Analysis of Cardiovascular Disease Risk Factors in Women

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Abstract

AIM: Study the cardiovascular risk factors in a feminine population vulnerable to cardiovascular events particularly to evaluate the principal factors or possible confounding variables.

METHODS: This is a cross-sectional descriptive study. Were analysed all the female patients from the Cardiovascular Rehabilitation Institute of Sports Medicine of Caxias do Sul who had the complete information on cardiovascular disease history, comorbidities and habits and who knew the complete gynaecological history by a phone interview.

RESULTS: A group of 91 patients were analysed. About the comorbidities and habits, 45.2% of these patients presented some tobacco load, 82.4% are hypertensive, 61.5% are dyslipidemic, 25.3% are diabetic and the BMI average was 29.27 (overweight). Between the patients who undergone a hysterectomy and had an episode of the acute coronary syndrome (10 patients), 70% had the event after the procedure. Between the post-menopause women with at least one episode of the acute coronary syndrome, 80.5% (33 patients) had the first event after the menopause.

CONCLUSION: We found multiple lifetime risk factors that predisposed the women of the sample to have cardiovascular disease. Between the women with specific to women risk factors and without, the prevalence of cardiovascular disease was very similar. This information supports the idea that these are just confounding factors of CVD and the principals involved are the genetic factors and habits. For this reason, the focus of CVD prevention and treatment should be directed towards these aspects.

Introduction

Coronary Heart Disease (CHD) is an important Cardiovascular Disease category (CVD) and is considered the most common cause of death in the United States (USA) as well as in Brazil.

Regarding epidemiology, diagnosis, treatment and prognosis of CVD, there are significant differences between men and women. These differences are extremely important for the care of women with a known or suspected disease and should be taken into consideration during medical care. In the past, CVD was considered a "male disease" since most studies excluded female patients or included them as a minority. However, this theory has been gradually disproved in light of new studies.

According to the American Heart Association´s statistics for Heart Disease and Cerebrovascular Accident updated in 2010, 17.6 million people have CVD in the USA, mainly men and women of more advanced age. The Framingham study showed that 40-year-old men have a lifetime risk of 49% to develop CVD while women, on the other hand, have a 32% risk. 70-year-old men have a 35% risk, while women of the same age have 24%. Furthermore, the occurrence of CVD at the age of 65-94 doubles in men and triples in women when compared to the incidence in the age range of 35-64 [1].

CVD generally manifests itself ten years later in women than in men and brings along an increased number of risk factors. Besides this, women tend not to identify its initial symptoms are delaying the moment of diagnosis and resulting in higher risk medical care. In pre-menopausal women, severe manifestations of CVD, such as acute myocardial infarction (MI) and sudden death, are relatively rare. On the other hand, in post-menopausal women, the

occurrence and severity of CVD increase sharply (three times more comparing to pre-menopausal women). Clinical manifestations of CVD have similarities and differences between the sexes. Chest pain is similar in both sexes both in prevalence and in pain level. Acute MI prevalence is higher in men, however, prevalence tends to decrease in men and an increase in women as the years go by. Regarding Heart Failure (HF), women tend to develop asymptomatic HF secondary to CVD more frequently than men. Lastly, men seem to have a more increased rate of sudden cardiac death in all ages and all levels of risk factors.

Apart from the classic CVD risk factors that are the same in men and women, existing literature describes that women also present unique risk factors. The first is menopause [2] during which the risk mechanism is not fully comprehended in the same way that it is not known if there is a direct causal relationship between menopause and CVD. Hysterectomy, oophorectomy, pre-menstrual syndrome, oral contraception and pregnancy complications such as systemic arterial hypertension (SAH), diabetes mellitus (DM), spontaneous abortion and preterm birth are also risk factors exclusive to women [3] [4] [5] [6].

Age, family history, DM, chronic kidney disease and metabolic syndromes are related to a significant increase in the risk of cardiovascular events in both sexes [7]. Nonetheless, risk factors related to lipoproteins present some peculiarities in women: low HDL is more predictive for cardiovascular events in women than a high LDL; Lipoprotein A is a risk determinant for CVD in pre-menopausal and post-menopausal women under the age of 66; the concentration of total cholesterol seems to be associated with CVD only in pre-menopausal women and triglycerides only in older women [8] [9]. A cross-sectional study conducted in Rio Grande de Sul found that obesity is a more prevalent risk factor for women, while SAH is for men [10].

Generally, women are a minority in CVR programs, and there are few studies on the subject, a fact that generates a lot of doubt about the handling and real evolution of women in these programs. Nevertheless, they seem to receive greater or similar benefits comparing to men [11].

The prevalence and mortality of cardiovascular disease are growing, especially when it comes to women, who are increasingly younger. Due to the lack of studies that focus on understanding the natural history, handling and prevention of CVD in women better, we aim to study the cardiovascular risk factors in a feminine population vulnerable to cardiovascular events particularly to evaluate the principal factors or possible confounding variables.

Methods

This is a cross-sectional descriptive study. The population surveyed included patients from the Cardiovascular Rehabilitation Institute of Sports Medicine of Caxias do Sul (SMI).

The data collection process for the study was conducted in three stages. Firstly, initial medical evaluation data were collected from all patients who entered the Cardiac Rehabilitation Service of SMI from 2007 to 2016 with several variables (identification, comorbidities, a medication used and exam results). Secondly, we selected all patients who fulfilled the following criteria: 1-female; 2-complete phone number data. In the end, we collected the gynaecological history by phone after making up to two attempts to contact patients during normal business hours. All data related to the gynaecological history of the patients were collected through an interview. The rest of the data was gathered from the initial evaluation made by a doctor of the service when the patient entered the CVR. After these proceedings, we used the following criteria for including patients in the study: 1-female; 2-Initial medical evaluation with complete information on cardiovascular disease history, comorbidities and habits; 3-Patient knows her complete gynaecological history. Exclusion criteria were as follows: 1-patients that did not recollect their complete gynaecological history; 2-incomplete initial medical evaluation; 3-unable to contact by phone after 2 attempts.

The initial medical evaluation variables taken into consideration were as follows: age of integration in the program, SAH (yes or no), DM (yes or no), dyslipidemia (yes or no), tobacco use (yes or no), body mass index (BMI), maximal oxygen uptake (VO$_2$ max) in ergometric tests or ergospirometry, acute coronary syndrome episode (ACS) (yes or no) and at what age the episode took place (pre or post-menopause).

The variables analyzed in the phone interview were the following: hysterectomy (yes or no), cause for hysterectomy (benign or malignant), oophorectomy (yes or no, and if yes how many ovaries were removed), use of oral contraception (if the patient has ever taken or not), use of hormonal replacement therapy (HRT), menarche (precocious; before the age of 11 [12], at the expected age, or late: after the age of 15 [13], menopause (didn't take place, precocious: before the age of 40 [14], at the expected age, or late: after the age of 55 [14].

The data was stored in an Excel® 2016 table and analysed with SPSS® software 22.0. We used descriptive statistics and a chi-square test for categorical variables to make the calculations.

This research was approved by the Ethics and Research Committee of Faculdade Cenecista of

Bento Gonçalves and all participants in the study signed a consent statement accepting to participate.

In the first phase, we chose 886 patients, 551 of which were female. Among all women, only 352 had informed their phone number. A first attempt was made to contact during business hours in which we find out that 142 (40.3%) patients had informed the wrong number or the information was out of date. Regarding the rest of the patients, we successfully contacted 112 cases (31.8%) and collected the gynaecological history of the patient through an interview conducted by the researchers. In the remaining 98 cases (27.9%) the phone number was correct. However, the patient did not have sufficient information regarding their gynaecological history or was unavailable to interview at the moment the call was made, even though we made up to two attempts to contact during business hours.

After collecting the gynaecological history from 112 patients, 21 were excluded because of incomplete information in their medical chart. In total, we analysed 91 patients, which represented 16.7% of all female patients in the rehabilitation service.

Results

The evaluation of general clinical characteristics showed that practically one-third of the patients (33%) were ex-smokers and 13.2% were active smokers. In other words, 45.2% of patients presented some tobacco load, and the other 53.8% had never smoked. BMI average was 29.27 kg/m2 with a standard deviation of 5.45. About the VO_2max, 23 patients (25.3%) did an ergometric test with the average VO_2max being 19.87 ml/kg/min and a standard deviation of 7.64. The remaining 68 patients (74.7%) did the ergospirometric test obtaining an average VO_2max of 14.81 ml/kg/min and a standard deviation of 6.23.

Table 1: The prevalence of additional risk factors

Comorbidity	Yes	No
Diabetes	23 (25.3%)	68 (74.7%)
SAH	75 (82.4%)	26 (17.6%)
Dyslipidemia	56 (61.5%)	35 (38.5%)

The analysis of variables related to gynaecological history showed that 66 patients (72.5%) did not have a hysterectomy. In the rest of the patients that informed having a hysterectomy, the majority (68%) did not know the reason for the surgery; one patient reported malignant cause and another 7 (28%) stated that it was a benign cause that motivated them to have the procedure. Regarding oophorectomy, 14 patients (15.4%) had the procedure, 5 of which (35.7%) removed just one ovary and 9 (64.3%) removed both ovaries. The median

menarche age was 13 years (average 12.87), taking into consideration that 5 patients (5.5%) had menarche classified as precocious, 82 (90.1%) within the expected period and 4 (4.4%) late. About menopause, 8 patients were still pre-menopausal. From the remaining 83 women, 9 (10.8%) had early menopause, 70 (84.3%) within the expected period and 4 (4.8%) late. When it came to oral contraception, 70 patients (76.9%) informed to have used contraception at some point in their life while 21 (23.1%) denied use. About HRT, 24 patients (26.4%) reported having gone through HRT and 67 (73.6%) reported that they had never been through HRT.

Lastly, around half of the patients (47.3%) had already had an ACS with the first episode taking place approximately at the age of 55 with a standard deviation of 11.42. Furthermore, the lowest age of the first ACS episode was 32 years and the highest 81 years. Regarding the number of events of ACS, 79% of patients only had one episode, 16.3% had two episodes, and 4.7% had 5 episodes.

Using the chi-square test, we analysed the women that had a hysterectomy and presented an ACS episode. This analysis resulted in a total of 10 (11%) patients, 7 of which (70%) experienced the first ACS episode after a hysterectomy and the other 3 (3%) experienced the first ACS episode before having a hysterectomy. The same observation was made about menopause, in that 33 women (80.5%) experienced the first ACS episode after menopause and 8 (19.5%) before menopause. In other words, 41 patients (45%) reported having been through menopause and having had at least one ACS event.

Discussion

Our study analysed 91 female patients of a CVR service. While selecting the patients, we initially noticed a higher number of women than men. This data would contradict most existing studies on this subject [11]. We believe that either this data found in our program is incidental to the period analysed or that women presented more events or they sought out the rehabilitation program more than men.

The metabolic profile of the participating women shows that most of them are hypertensive (82.4%), 61.5% are dyslipidemic, 25.3% are diabetic, and the BMI average was 29.27 (overweight). It is known that women have a greater prevalence of hypertension after the age of 50 and this prevalence tends to increase with age reaching up to 80-90% of women older than 70 years in the population [15] [16]. Regarding dyslipidemia, as it has already been explained, there are particularities in women. Prevalence also matches the population data, as it was shown in a study made in Sao Paulo according to

which the average hovers at around 60% [17]. Women also tend to have a greater prevalence of diabetes in the population; however, the DM prevalence analysed in our sample was significantly superior to the national average of prevalence in women (8.8%), possibly because of being part of a specific group with more CVD risk [7]. In general, despite the reduced number, the resulting metabolic profile matched the results of the population studies with a tendency for greater risk factor prevalence because of being a select group of patients.

Practically half of the patients analysed (47.3%) experienced at least one episode of the acute coronary syndrome (ACS). The majority of the remaining patients have some kind of heart disease, mainly atherosclerotic, which makes us conclude that the group of patients under analysis is at high risk to develop a more severe event or even die. It is known that in Brazil, ischemic heart disease is one of the main causes of death and it is responsible for 31% of deaths caused by cardiovascular diseases while the Ischemic stroke is responsible for 30% of deaths caused by cardiovascular diseases. The age average for the first Acute Myocardial Infarction (AMI) matched the expected age based on other studies in which the age range for this event to be more likely is for women above the age of 50 [18]. Several studies show that the incidence of acute myocardial strokes grows drastically after menopause [19] [20] [21] and in some studies, a greater number of incidents was found among women with early menopause [2] [22]. There are various physiological explanations for such an occurrence. However, there is no concrete proof that menopause is a CVD causal factor. Some hypotheses are based on the fact that estrogen, just like progesterone, suppresses some endothelium and vascular smooth muscle proliferation factors mainly through intracellular receptors. There are studies which suggest that estrogen can stimulate the release of nitric oxide the same way progesterone stimulates COX-2 and consequently PGI2. Furthermore, estrogen aids in the lipolysis and lipogenesis responses, anti-inflammatory effects and antioxidants [21].

Nevertheless, men also present an increase in cardiovascular events as the years go by, which weakens the theory that menopause is an independent causal factor of CVD [1]. Another factor that would contradict the estrogenic protection theory is the great change of habits in women and the increase of cardiovascular events in younger women, mainly related to the smoking habit and the stress at work and routine [23]. Men were not evaluated in our sample, and therefore we shall not hypothesise on this subject. In our sample, approximately 80.5% of the female patients that presented AMI during their lifetime suffered the event after menopause. Even if from a known physiological point of view this makes sense, we still cannot confirm a definite causal relationship based on this information.

An important point to be discussed is about the genetic risk and healthy lifestyle. The evidence on this subject is well established in the literature, and the strong influence of these factors on increased cardiovascular risk must be taken into account. A study based on three prospective cohorts and one cross-sectional study showed that high genetic risk is independent of a healthy lifestyle and is associated with an increased risk (hazard ratio 1.91). There are up to 50 single-nucleotide polymorphisms related to CHD, and it is possible to calculate the polygenic risk score for this disease. Also, adherence into the healthy lifestyle (no current smoking, no obesity, regular physical activity, and a healthy diet) was associated with a significantly decreased risk, within any genetic risk category [24].

Due to the discoveries made about the protective cardiovascular role played by estrogen, many studies were conducted about HRT and cardiovascular prevention. However, many well-conducted studies found exactly the contrary, an increased risk of several incidents with this type of therapy [25]. Given this, most global guidelines do not recommend the prescription of medication with a cardiovascular prevention purpose. Among the patients analysed in our study, 26.4% went through hormonal rehabilitation. There is a lack of data and sample size for the realisation of a persistent comparison of this type of therapy and cardiovascular events in our study.

Apart from menopause, there are also assumptions related to the age of menarche and future risk for CVD. It is believed that early menarche is associated with a greater CVD risk and mortality caused by CVD [25]. In our sample, most patients had menarche at the expected age; therefore, this variable is difficult to analyse to link it to cardiovascular events.

As far as oral contraception is concerned, it is known that the women who used this medication in the past do not have an increased risk for cardiovascular events [26]. There are only a few studies related to oral contraception use and events taking place at the same time and since the use is made at a younger age and cardiovascular events are extremely rare at this age group it is difficult to establish a relationship. Therefore, even if most of our patients had used this type of medication, we can be quite sure that there is little correlation between the number of cardiovascular events.

Other analysed variables in our study were: going under hysterectomy and oophorectomy since there have been hypotheses of connection to increased CVD risk through undefined mechanisms. Very few patients of our study went through this procedure so it would be inappropriate to conclude the existence of any causal relationship. What´s more, according to bigger studies about this subject, the correlation between hysterectomy with or without ovary removal and cardiovascular events was not very

consistent, both in the pre-menopause and post-menopause phase and for this reason, this hypothesis is hardly considered nowadays [3] [27].

Our study was conducted with high-risk cardiovascular patients. The treatment choice for these patients needs to be very well planned with the interaction of drug and non-drug therapies. Taking this into consideration, CVR is a method that presents strong evidence of being a very important tool in the primary and secondary prevention for this kind of patient [28] [29]. However, there are very few studies specific to women and their evolution in this type of program.

Bearing in mind that our study was conducted in a CVR program we can infer that, based on our data, the patients of the program have a very low functional capacity in their initial evaluation regardless their age range [30]. Most patients were evaluated with an ergospirometric test which is quite accurate for measuring such a variable. This is a positive point for our study since most research in CVR programs uses ergometric tests which overestimate results, as it was clearly shown in our findings.

We can conclude that the patients analysed present various accumulated risk factors that predisposed them to CVD. Low functional capacity proves that they are critically ill patients who require meticulous care. Furthermore, there are specific risk factors for women that are still very controversial literature-wise. Although our sample presents risk and a high incidence of ACS, the theoretical risk factor rates specific to women (such as early menopause) were similar to the female population in general. Besides this, among the women in the analysed sample with and without risk factors specific to women, the ACS prevalence was similar.

This information supports the idea that these are just confounding factors of CVD and the principals involved are the genetic factors and habits. For this reason, the focus of CVD prevention and treatment should be directed towards these aspects.

Limitations

The sample of the study ended up being limited due to lack of information in the charts and difficulty to contact patients, apart from the fact that the CVR public is of low numbers. What´s more, the average age of the initial evaluation was not taken into consideration in the study, as it was deemed more important to evaluate only the timeline of the exposure factors and outcome.

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