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Stress Dresses Woman: Sex and Gender Differences

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"...the physician must study the customs, the regimen,

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because, the biggest mistake that is committed today

is to separate the psyche from the soma...."

-Hippocrates

Abstract

Stress is defined as a real or interpreted threat to physiological or integrity of an individual that results in physiological and behavioral responses; as a reaction to internal/external stimuli, it is considered a normal physiological response of the body to protect or to adapt itself to changed conditions occurring at biochemical or biological or behavioral level. Depending on different cultures, stress is viewed as an absence of inner peace (eastern countries) or as a loss of control (western countries). Stress responses are quite different in man and woman in many situations as well as their susceptibility to lifestyle changes, risk factors and diseases. Woman is more exposed to stress due to her different biological, neuro hormonal and psycho behavioral structures influencing day life, the occurrence of specific diseases, social condition and the continuous attempt to overcome inequality. The present paper tries to review the knowledges about the physiopathology of stress, the sex/gender different structures, the prevalence of stress related risk factors and diseases with special reference to woman and the different stress responses, with the addition of a short personal experience.

Keywords: *Stress; Physiological and Behavioral Responses; Internal/External Stimuli; Woman*

Introduction

Stress as a reaction to internal/external stimuli is considered a normal physiological response of the body to protect or to adapt itself to changed conditions occurring at biochemical or biological or behavioral level [1,2].

The physiological long acting maladaptive response to acute and chronic stress exposure has long been recognized as a potent modulator of immune, endocrine and metabolic pathways, even its direct implications for cardiovascular disease development and progression. It is widely considered to have an important involvement in cardiocerebrovascular disease, atherosclerotic disease and endothelial dysfunction, immune, endocrine, metabolic pathways and lifestyle and behavioral risk factors [3-15]. In particular more attention is given to the bidirectional interaction between psychological and physical health in relation to cardiovascular disease and to its contribution to atherosclerosis development through adverse life events, behavioral risk factors, metabolic and immunologic maladaptation that may affect the diseases and their progression [15].

There is the need to determine the psycho behavioral profile definition of the patients through the detection of maladaptive responses due to chronic stress as Hippocrates suggested: …the physician must study the customs, the regimen, the lifestyle, the age of each patient; the speeches, the silences, the thoughts, the sleep, the insomnia, the dreams - how and when - the involuntary deeds - tearing their hair, scratching, crying ... because, the biggest mistake that is committed today is to separate the psyche from the soma…. [16].

This may be considered the first step of the assessment of the patient to fully and better understand her/his problems (verum scire est scire per causas… knowing the truth through knowing the causes) [17].

Today some AA suggest the necessity to institute the Behavioral cardiology, an emerging field of clinical practice based on the recognition of adverse lifestyle behaviors, emotional factors, and chronic life stress that may promote atherosclerosis and adverse cardiac events [2]; an organized method of study and application of psychosocial factors in the assessment and reduction of cardiovascular risk [18].

Not so definitively established is the different stress involvement of woman compared to man (if there is) and if there is any difference in prevalence, affection and modalities of responses. Studies show that women are more likely than men to experience stress and at the same time, post-traumatic stress, depression, anxiety and mood disorders [19-22].

The aim of this paper is to report some knowledges on structural differences (sex-related) of women versus men, to look at physiopathology of stress and its clinical presentations (sex- and gender-related) and to highlighten eventual different stress involvement in lifestyle, behavioral cardiovascular risk factors and the occurrence of diseases.

Differences woman vs man

Gender is the range of characteristics pertaining to, and differentiating between masculinity and femininity. Depending on the context, these characteristics may include biological sex (i.e. the state of being male, female, or an intersex variation), sex-based social structures (i.e. gender roles), or gender- based (i.e. gender identity). More precisely the WHO defines gender as the result of socially constructed ideas about the behavior, actions, and roles a particular sex performs, a term used to exemplify the attributes that a society or culture constitutes as "masculine" or "feminine" [23-25]. The word 'gender' has acquired the new and useful connotation of cultural or attitudinal characteristics (as opposed to physical characteristics) distinctive to the sexes. That is to say, gender is to sex as feminine is to female and masculine is to male [26]. David Haig stated, "Among the reasons that working scientists have given me for choosing gender rather than sex in biological contexts are to desire to signal sympathy with feminist goals, to use a more academic term, or to avoid the connotation of copulation" [24]. Gender was described as early as in 1949 by the French author Simone de Beauvoir [27]: "One is not born, but rather becomes, a woman"; that means "male or female is born, man or woman becomes".

Gender medicine is a dimension of medicine that studies the sex influences on pathophysiology, clinical signs, prevention and therapy of diseases. It is the medicine neither of gender-related diseases nor of diseases prevalent in a gender, mainly related to reproductive functions; it is rather a specific medical field that aims to focus the attention and efforts of the scientific community on understanding the differences of patho-physiology, clinical signs, prevention and treatment of diseases equally represented in men and women [28].

From a structural point of view Male and Female are referred to the Sex (Nature), genetic structure that defines all of the genes and hereditary factors that influence who we are (genetic inheritance) - from our physical appearance to our personality characteristics; the set of biological, physical and anatomical characters that produce male/female dimorphism (presence or absence of Y chromosome, type of gonads, sex hormones, internal reproductive anatomy, external genitalia) (Biological Sex). Man and Woman are referred to the Gender (Nurture), environmental factors that define all the environmental variables that impact who we have become and how we present ourselves (environmental acquisition), including our early childhood experiences, how we were raised, our social relationships, and our surrounding culture, representation, definition and incentivization of behaviors that determine the status of man/woman (acquired non-innate character, behavior, work, lifestyle, language, social role, etc.) (Person Identity) [23,29].

Structural characteristics

The individual may be summarily defined as a complex organization in which neural, hormonal, cellular, and genetic mechanisms are strictly related to social behaviors whose main task is to help the organism to survive, reproduce, and care for offspring sufficiently long that they too reproduce [31]. This means that neuro hormonal structure of individual is related to psycho behavioral one and that both influence one to each other [32]. It seems that there is evidence of the relationship between social events and biological ones and the possible role that social constructs, once reduced to their neural, hormonal, and genetic components, may have [32]. Many of these activities are related to the activity of the brain close to the limbic system and the limbic system itself, the emotional brain first born and then first site of memories.

The female brain has some different anatomical structure compared with male. The anterior cingulate cortex, worry center, is larger in women; it weighs options and pushes to make decisions; the prefrontal cortex rules and modulates the emotions and controls the amygdala, larger and faster in women; the insula, larger and more active in women, processes gut feelings; the pituitary gland produces hormones of fertility, milk production and nurturing behavior [33]. The limbic system is the portion of the brain that deals with three key functions that are emotions, memories and arousal (or stimulation) and connects parts of the brain that deal with high and low functions. The main components of the limbic system are [34] the thalamus, which is responsible for detecting and relaying information from our senses, such as smell and vision, and that contributes to the pathway of information into the cerebrum, responsible for thinking and movement (there is a greater myelinic connectivity in female) [35], the hypothalamus, which is responsible for producing multiple hormones and for ruling them, starts stimulating earlier at puberty in female, sends chemical messengers involved in the control of water levels in the body, sleep cycles, body temperature and food intake (it stimulates gonads and it is site of sexual excitation; it is greater in male) [33], the cingulate gyrus, which serves as a pathway that transmits messages between the inner and outer portions of the limbic system, the amygdala that is responsible for preparing the body for emergency situations, storing memories of events for future recognition, particularly those related to emotional events and emergencies, site of fear emotion and panic, but also of pleasure and sexual arousal (the left side is greater in female, the right one is greater in male) [33], the hippocampus that is responsible for converting short- into long-termed memories in cooperation with amygdala, it never forgets a fight, a romantic encounter, or a tender moment-and won't let you forget it (either larger and more active in women) [33], the stria terminalis, typically masculine, elaborate unconscious answers to danger and fear stimuli [36], the periventricular anteroventral region, typically feminine, plays an important role in the electrolytic balance, cardiovascular and blood pressure control [37].

The gender-related difference in the limbic-thalamo-cortical circuitry may explain the gender differences in thalamic activation during the processing of emotional stimuli or unpleasant linguistic information concerning interpersonal difficulties [38]. In addition, men appear to have more gray matter (non myelin) (processing center), made up of active neurons (facilitated information processing, from analysis to synthesis processing) and many intrahemispheric connections that facilitate the link between the perception and the coordinating actions, while women appear to have more white matter (myelin)(connection center) for the neuronal communication (faster information transfer, from synthesis towards analysis processing) between different areas of the brain and many interhemispheric connections that give better communication between analytic and intuitive processes [38]. The two components are complementary and not in opposition. Another important point is that the brain is sexually differentiated by the activity of male gonads during birth [30].

Sex-related differences are increasingly being investigated not only at the macro-anatomic and functional analysis of connections within the brain, but also at a histological and cellular level; from this perspective, it has been reported that differences exist in serotonin metabolism and receptor expression between males and females, which fit well with the long-known higher incidence of depression in the female sex [39]. Differences are also reported in the concentrations of dopamine and GABA, possibly accounting in part for sex-related differences in diseases such as schizophrenia and in premenstrual dysphoric disorder [40,41]; at the level of microglial activity,

differences between males and females have been reported in the production of tumor-necrosis-factor alpha and of IL-10, with a higher production in females [42].

There exists a wide literature reported in an interesting review [43] that lists the numerous examples of reciprocal influence of neuro hormonal and psycho behavioral structures. In an interesting paper Rozanski., *et al*. [2] consider three psychological components that may be central to developing emotional and coping flexibility: Vitality, Emotional Competence and Positive response mechanisms. Vitality reflects the presence of energy and enthusiasm and a sense of aliveness [2,44]; it is characterized by two positive emotions, joy and interest, it is fueled by both a sense of purpose and a sense of self-worth and connotes a sense of positive excitement [2] and attitude. Vitality promotes two adaptive responses (which may in turn positively influence vitality itself) that are the development of various positive response mechanisms (such as patience, discipline, impulse control, strong social support, positive coping skills, optimism) and emotional competence, that represents the ability to regulate emotions across a range of situations [2,45], important trait termed "emotional flexibility" [2,46].

Shortly, a strong sense of purpose coupled with a sense of self-worth derives benefit in terms of a greater sense of vitality; this provides energy needed to develop and maintain greater emotional competence and positive response mechanisms that in turn provide a stabilizing force for maintaining a sense of vitality [2].

All this processes well represent the individual's relationship (balance) between inner and outer and between neuro hormonal and psycho behavioral structure activity. When several factors negatively affect the structures, the relationship is unbalanced and anxiety, depression, mood abnormalities, affective disorders and psychological instability arise and grow up.

What is stress?

Initially, Hans Selye described a syndrome produced by diverse nocuous agents presented as a three-stage reaction of the organism in response to stimuli such as temperature changes, drugs, muscular exercise, etc. and the involvement of endocrine system and the majority of organs affected [47].

Acute stress: Acute stress represents a non-specific response of the body to a more or less violent internal/external stimulus (microbial, toxic, traumatic, thermal, emotional, etc.) through which the body tries to adapt itself to changed conditions. Stressors are internal/external factors acting on hypothalamus that activates both the sympathetic nervous system and the adrenal-cortical system, that cause multiple peripheral effects both neuro-hormonal such as endothelial dysfunction, insulin resistance, hypertension, increased heart rate and cardiac output, lipolysis, glycogenolysis, bronchiolysis, inflammation, platelet activation, etc. and psycho-behavioral such as better motor and cognitive performance, increased attention and alertness, increased mnesic capacity, etc. [2,31,32]. The responses may be various such as fight-or-flight, an attempt to help to survive a dangerous situation by preparing a person to either run or fight (bypassing or coping the problems) for his/her life [2], personal lifestyle, resilience, adaptation, recovery [48,49]. Environmental stressors, life events, trauma and abuse, and other progressively long acting psychological situations affect the person; the effect is an unbalancing of neuro hormonal and psycho behavioral structures that reduce the sense of purpose and the sense of self-worth negatively modifying vitality, emotional competence and positive response mechanisms and consequently reinforcing risk factors [2]. All these destabilize the allostasis (the active process by which the body responds to daily events and maintains the stability through continuous internal and external changes) [50] and influence the body's responses, depending on the individual differences (genetic, development, experience). The allostatic overload, the wear and tear determined by chronic stress and negative adaptation ability and behavioral responses may result in the illness occurrence [48,49].

Chronic stress: Chronic stress may be defined as a chronic and exhausting response to long acting stressors whose modality of presentation is depression or anxiety or mood disorders individually, both or all together. The first step of presentation of chronic stress is through

a maladaptive response of somatic and behavioral type with psychoneurotic symptoms such as physical complaints without disease, chest pain, palpitations, high blood pressure, gastrointestinal, sleeping, breathe shortening, fatigue, cold/sweaty hands, dizziness, libido depression, headache, muscle tension, a reduced sense of purpose/self-worth, vitality, emotional competence, feelings of anxiety, obsessional thoughts, compulsive acts, excessive indecision, high degree of social or interpersonal maladjustment, etc. [51].

Chronic stress, through its modality of presentation, may be considered one of the main promoters affecting cardiovascular risk factors such as physical inactivity, smoke, hypertension, sexual inactivity, and unhealthy eating and consequently obesity, diabetes, dyslipidemia [2,52-55]. It is present in 77% of adult population (experienced physical symptoms due to stress 77%, experienced psychological symptoms due to stress 73%, living with extreme stress 33%) [56] and represents the common risk factor of 75% - 90% of the diseases [53]; the most common stress-related diseases are hypertension, diabetes, atherosclerosis, Alzheimer, tumors [52] and, in addition, cardiovascular risk factors in world areas included lifestyle factors in > 55% of cases and psychosocial factors in > 35% of cases [57]. Hypertension is one of the important cardiovascular risk factors in which stress plays a significant role; in fact, in two interesting papers meta-analysis-based, hypertension was significantly reduced after transcendental meditation programs [58,59].

According with Rozanski [2] it is possible to hypothesize that internal factors, such as choices, beliefs, mind traps, negative views, etc., external such as environment, social, economic, work, health, etc. and hidden ones such as hormones, immune, digestion, nervous dysfunction, etc. may act determining emotional distress and discomfort, unsuitable choices and actions and progressively worsening of lifestyle; the consequent psycho-behavioral unbalance may address individuals towards risk factors, psycho-behavioral and somatic-functional symptoms and then occurrence of organ damages and diseases [2,60-67].

Stress and women

Due to the anatomical brain structure and function (as reported above), to the neuro-hormonal structure that determines monthly cyclic variations in women and to the gender and psycho behavioral exposures, stress affects women differently from men in many situations. Women are emotionally more unstable than men, have a lower anxiety and sensitivity threshold and are more exposed to stress and its modality of presentation (anxiety, depression and mood disorders) [33]; this may be associated to the slower production of serotonin in women knowing that an increase of serotonin improves the response to stress [68]. Also oxytocin, low in anxiety and depression, facilitates the control of stress, anxiety and fears and the release of endorphins which increase the production of estrogen [69].

The female stress response primarily involves the limbic system including ventral corpus striatum, putamen, insula and anterior cingulate cortex [70]; the right prefrontal cortex is also involved and its function is to regulate the anterior cingulate cortex and limbic system hyperactivity [70]. In particular, the ventral striatum including caudate and globus pallidus are critical substrates of the reward system that possess rich receptors for oxytocin, vasopressin, dopamine and endorphin [70]. The limbic activation to stress in female subjects is more consistent with a tend-and-befriend rather than a fight-or-flight model [70], prevalent in men. The human stress response, characterized physiologically and behaviorally as fight-or-flight both in men and women, is in women behaviorally more marked as tend-and-befriend response [71], whereas tending involves nurturant activities designed to protect the self and offspring promoting safety and reducing distress, and befriending is the creation and maintenance of social networks that may aid in this process; the mechanism underlying this response appears to be related to oxytocin, in conjunction with female reproductive hormones and endogenous opioid peptide [72].

Since stress reactivity includes the activity of the hypothalamic-pituitary-adrenal axis (e.g. cortisol) and sympathetic nervous system (e.g. heart rate and blood pressure), their acute responses has been found greater in men compared to women; this, probably innate, may be greatly due to the female sex hormones that attenuate the hypothalamic-pituitary-adrenal and sympathetic nervous responsiveness [68]. Their dysfunction is associated to manifestations of psychosomatic and psychiatric disorders and some diseases such as depression, social phobia, panic disorder, generalized anxiety, obsessive–compulsive disorder, susceptibility to infectious diseases, cardiovascular

disorders, lupus erythematosus, multiple sclerosis, and neurodermatitis, tumors, dementia [68]. In this activity and in a complex way, oxytocin and serotonin play an important role in the hypothalamic-pituitary-adrenal responsiveness [73,74].

Stress is present in 51% of women and 32% of men and, among adolescents, 25,2% of girls have stress in their daily lives higher compared to boys that is 14,8% [56,75], whereas its manifestations are present in women as depression in 21%, anxiety in 28,8% and mood disorders in 20.8% largely higher versus men [76-78]. In an Italian observational study, more than 55% of female students, workers and unemployed ones declared to have a daily stress feeling compared with about 30% of male [79]. Lifestyle and psychosocial factors for cardiovascular diseases are largely higher in women compared to men [57] and may be considered common key factor acting behind in affecting lifestyle and cardiovascular risk factors such as physical inactivity, smoke, unhealthy eating (dyslipidemia, diabetes and obesity), hypertension, sexual inactivity, whose prevalence is higher in some cases, or lower but continuously increasing in some others, in women compared to men [54-56,76]. This is associated with higher prevalence in women compared with men of Alzheimer, hypertension, diabetes, atherosclerotic diseases, tumors and chronic obstructive pulmonary diseases [80,81].

Perceived stress is a powerful predictor of cardiovascular risk in young and middle-aged women [82,83]. In the last two decades, psychosocial stress increased in women due to a continuous increase in women's economic participation and educational attainment [84]; at the same time also cardiovascular risk factors increased in women versus men with modification of the gap that in some cases is reduced such as in female smokers and is enlarged such as in female hypercholesterolemia and obesity compared to male [66,85]. Low socioeconomic status has been found inversely associated with global coronary risk and with a higher excess risk on women as compared to men [86,87] and feminine roles and personality traits seem to be associated with higher rates of acute coronary syndrome as compared to masculine ones [88]. Emotional stress is associated with increased risk of cardiovascular disease; limbic system and long-term cardiovascular outcome link has been demonstrated and shown to be pathogenic in women, but not in men [88,89]. Recently, Haider [67] reported the main differences in women compared with men regarding the acute coronary syndrome: women are generally older and have more comorbidities, including a higher prevalence of hypertension, dyslipidemia, smoking, obesity, diabetes, heart failure, psychosocial and emotional stress, chronic kidney disease, rheumatoid arthritis and atrial fibrillation; in women the onset symptoms are abdominal discomfort, anxiety, nausea, vomiting, shortness of breath, and preceded by emotional stress, whereas the characteristics of myocardial ischemia in women versus men are atherosclerotic plaque erosion, microvascular disease, Takotsubo cardiomyopathy, vasospasm, higher risk of restenosis, mental, emotional and psychosocial stress [67].

Data address to think that the prize that women pay to reduce the gender gap is high and if the tendency to social and economic balance improves, as well as the women's life and their involvement in the social, political, work and economical activities, in many cases their lifestyle worsens and risk factors increase in parallel to the occurrence of pathologies; the prevalence of hypertension, depression, anxiety, arthritis, asthma, diabetes, obesity, obstructive pulmonary disease, smoke, hyperlipidemia have been found increased in women compared to men in an observed period between 2000 - 2001 and 2014 - 2016 [66,85] and the trend and projections of heart disease and cancer mortality in USA between 1969 and 2020 have been found less reduced in women compared to men (the former 68,4% vs 67,6%, the latter 21,9% vs 15,6%) [90]. In addition, pathologies more prevalent in men in the past such as lung tumors, are increasing in women, mainly due to smoke and behavioral changes [91].

Emotional and behavioral stress, to which women are more exposed, is mainly related to all these pathologies [52,53,80,88,89] and represents the main link acting behind the risk factors [55] through the influence of the lifestyle changes; emotional stress is the cause more frequently reported by women prior an acute coronary syndrome onset [67]. Moreover, stress seems to alter the composition of the gut microbiota and can also trigger mood disorders like anxiety and depression promoting obesity and suggesting that the impact of stress on mood disorders and obesity might be at least partially attributable to the changes it causes in the gut microbiota [92]; there is emerging evidence for increased microbiome mediated contribution in women to cardiovascular risk factors and comorbidities including inflammatory processes, autoimmune disease, cardiometabolic disorders, and major depression [93].

Genetic and epigenetic aspects

Sex (genetically determined) and gender (environmental determined) interact and influence each other, that means that environment and lifestyle may modify the behavior of the genes; since behavior is always an interaction between nature and nurture, socialization may modify significant differences of sex [30,94,95] as well as gender may influence both the incidence of a disease and the biological sex [30]. In the last decades the research on genetic differences in both sexes increased. A recent research shows that 6,000 genes (of our 23,000 total) are active in different ways in men and women, presumably controlled directly or indirectly by SRY (sex-determining region Y gene), hormones and other genes on the X and Y. [96]. The hemostasis and the difference in the behavior of male and female cells have been investigated in the last years; in particular, a disparity in response to stress (e.g. the same oxidative stress) has been found in XX and XY cells, independently from their origin of species or histological origin, that is, XX cells are more prone to senescence and autophagic protection, whereas XY cells are more prone to apoptosis [97-100]. Many of these genes and cell sex response impact the likelihood of various diseases, becoming determinant in their onset or progression as well as the response to drugs and treatments [101] (e.g. the use of Aspirin in patients with cardio and cerebrovascular disease showed a 24% reduction of stroke in women and 32% reduction of cardiac attacks in men [102], whereas many other genes on X and Y chromosome of female type are involved in cardiovascular homeostasis and diseases, osteoporosis, neurodegeneration and cancer [103] and genes of male type are involved in hypertension [104]; this may explain why men and women differ greatly in the susceptibility to particular diseases - for example, Parkinson's disease is much more common in men, multiple sclerosis in women [104].

Interaction between sex and gender during lifetime determined by societal conditions (gender-sensitive environmental factors and epigenetic modifiers) as well as biological facts (sex hormones and sex-specific gene expression) affects germ cells, the newborn, the adult, and the development of disease in women and men [105]. In a recent clinical review Heider., *et al*. [67] refer that epigenetic modifications of genome, such as dysregulation of DNA methylation, contributes to adverse changes in gene expression and may affect cardiovascular risk factors including obesity, atherosclerosis, inflammation, hypertension, blood lipids and glucose metabolism leading to an increased risk to develop coronary artery disease.

There is much to do to better understand the complex biological and behavioral function of individual and the mechanism related to its responses to stress. The great challenges for the future are: 1) translation of stress effects on the brain and body from animal models to the human organism and vice versa; 2) evidence for stress effects on human brain structure and on mood and anxiety disorders in relation to gastrointestinal activity and food intake control; 3) current understanding as to how socioeconomic status affects brain and body health [106] and how stress affects more frequently women.

Short personal observation

During the routine activity of outpatient cardiological consultation, within 400 patients clinically assessed in 3 months, we examined 160 (40%) patients whose age was under 55 years old (75% female and 25% male). All of these patients came for at least one of the following cardiovascular symptoms: dyspnea, undefined chest pain, palpitations, hypertension or hypertensive episodes. During a 20 minute anamnestic and clinical assessment, each patient presented as frequent episodes, at least 3 additional or more somatic symptoms (nausea, muscular tension, reduced voluntary control, cold/sweaty hands, reduced sensorial function, shortness of breath, episodes of panic attack, fatigue, numbness/tingling in hands, inability to be still and calm, tiredness, dizziness, skin irritations, headache, chest pain, undefined pain in the body, sleeping disorders, frequent infections, gastroesophageal reflux, dyspepsia, sex drive loss, nightmares, others) and at least 3 additional or more behavioral symptoms (anxiety, insecurity, irritability, apathy, emotional instability, altered perception and management of emotions, morbid doubts, depression, low sense of purpose, obsessions, unsatisfaction, low self-worth sense, irrational fears, fall of motivation, excessive worry, inability to enjoy social relations, psychological dependence, concentration difficulties, indecisions, psychological discomfort, interpersonal maladjustment, loss of confidence, disturbed relationship with food and eating, smoke,

alcohol abuse, perfectionism, others). In about 75%, 120 patients, cardiovascular symptoms were expression of emotional/behavioral stress (negative clinical and instrumental evaluation for cardiac pathology), in about 25%, 40 patients, stress increased the expression of the real cardiovascular symptoms (positive cardiac pathology). During the evaluation we identified different factors acting behind and contributing to the occurrence of symptoms; the most frequent of these were job loss, job change, parent assistance, family problems (related to partner, children, parents), drug addiction of a family member, beliefs, duties and some other restrictions in lifestyle. A more or less short period of counseling (performed in few pts for 3 - 4 months) contributed to have an improved perception of symptoms and reduced perception of anxiety without medication (expressed by a slight improvement of mindfulness and awareness of the problems, progressive recovery of resilience and management of situations). These observations are in agreement with what we have observed many years ago studying patients (mainly women) with mitral valve prolapse and anxious syndrome, where anxiety and somatic symptoms were demonstrated to be mainly of iatrogenic origin, due to scarce information given by doctors; after a specific counseling treatment, the anxiety symptoms improved in prolapse patients, not in controls [107]. Previously and in the present observation, men showed a positive response earlier than women presumably due to the fact that stress was present in women since a long time and their global situation was more complex compared to men. The association of the assessment of the behavioral profile to the anamnestic and clinical consultation has revealed useful in detecting somatic and behavioral symptoms and maladaptive responses due to chronic stress; patient understanding as a whole person with her/his disease represents the most important base for the doctor-patient alliance for a better management of the disease.

Final Considerations

The level of civilization of a people can be assessed on the basis of the more or less bearable condition of women within the social organization [108,109]. Women have gone through history under the pressure of their role in the family and society. In ancient Egypt there was equality between man and woman for many centuries [110], but in most civilizations this equality disappeared due to assigned role by men and to cultural, religious, social, familiar, economic, political reasons but also prejudices, conveniences, convictions and many others; with the hellenization of Egypt by Greeks women become controlled and pass into custody, not presentable in public without being accompanied by a man, no social involvement, etc. [110], lasting many centuries until today in some societies. Gender importantly influenced women's behavior and the development in any field contributed to the evolution of women's condition. This process has not been free of objective and subjective difficulties that contribute to make the pathway long and tortuous and at the same time not yet concluded. Development and social achievements are stressful in themselves but for women they have been much more so. Stress, defined as a real or interpreted threat to physiological or integrity of an individual that results in physiological and behavioral responses, has been viewed in eastern cultures as an absence of inner peace and in western ones as a loss of control [19]. Stress may be considered the main link acting behind behavior and lifestyle of the majority of people and it is growing up with the development contributing to the evolution of women's conditions, to increase the social, political, economic and health attainments and to reduce the inequality. Stress, cultures, lifestyle and social situation probably influenced the different degree of success and social conditions reached by women, the differences in stress reactivity as potentially important risk factor and the different susceptibility to diseases in women within different cultures and societies [19,72].

In this hard, heavy and tiring pathway the evolutive process towards equality is slow, long and difficult as well as the prevalence of stress on general population is increasing, especially on women; these are most exposed to stress due to the typical cyclic neuro hormonal, psycho behavioral and cerebral structures and conflicting social, economic and cultural situations. So, women are called to pay a cost in terms of risk factors, lifestyle changes and diseases. In these conditions, what before appeared a strength in women, due to the biological protection, it is going to transform itself in weakness or less (no more) strength, the worst way to reach equality.

To consider man different from woman or equal to her, in our opinion is a big mistake. In reality man and woman are different biologically (nature, sex), should be equal socially, economically, politically and culturally (nurture, gender), but, due to their individualism, they

are definitively complementary in purpose and actions, they together complete each other due to their different characteristics. If this is correct and appliable, there is no need for women to load wrong lifestyle and uncorrected uses (and consequently risk factors, stress and diseases) in reaching equality in economic, social, political, cultural and work field. I think that the mindfulness of complementarity is the key for collaboration and integration among individuals of different sexes (and also different sexual identities, races, cultural extractions and social levels), reciprocal help and mutual support to win without pathological stress and to give a great impulse to much more important development. Society needs both, not warlike but collaborative and functionally complementary. Considering that stress may be controlled and reduced, equality and complementarity may be reached with an integration of the different characteristics of both, in the reciprocal respect of individualism, using a good lifestyle, less or no risk factors, probably in a better healthy way. Woman (man also) has to decide which dress she wants to wear; in our opinion stress dress is not the good choice.

Bibliography

1. Hans Selye. "A Syndrome produced by Diverse Nocuous Agents". *Nature* 138 (1936): 32.

2. Rozanski A., *et al.* "The Epidemiology, Pathophysiology, and Management of Psychosocial Risk Factors in Cardiac Practice. The Emerging Field of Behavioral Cardiology". *Journal of the American College of Cardiology* 45.5 (2005): 637-651.

3. Jenkins CD. "Recent evidence supporting psychologic and social risk factors for coronary disease". *The New England Journal of Medicine* 294.19 (1976): 987-994.

4. Jenkins CD. "Recent evidence supporting psychologic and social risk factors for coronary disease". *The New England Journal of Medicine* 294.19 (1976): 1033-1038.

5. Friedman M and Rosenman RH. "Association of specific overt behavior pattern with blood and cardiovascular findings". *The Journal of the American Medical Association* 169.12 (1959): 1286-1296.

6. Matsumoto Y., *et al.* "Do anger and aggression affect carotid atherosclerosis?" *Stroke* 24.7 (1993): 983-986.

7. Kheirabadi GR., *et al.* "Is there any association of anxiety-depressive symptoms with vascular endothelial function or systemic inflammation?" *Journal of Research in Medical Sciences* 18.11 (2013): 979-983.

8. Lichtman JH., *et al.* "Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: systematic review and recommendations: a scientific statement from the American Heart Association". *Circulation* 129.12 (2014): 1350-1369.

9. Tim S Nawrot., *et al.* "Public health importance of triggers of myocardial infarction: a comparative risk assessment". *Lancet* 377.9767 (2011): 732-740.

10. Spindler H and Pedersen SS. "Posttraumatic stress disorder in the wake of heart disease: prevalence, risk factors, and future research directions". *Psychosomatic Medicine* 67.5 (2005): 715-723.

11. Orth-Gomér K., *et al.* "Marital stress worsens prognosis in women with coronary heart disease: the Stockholm Female Coronary Risk Study". *The Journal of the American Medical Association* 284.23 (2000): 3008-3014.

12. Roest AM., *et al.* "Anxiety and risk of incident coronary heart disease: a meta-analysis". *Journal of the American College of Cardiology* 56.1 (2010): 38-46.

13. Roest AM., *et al.* "Prognostic association of anxiety post myocardial infarction with mortality and new cardiac events: a meta-analysis". *Psychosomatic Medicine* 72.6 (2010): 563-569.

14. Rozanski A., *et al.* "Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy". *Circulation* 99.16 (1999): 2192-2121.

15. Lagraauw HM., *et al.* "Acute and chronic psychological stress as risk factors for cardiovascular disease: Insights gained from epidemiological, clinical and experimental studies". *Brain, Behavior, and Immunity* 50 (2015): 18-30.

16. Hippocrates. De epidemiae in Opere, a cura di Mario Vegetti, Torino, UTET, 1965 (1996).

17. Aristotle, Fisica, I, 1, 184a, 10.

18. Thomas RJ. US Cardiology 2.1 (2005): 1-5.

19. Verma R., *et al.* "Gender differences in stress response: Role of developmental and biological determinants". *Industrial Psychiatry Journal* 20.1 (2011): 4-10.

20. Bangasser DA. "Sex differences in stress-related receptors: "micro" differences with "macro" implications for mood and anxiety disorders (link is external)". *Biology of Sex Differences* 4.2 (2013).

21. Wiegner L., *et al.* "Prevalence of perceived stress and associations to symptoms of exhaustion, depression and anxiety in a working age population seeking primary care - an observational study". *BMC Family Practice* 16 (2015): 38.

22. U.S. Department of Veteran Affairs, National Center for PTSD. Women, Trauma, and PTSD (2015).

23. World Health Organization. "What do we mean by "sex" and "gender"?" (2017).

24. Haig D. "The Inexorable Rise of Gender and the Decline of Sex: Social Change in Academic Titles, 1945–2001" (PDF)". *Archives of Sexual Behavior* 33.2 (2004): 87-96.

25. Udry J R. "The Nature of Gender". *Demography* 31.4 (1994): 561-573.

26. Scalia A. "United States Supreme Court Justice in J.E.B. v. Alabama ex rel. T.B., 114 S. Ct. 1419, 1436 n.1 (1994).

27. De Beauvoir S. "Il secondo sesso, 1949". Edition Italiana Il Saggiatore, Milano (2008).

28. Baggio G., *et al.* "Gender medicine: a task for the third millennium". *Clinical Chemistry and Laboratory Medicine* 51.4 (2013): 713-727.

29. Cherry K. "Psychology book, Holbrook, MA, United States".

30. Della Torre S and Maggi A. "Sex Differences: A Resultant of an Evolutionary Pressure?" *Cell Metabolism* (2017): 499-505.

31. Sheridan SL., *et al.* "The effect of giving global coronary risk information to adults: a systematic review". *Archives of Internal Medicine* 170.3 (2010): 230-239.

32. Cacioppo JT., *et al.* "Social neuroscience and its relationship to social psychology". *Social Cognitive* 28.6 (2010): 675-685.

33. Brizendine L. "The female brain". Broadway Books, New York (2006).

34. Rajmohan V and Mohandas E. "The limbic system". *Indian Journal of Psychiatry* 49.2 (2007): 132-139.

35. Tomasi D., *et al.* "Sex differences in sensory gating of the thalamus during auditory interference of visual attention tasks". *Neuroscience* 151.4 (2008): 1006-1015.

36. Ramirez-Moreno DF and Sejnowski TJ. "A computational model for the modulation of the prepulse inhibition of the acoustic startle reflex". *Biological Cybernetics* 106.3 (2012): 169-176.

37. Marson O., *et al.* "The Anteroventral Third Ventricle Region Participation in the Regulation of Blood Pressure in Conscious Dogs". *Hypertension* 7 (1985).

38. Xin J., *et al.* "Brain Differences Between Men and Women: Evidence From Deep Learning". *Frontiers in Neuroscience* 13.185 (2019): 1-10.

39. Cosgrove KP., *et al.* "Evolving knowledge of sex differences in brain structure, function, and chemistry". *Biological Psychiatry* 62 (2007): 847-855.

40. Parsey R., *et al.* "Effects of sex, age, and aggressive traits in man on brain serotonin 5-HT1A receptor binding potential measured by PET using (C-11) WAY-100635". *Brain Research* 954 (2002): 173-182.

41. Sanacora G., *et al.* "Reduced cortical GABA levels in depressed patients determined by proton magnetic resonance spectroscopy". *Archives of General Psychiatry* 56 (1999): 1043-1047.

42. Nissen JC. "Microglia function across the spectrum of age and gender". *International Journal of Molecular Sciences* 18 (2017): 1-13.

43. Soares MC., *et al.* "Hormonal mechanisms of cooperative Behavior". *Philosophical Transactions of the Royal Society B* 365 (2010): 2737-2750.

44. Ryan RM and Frederick C. "On energy, personality, and health: subjective vitality as a dynamic reflection of well-being". *Journal of Personality* 65.3 (1997): 529-565.

45. Gross JJ. "Antecedent- and response-focused emotion regulation: divergent consequences for experience, expression, and physiology". *Journal of Personality and Social Psychology* 74.1 (1998): 224 -237.

46. Bonanno GA., *et al.* "The importance of being flexible: the ability to enhance and suppress emotional expression predicts long-term adjustment". *Psychological Science* 15.7 (2004): 482-487.

47. Selye H. "A Syndrome Produced by Diverse Nocuous Agents". *Nature* 138 (1936): 32.

48. Bruce S McEwen. "Physiology and Neurobiology of Stress and Adaptation: Central Role of the Brain". *Physiological Reviews* 87 (2007): 873-904.

49. Mariotti A. "The Effects of Chronic Stress on Health: New Insights Into the Molecular Mechanisms of Brain-Body Communication". *Future Sci OA* 1.3 (2015): FSO23.

50. Sterling P and Eyer J. "Allostasis: a new paradigm to explain arousal pathology". In: Handbook of Life Stress, Cognition and Health, edited by Fisher S, Reason J. New York: Wiley (1988): 629-649.

51. Dictionary.com Unabridged. Retrieved April 24, 2017 - Random House Dictionary, © Random House, Inc (2017).

52. Cohen S., *et al.* "Psychological stress and disease". *The Journal of the American Medical Association* 298 (2007): 1685-1687.

53. Liu Y-Z., *et al.* "Inflammation: The Common Pathway of Stress-Related Diseases". *Frontiers in Human Neuroscience* 11 (2017): 316.

54. Gullace G and Khalaf H. "Preclinical Diagnosis and Risk Assessment of Atherosclerosis –At Birth? At Event? When is Best?" *European Cardiology* 7.3 (2011): 164-166.

55. Gullace G. "Behavioral Cardiovascular Risk Factors: Changing Perspective to Approach the Problem". *Journal of Cardiology and Cardiovascular Therapy* 2.1 (2016): 1-5.

56. Statistic Brain Research Institute, American Institute of Stress, NY (2017).

57. Yusuf S., *et al.* "Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study". *Lancet* 364 (2004): 937-952.

58. Rainforth MV., *et al.* "Stress Reduction Programs in Patients with Elevated Blood Pressure: A Systematic Review and Meta-analysis". *Current Hypertension Reports* 9 (2007): 520-528.

59. Anderson JW., *et al.* "3Blood Pressure Response to Transcendental Meditation: A Meta-analysis". *American Journal of Hypertension* 21 (2008): 310-316.

60. Lehman BJ., *et al.* "Relationship of early life stress and psychological functioning to blood pressure in the CARDIA study". *Health Psychology* 28 (2009): 338-346.

61. Ali T and Harty RF. "Stress-induced ulcer bleeding in critically ill patients". *Gastroenterology Clinics of North America* 38 (2009): 245-265.

62. Bauer ME., *et al.* "The role of stress factors during aging of the immune system". *Annals of the New York Academy of Sciences* 1153 (2009): 139-152.

63. Black PH. "Stress and the inflammatory response: a review of neurogenic inflammation". *Brain, Behavior, and Immunity* 16 (2002): 622-653.

64. Kelly KW. "From hormones to immunity: the physiology of immunology". *Brain, Behavior, and Immunity* 18 (2004): 95-113.

65. Ippoliti F., *et al.* "Women and stress: influence of psychological status on immunity". *Acta Médica Rome* 2-3 (2003): 286-294.

66. Tran., *et al.* "Patterns and temporal trends of comorbidity among adult patients with incident cardiovascular disease in the UK between 2000 and 2014: A population-based cohort study". *PLOS Medicine* 15.3 (2018): e1002513.

67. Haider A., *et al.* "Sex and gender in cardiovascular medicine: presentation outcomes of acute coronary syndrome". *European Heart Journal* 41 (2020): 1328-1336.

68. Takeda E., *et al.* "Stress control and human nutrition". *Journal of Investigative Medicine* 51 (2004): 139-145.

69. Carson DS., *et al.* "Cerebrospinal fluid and plasma oxytocin concentrations are positively correlated and negatively predict anxiety in children". *Molecular Psychiatry* 20.9 (2015): 1085-1090.

70. Wang J., *et al.* "Gender difference in neural response to psychological stress". *SCAN* 2 (2007): 227-239.

71. Taylor SE., *et al.* "Biobehavioral responses to stress in females: Tend-and-befriend, not fight-or-flight". *Psychological Review* 107 (2000): 411-429.

72. Kajantie E and Phillips DI. "The effects of sex and hormonal status on the physiological response to acute psychosocial stress". *Psychoneuroendocrinology* 31 (2006): 151-178.

73. Love TM. "The impact of oxytocin on stress: the role of sex". *Current Opinion in Behavioral Sciences* 23 (2018): 136-142.

74. Matsushita H., *et al.* "Oxytocin and Stress: Neural Mechanisms, Stress-Related Disorders and therapeutic approaches". *Neuroscience* 417 (2019): 1-10.

75. Weissman MM and Olfson M. "Depression in women: implications for health care research". *Science* 269 (1995): 799-801.

76. Istat: La situazione del Paese nel 2008. Rapporto annuale, Roma (2009).

77. Epidemiological Catchment Area (ECA) survey and National Comorbidity Survey (NCS) in the US (2000, 2003).

78. US National Institute of Mental Health. The Numbers Count Mental Disorders in US (2006).

79. Demos: Osservatorio sul Nord Est (2017).

80. Comitato Nazionale di Bioetica. "La sperimentazione farmacologica sulle donne (2008).

81. Aryal S., *et al.* "COPD and gender differences: an update". *Translational Research* 162 (2013): 208-218.

82. Shah AJ., *et al.* "Depression and history of attempted suicide as risk factors for heart disease mortality in young individuals". *Archives of General Psychiatry* 68 (2011): 1135-1142.

83. Rich-Edwards JW., *et al.* "Physical and Sexual Abuse in Childhood as Predictors of Early-Onset Cardiovascular Events in Women". *Circulation* 126 (2012): 920-927.

84. Schwab K., *et al.* "Insight the Global Competitiveness Report 2016–2017". Report of the World Economic Forum, Geneva (2016): 8-30.

85. Peters SAE., *et al.* "Sex differences in the prevalence of and trends in cardiovascular risk factors, treatment and control in the United States 2001 to 2016". *Circulation* 139 (2019): 1025-1035.

86. Backholer K., *et al.* "Sex Differences in the Relationship Between Socioeconomic Status and Cardiovascular Disease: A Systematic Review and Meta-Analysis". *Journal of Epidemiology and Community Health* 71 (2017): 550-557.

87. Pelletier R., *et al.* "Sex Versus Gender-Related Characteristics: Which Predicts Outcome After Acute Coronary Syndrome in the Young?" *The American College of Cardiology* 67 (2016): 127-135.

88. Tawakol A., *et al.* "Relation Between Resting Amygdalar Activity and Cardiovascular Events: A Longitudinal and Cohort Study". *Lancet* 389 (2017): 834-845.

89. Fiechter M., *et al.* "Association between resting amygdalar activity and abnormal cardiac function in women and men: a retrospective cohort study". *European Heart Journal - Cardiovascular Imaging* 20 (2019): 625-632.

90. Weir HK., *et al.* "Heart Disease and Cancer Deaths - Trends and Projections in the United States, 1969-2020- Prev". *Chronic Diseases* 13 (2016): 160211.

91. Egleston BL., *et al.* "Population-based Trends in Lung Cancer Incidence in Women". *Seminars in Oncology* 36.6 (2009): 506-515.

92. Bridgewater LC., *et al.* "Gender-based differences in host behavior and gut microbiota composition in response to high fat diet and stress in a mouse model". *Scientific Reports* 7 (2017): 10776.

93. Markle JG., *et al.* "Sex differences in the gut microbiome drive hormone-dependent regulation of autoimmunity". *Science* 339 (2013): 1084-1088.

94. Mills M. "Wrong Question: Is It Nature or Nurture?" Psychology Today (2011).

95. Mills M. "Sex Difference vs. Gender Difference?" Psychology Today (2011).

96. Gershoni M and Pietrokovski S. "The landscape of sex-differential transcriptome and its consequent selection in human adults". *BMC Biology* 15 (2017): 7.

97. Chen C., *et al.* "Apoptosis and autophagy contribute to gender difference in cardiac ischemia-reperfusion induced injury in rats". *Life Sciences* 93 (2013): 265-270.

98. Muralimanoharan S., *et al.* "Sexual dimorphism in the fetal cardiac response to maternal nutrient restriction". *Journal of Molecular and Cellular Cardiology* 108 (2017): 181-193.

99. Du L., *et al.* "Starving neurons show sex difference in autophagy". *Journal of Biological Chemistry* 284 (2009): 2383-2396.

100. Straface E., *et al.* "Cell sex determines anoikis resistance in vascular smooth muscle cells". *FEBS Letters* 583 (2009): 3448-3454.

101. Meyer BJ. "Sex and death: from cell fate specification to dynamic control of X chromosome structure and gene expression". *Molecular Biology of the Cell* 29 (2018): 2616-2621.

102. Berger JS., *et al.* "Aspirin in the primary prevention of cardiovascular disease in women and men: a gender-specific meta-analysis". *The Journal of the American Medical Association* 295 (2005): 306-313.

103. Franconi F., *et al.* "Human cells involved in atherosclerosis have a sex". *International Journal of Cardiology* 228 (2017): 983-1001.

104. Graves J. "X, Y and the genetics of sex". The conversation (2017).

105. The EU Gen Med, Cardiovascular Clinical Study Group". *European Heart Journal* 37 (2016): 24-34.

106. McEwen BS. "Physiology and Neurobiology of Stress and Adaptation: Central Role of the Brain". *Physiological Reviews* 87 (2007): 873-904.

107. Gullace G., *et al.* "Aspetti neurochirurgici e psicologici del prolasso della mitrale". In: Prolasso della Mitrale. Sigma Tau. Roma (1987): 33.

108. Ziegler HDC and Champollion H. "L'Egypte de Jean-Francois Champollion Lettres and Journaux De Voyage (1828-1829)" 1998.

109. Champollion-Figeac, Egypte ancienne, coll. L'Univers (1839).

110. Jacq C. "Le donne dei faraoni. Arnoldo Mondadori Editore, Milano 1997. From Les Aegyptiennes. Librairie academique Perrin (1996).

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