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Severe Pulmonary Hypertension in Postmenopausal Obese Women

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Abstract

Context: Severe pulmonary hypertension (PH) is a rare disorder triggered by a variety of factors and disease conditions and characterized by a shared pathophysiology. Two decades ago it was widely held that "primary" (idiopathic) pulmonary hypertension (PPH) is a disease of young women. However, we noticed recently in the UCHSC Pulmonary Hypertension Center that women with severe PH are frequently postmenopausal and overweight or obese.

Objectives: To determine whether severe PH is a disease not only of young women but also of postmenopausal women who are overweight or obese.

Design, Setting, and Participants: The medical records of 541 postmenopausal female patients at the UCHSC Pulmonary Hypertension Center were reviewed. The patients were divided into two groups based on their diagnosis of either primary or secondary PH.

Main Outcome Measures: The medical records of postmenopausal women with severe PH were further reviewed for history of diabetes, systemic hypertension, and the use of anti-depressants, hormone replacement therapy, combination of anti-depressants and hormone replacement therapy, as well as anorexigens. Laboratory data such as elevated cholesterol, elevated uric acid, and elevated C-reactive protein (CRP) were recorded in these patients, as well as physical exam data to determine the body-mass index (BMI) of the patients.

Results: 56% of all pulmonary hypertensive women who were patients at the UCHSC Pulmonary Hypertension Center were postmenopausal. 39% of postmenopausal women with PPH and 48% with secondary severe PH were obese. In addition, postmenopausal obese women frequently had systemic hypertension and were on hormone replacement therapy as well as antidepressant medication.

Conclusions: Obesity, hormone replacement therapy and anti-depressant therapy may contribute to the development of severe PH in genetically predisposed women. Further investigation, in the form of a prospective, case-control study, is needed to determine whether these factors exert a causative effect in postmenopausal women.

Key words: Severe pulmonary hypertension, obesity, menopause, anorexigen

Abbreviations: PH = pulmonary hypertension, PPH = "primary" (idiopathic) pulmonary hypertension, UCHSC = University of Colorado Health Sciences Center, COMIRB = UCHSC institutional review board, CRP = C-reactive protein, BMI = body-mass index, VEGF = vascular endothelial growth factor, KDR = VEGF receptor II

Introduction

Severe pulmonary hypertension (PH) [1] occurs in a familial and sporadic form (idiopathic or so-called primary form) and more frequently as severe PH associated with a number of disorders or conditions such as congenital heart malformations, collagen vascular diseases or HIV infection [2]. These associations were noted empirically and then accepted as probably causative, although the precise pathogenetic mechanisms, which can explain the development of severe PH in individual patients, are not understood [1; 3-5]. We believe that a genetic predisposition [6] is required for all forms of severe PH, not only for the so-called primary PH, to develop. The incidence of sporadic primary PH is estimated to be 2 per 1 million per year [7], the number of patients with AIDS who develop severe PH is small [8] and not every patient with an atrial septal or ventricular septal defect develops severe and progressive PH. Likewise is the number of patients with anorexigen-induced severe PH small given that millions of people have been exposed to these drugs [9; 10]. Because obesity is prevalent [11] and anorexigens tend to be used by obese people, Abenhaim et al [7] considered that obesity might be a risk factor by itself, yet in their case-control study they could not establish a statistically significant link between obesity and primary pulmonary hypertension perhaps because of the relatively small sample size. Several decades ago it was felt that primary PH was a disease of young women [11], however, we had noticed in the last decade that more and more postmenopausal and also obese

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women had been diagnosed with severe primary or secondary PH (unpublished own observation). Because estrogen is an angiogenesis factor and serotonin is a growth factor [12] for pulmonary vascular smooth muscle cells [13] we examined our pulmonary hypertension patient cohort for a history of hormone replacement and serotonin reuptake inhibiting antidepressant therapy. Morse et al [14] had recently suggested that hormone replacement therapy might be a risk factor for familial PPH.

Here we reviewed retrospectively the records of patients diagnosed with and treated for severe PH in the Pulmonary Hypertension Center at the UCHSC to assess the prevalence of obesity and comorbidities of obesity in postmenopausal women with severe PH. We find that physicians of our PH referral center follow a sizeable number of postmenopausal obese women with severe PH and here describe the clinical profile of these patients.

Methods

In this retrospective cohort study, the records of 541 postmenopausal women diagnosed with pulmonary hypertension were reviewed, and data were collected regarding coexisting illnesses and medications. The data were further stratified according to the patient's BMIs. Permission to inspect the patients' medical records had been granted by the UCHSC institutional review board (COMIRB). The entry criteria used to assign patients to the group which was examined in more detail were that the women were over 45 years of age and had been diagnosed with pulmonary hypertension – either primary or secondary. All of the patients considered for this retrospective analysis had documentation of severe PH by right heart catheterization and had a mean pulmonary artery pressure >45 mm Hg.

Some patients had to be excluded from the analysis either because their medical record could not be found or because their height had not been recorded, making it impossible to calculate the BMI. Patients with the diagnosis of hypothyroidism were on thyroid hormone replacement therapy and patients carrying the diagnosis of high blood pressure were on anti-hypertensive medication prior to the diagnosis and treatment of their PH. Not all blood tests had been ordered in a standardized fashion by all physicians of the UCHSC Pulmonary Hypertension Center and the data reported for uric acid [15], cholesterol, and C-reactive protein (CRP) are those available for analysis.

Results

In this survey of patients in the Pulmonary Hypertension Center, we found that we had a total of 1367 patients, comprised of 971 women (71%) and 396 men (29%). In the group of women with the definitive diagnosis of severe PH, 541 were postmenopausal women (56% of all women), 72 of them (13%) were diagnosed with primary PH (PPH), while 469 (87%) carried the diagnosis of secondary PH (Fig. 1).

We also assessed the incidence of other diseases in this cohort of patients with severe PH, and found that 32 (44%) PPH patients had systemic hypertension, 18 (25%) had thyroid gland disease, 9 (13%) had cancer, 8 (11%) had a family history of cancer, 6 (8%) had sleep apnea, and 5 (7%) had diabetes (Table 1).

We examined the same factors in patients with secondary pulmonary hypertension, and found that 175 (37%) patients had systemic hypertension, 108 (23%) patients had thyroid gland disease, 43 (9%) patients had cancer, 69 (15%) patients had a family history of cancer, 100 (21%) patients had sleep apnea, and 63 (13%) patients had diabetes (Table 2).

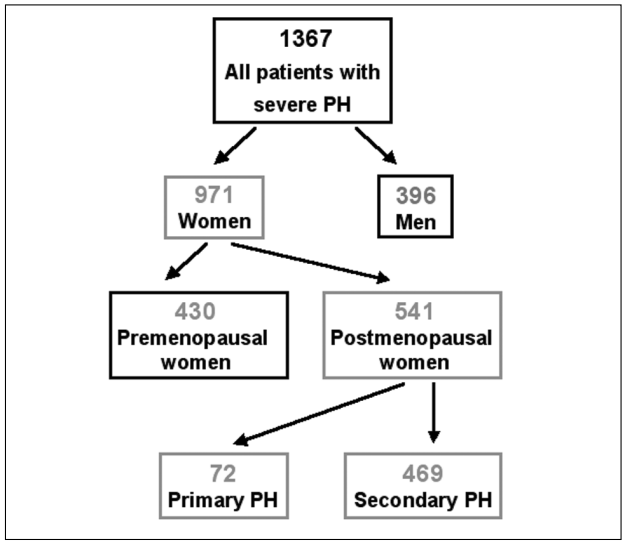

Fig. 1. A schematic distribution of patients in the Pulmonary Hypertension Center according to gender, menopause status, and diagnosis of primary or secondary pulmonary hypertension (PH).

Table 1. Other diseases and family history of any cancer identified in postmenopausal women with primary PH.

Disease state/family history	% of patients
Systemic hypertension	44
Thyroid gland disease	25
Cancer	13
Family history of cancer	11
Sleep apnea	8
Diabetes	7

Table 2. Other diseases and family history of any cancer identified in postmenopausal women with secondary PH.

Disease state/family history	% of patients
Systemic hypertension	37
Thyroid gland disease	23
Cancer	9
Family history of cancer	15
Sleep apnea	21
Diabetes	13

Table 3. Other disease states, estrogen replacement therapy, antidepressant and anorexigen use, as well as elevated laboratory data, grouped according to BMI in postmenopausal women with primary pulmonary hypertension.

BMI	<25	25-30	>30	
Systemic Hypertension	7	9	14	30
Diabetes	1	1	2	4
Estrogen Use	9	11	11	31
Antidepressant Use	4	2	7	13
Antidepressant + Estrogen Use	3	0	4	7
Anorexigen	2	5	11	18
Elevated Cholesterol	5	1	5	11
Elevated Uric Acid	7	4	5	16
Elevated CRP	1	1	1	3
Total women	19	21	26	66
				Total women

Table 4. Other disease states, estrogen replacement therapy, antidepressant and anorexigen use, as well as elevated laboratory data, grouped according to BMI in postmenopausal women with secondary pulmonary hypertension.

BMI	<25	25-30	>30	
Systemic Hypertension	34	31	95	160
Diabetes	9	7	42	58
Estrogen Use	48	46	76	170
Antidepressant Use	24	29	74	127
Antidepressant + Estrogen Use	6	18	39	63
Anorexigen	6	13	60	79
Elevated Cholesterol	9	7	32	48
Elevated Uric Acid	19	10	42	71
Elevated CRP	6	6	13	25
Total women	122	88	191	401
				Total women

In order to examine the prevalence of obesity in combination with the above-mentioned disorders as well as other potential risk factors for pulmonary hypertension, we stratified the prevalence of these factors according to the patients' body-mass index (BMI). We once again divided the patients into two groups, one group consisted of patients with primary PH and the other of patients with secondary PH. These were further divided into: BMIs less than 25 (ideal body weight), BMIs of 25 to 30 (indicating that the patients were overweight), and BMIs of more than 30 (indicating obesity). The results for the primary PH group are presented in Table 3.

About 71% of the women with primary pulmonary hypertension were either overweight or obese, with 39% being obese. There was increased anorexigen use by women in the obese category, and there was also more systemic hypertension as well as a somewhat increased use of anti-depressants and hormone replacement therapy in this group. Systemic hypertension, diabetes and use of the three classes of drugs seen in this rather small sample size of patients are more prevalent in the larger group of women with secondary PH as indicated in Table 4. We found that 69.5% of the women with secondary pulmonary hypertension were either overweight or obese (BMI >25), and that 47.6% of them were obese (BMI >30). Also, there was an increasing prevalence of diabetes and systemic hypertension in obese women, as well as increased estrogen use, increased anti-depressant use, as well as an increase in the use of both classes of drugs in combination. A higher proportion of women with secondary pulmonary hypertension who were obese had elevated cholesterol, uric acid levels and C-reactive protein levels when compared to women who were overweight or of ideal body weight. Obese women also had more frequently a history of anorexigen intake when compared to non-obese postmenopausal women.

Discussion

The principle information derived from our retrospective chart review is that large proportions of our female patients with severe PH are postmenopausal (56%) and also have a BMI of 25 or greater (69.5-71%). The prevalence of obesity in this cohort of patients is greater than that in the adult US population [16]. Although missing data did not allow for the calculation of BMI in 74 of our patients (6 with PPH and 68 with secondary PH), in a large enough representative group of patients with severe PH we come to the

conclusion that severe PH is also a disease of obese postmenopausal women. We also found that hormone replacement therapy was prevalent in our cohort of postmenopausal women with severe PH – obese or overweight (31 of 66 patients with primary PH and known BMI and 170 of 401 patients with all forms of secondary severe PH and known BMI (Table 3 and 4).

Forty six percent of women with a BMI of 25 and greater had been treated with estrogens in the primary PH group compared to 43 percent of women in the secondary severe PH group. The percentage of women in this age group treated with hormone supplements reflects the prescribing practice of physicians in this country [17] and since estrogens are angiogenic growth factors [18], it raises the question whether estrogens could contribute to the development of severe PH in women. An association between primary PH and hypothyroidism has been previously discussed [17] and thyroid gland disease, overwhelmingly hypothyroidism, was found in this survey in 25 % of patients with primary PH and 23% of patients with severe secondary PH. We were surprised to find that about 40% of our postmenopausal women also had systemic hypertension. Hypercholesterolemia and hyperuricemia [15] occurred more frequently in the pulmonary hypertensive women with a BMI >30.

As already stated, we wonder whether the roughly 300 obese, menopausal and postmenopausal women followed and treated in our center for severe PH constitute a previously not described syndrome. Clearly, this type of retrospective survey cannot answer this question, and a prospective, case-controlled study will be necessary.

There are however, theoretical or hypothetical considerations which we would like to mention, which perhaps could explain why this patient phenotype, when given a still ill defined genetic susceptibility, may develop severe PH. It is now understood that most patients with severe chronic PH have fixed PH [19] and that their pulmonary circulation demonstrates various degrees of vascular remodeling characterized by precapillary artery media hypertrophy, endothelial cell growth, and lumenal obliteration [5; 20; 21]. In addition to vasoconstriction, growth factors are considered important in the development of severe PH [22]. For example, vascular endothelial growth factor (VEGF) and serotonin have been implicated in the pathogenesis of severe PH [5; 21; 22], but other angiogenesis factors may also be involved in genetically susceptible patients. It is known that adipose tissue provides a depot or storage site for estrogens [23] and that obesity is a high-leptin state [24] and that both estrogen and leptin are angiogenesis factors [12; 25]. Interactions between estrogen and VEGF [18; 26; 27] and estrogen and leptin [28; 29] have been described. Estrogen regulates the expression of the VEGF receptor KDR [18] and the VEFG gene contains a functional estrogen response element [26]. Hormone replacement therapy causes an increase in leptin production [29] and in VEGF serum levels in postmenopausal women when compared to those not receiving this therapy [30] and treatment of hypertension and hypercholesterolemia reduces plasma VEGF levels in postmenopausal women [20]. Leptin plasma levels correlate with body fat mass, plasma leptin levels fall in postmenopausal women and this fall is prevented by hormone replacement therapy [28]. If indeed obesity can be considered a risk factor for severe PH, then one or several of these interactions might be involved. To what extent the lung is a "target organ" in diabetes [31] is unclear, but both obesity and insulin resistance have been associated with endothelial dysfunction [32] and endothelial cell dysfunction is a feature of severe PH [33].

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