD	25.4 $\pm$ 7.4	1.1 (0.99–1.2)	0.08	1.14 (1.01–1.27)	0.04
Body mass index category, n (%)					
Normal	32 (64)	1.0			
Overweight	7 (14)	2.8 (0.5–17)	0.15		
Obese	11 (22)	3.0 (0.7–14)	0.26		
Smoking, n (%)	15 (30)	8.7 (1.7–44)	0.01		
Hyperlipidemia, n (%)	19 (38)	8.4 (2.0–35)	0.004		
Hypertension, n (%)	13 (26)	2.1 (0.56–8.2)	0.27		
Number of cardiovascular risk factors (of 4) [†] , median (range)	2 (0–4)	2.9 (1.4–5.9)	0.003		
Number of cardiovascular risk factors (category), n (%)					
None	14 (28)	1.0			
1	16 (32)	3.7 (0.7–18)	0.12		
2	12 (24)	18 (2.5–133)	0.005		
3 or 4	8 (16)	26 (2.2–298)	0.01		

*Determined by logistic regression. Adverse clinical outcome defined as attainment of an aortic root diameter of 55 mm requiring surgical intervention or the presence of aortic dissection; [†]Cardiovascular risk factors included male sex, smoking, hypertension and hyperlipidemia. Obesity was not included in the calculation of the number of risk factors to allow for determination of the independent effect of body mass index

METHODS

The present institutional ethics board-approved study was conducted at a tertiary care centre with a Marfan subspecialty cardiology clinic receiving referrals from a population base of four million persons. Patients included in the study were those diagnosed with Marfan syndrome – in accordance with the revised Ghent criteria (11) – who had not undergone surgical intervention at the time of enrollment in the study and who were followed serially during the period from 2003 to 2006.

Demographic data – including age at diagnosis, current age or age at adverse outcome, weight, height and medications – were recorded. Previously identified risk factors for adverse outcome – including absence of a family history of Marfan syndrome, family history of aortic dissection in the setting of Marfan syndrome, and sex – were noted.

Cardiovascular risk factors were considered individually, as well as a combined total for number of risk factors. Smoking status was recorded. Body mass index (BMI) was calculated for all patients. Patients were classified as underweight (BMI of less than 18.5 kg/m²), normal weight (BMI of 18.5 kg/m² to 24.9 kg/m²), overweight (BMI of 25 kg/m² to 29.9 kg/m²) or obese (BMI of 30 kg/m² or greater) in accordance with the Centers for Disease Control and Prevention (USA) classification (12). All patients underwent a fasting lipid profile test with quantification of total cholesterol, high-density lipoprotein, low-density lipoprotein and triglycerides. Patients received treatment for hyperlipidemia based on the current standard of care determined by their primary caregiver. Patients were classified as having hyperlipidemia if they were placed on medical therapy, or if they had a low-density lipoprotein level of greater than 3.3 mmol/L or a total cholesterol level of greater than 5.2 mmol/L. All patients had a fasting blood glucose test performed, and a level of 6.1 mmol/L or greater was considered elevated (12). All patients were taking atenolol for prevention of aortic complications because this was historically the standard therapy for adult patients at The University Hospital, University of Colorado Health Sciences Center (Colorado, USA). Patients were considered hypertensive if they had documented hypertension (blood pressure of 140/90 mmHg or greater) before starting medical therapy, or had a blood pressure of 130/80 mmHg or greater on

standard medical therapy (atenolol 50 mg/day), thereby necessitating escalation of medical therapy. All patients were mobile without assistance, but all were sedentary as defined by aerobic exercise of less than 30 min per session fewer than three times per week.

The presence or absence of an adverse outcome, defined as attainment of an aortic root diameter of 55 mm requiring surgical intervention (13), or the presence of aortic dissection was noted.

Data are described as frequencies, medians with ranges or mean $\pm$ SD as appropriate. Mantel-Haenszel χ^2 analysis was used to determine any trend between the number of cardiovascular risk factors (hypertension, hyperlipidemia, smoking and male sex) and overweight and obesity. Logistic regression analysis was used to determine the univariate and multivariate relationship of variables with the composite adverse outcome. All analyses were performed using SAS statistical software version 9.1 (SAS Institute Inc, USA) using default settings.

RESULTS

Fifty patients (20 male and 30 female) were studied. Descriptive characteristics and the prevalence of cardiovascular risk factors are shown in Table 1. The median weight and height for the entire patient cohort was 83 kg (range 50 kg to 152 kg) and 180 cm (range 165 cm to 205 cm), respectively. Using the BMI criteria described above, 11 (22%) patients were classified as obese, and 18 (36%) patients as overweight or obese. The mean BMI was 25.4 $\pm$ 7.4 kg/m².

Adverse outcome, as defined above, was present in 27 (54%) patients. In univariate logistic regression, an increased risk of the composite adverse outcome was significantly associated with the absence of a family history of Marfan syndrome (index case), increasing number of cardiovascular risk factors, and the presence of smoking and hyperlipidemia (Table 1). In multivariable logistic regression, the absence of a family history of Marfan syndrome remained a significant risk factor (OR 44; P<0.001), and higher BMI became significantly and independently associated with increased risk (Hosmer-Lemeshow goodness-of-fit P=0.59; c-statistic 0.90). Also, there was a trend toward an increasing number of cardiovascular risk factors significantly associated with an increased risk of adverse outcome after adjustment for the absence of a family history of Marfan

syndrome (OR 2.1; $P=0.08$), but not in the presence of BMI ($P=0.18$). There was no significant association between the number of cardiovascular risk factors and BMI (Spearman correlation $r=0.12$, $P=0.39$) and, thus, no evidence of colinearity. After controlling for the absence of a family history of Marfan syndrome and BMI, no other factor was significantly and independently associated with an increased risk of the composite adverse outcome.

DISCUSSION

Obesity is common in adults with Marfan syndrome in the United States. The prevalence of obesity among the present study's Marfan population was not significantly different from the 20% incidence of obesity in the general population of the state in which these patients resided (12). The increased prevalence of obesity is not without clinical effect. We have documented a significantly higher rate of aortic complications in patients with a greater BMI. This is not surprising. Adipose tissue is a profoundly active endocrine organ (14) responsible for the release of several different cytokines and vasoactive substances that can adversely affect aortic histology and aortic biomechanics. These factors include angiotensin II, angiotensin-converting enzyme (ACE) and transforming growth factor-beta. In animal models, angiotensin II infusion leads to increased matrix metalloproteinase activity in the vasculature, resulting in vascular smooth muscle cell apoptosis and aneurysm formation (15). In addition, higher ACE levels occurring in the setting of an ACE gene variant (DD genotype polymorphism) are associated with a greater propensity for aortic aneurysm (16). Transforming growth factor-beta activity is increased in the vasculature of patients with Marfan syndrome and is believed to play an integral role in disease progression (17). In addition to these structural changes, these vasoactive modulators have a detrimental effect on endothelial function, resulting in impaired vasodilation (18,19). As expected, other cardiovascular risk factors that adversely affect vascular function, including hyperlipidemia and

smoking status, were associated with adverse outcome on univariate analysis. However, increased BMI overshadowed the impact of all other risk factors on multivariate analysis.

Limitations

It is not at all clear how one should best characterize obesity in patients with connective tissue disorders. The bioelectrical impedance properties of the connective tissues in these patients is unknown, making bioelectrical impedance measurements limited in value. Similarly, given the cutaneous laxity and altered connective tissue properties of these patients, body fat assessment using caliper measurement or measured waist circumference is likely to lead to an overestimation or underestimation of body fat, respectively. We chose to use the current Centers for Disease Control and Prevention definition of obesity to avoid these pitfalls, but realize that such definitions may underestimate obesity in these patients due to their relatively long limbs and increased sitting height to stature ratio (20). Thus, we may have underestimated the prevalence of obesity in Americans with Marfan syndrome. Another potential limitation of these data is that we found no relationship between hypertension, as defined herein, and adverse outcome. This is not entirely surprising because resting blood pressure in all patients was maintained in the normal range with additional medical therapies. Twenty-four hour blood pressure assessment was not performed, but may be of some value to ensure adequate blood pressure control, given that hypertension adversely affects aortic biomechanical properties (18).

SUMMARY

Obesity is common among adults with Marfan syndrome. Such patients have historically been counselled to avoid strenuous activities, which has often been translated into avoiding any physical activity. Such patients need to be counselled regarding the prevention of obesity, and should be encouraged to participate in dietary and exercise programs that will allow them to achieve these goals.

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