

The Metabolic Syndrome, Depression, and Cardiovascular Disease: Interrelated Conditions that Share Pathophysiologic Mechanisms

Rijk O.B. Gans, MD, PhD

University Medical Center Groningen, Hanzeplein 1 9700 RB, Groningen, The Netherlands

The metabolic syndrome

The concept of the metabolic syndrome has existed for at least 80 years [1]. It was first described in the 1920s by Kylin, a Swedish physician, who noted a clustering of hypertension, hyperglycemia, and gout. Next, the concept of upper-body adiposity (android or male-type obesity, as opposed to female-type obesity) was recognized as the obesity phenotype that was commonly associated with the metabolic abnormalities associated with type 2 diabetes and cardiovascular disease. In 1988 Reaven described insulin resistance as the central feature of syndrome X, a constellation of hyperglycemia, hypertension, low high-density lipoprotein cholesterol levels, and elevated very-low-density lipoprotein triglyceride levels. More recently, the term “metabolic syndrome” (visceral obesity, dyslipidemia, hyperglycemia, and hypertension) was coined, mostly because its clinical phenotype, foremost an increase in waist circumference, helps identify individuals who are at increased risk for type 2 diabetes and cardiovascular disease.

Several sets of diagnostic criteria with different cut-off values for waist circumference, blood pressure, glucose, high-density lipoprotein cholesterol levels, and triglycerides have been, proposed by various medical societies. The International Diabetes Federation recently proposed a worldwide definition that incorporates ethnic-specific waist circumference cut-off values [2]. It should be realized, however, that the concept of the metabolic syndrome as a medical diagnosis is under debate, largely because this cluster

E-mail address: r.o.b.gans@int.umcg.nl

of metabolic abnormalities and cardiovascular risk factors lacks a definitive single or major unifying pathophysiologic process, and treatment of the syndrome does not differ from treatment of its components [3]. Nonetheless, this clustering of closely related cardiovascular risk factors has been focus of much interest because of its putative association with cardiovascular disease and diabetes and also with a vast array of other diseases, including cancer, schizophrenia, and depression (Box 1).

Box 1. The metabolic syndrome: changes associated with insulin resistance

Lifestyle

Cigarette smoking
Sedentary behavior

Lipoproteins

Increased free fatty acids
Increased apolipoprotein B
Decreased apolipoprotein A-1
Small, dense low-density lipoprotein and high-density lipoprotein
Increased apolipoprotein C-III

Prothrombotic

Increased fibrinogen
Increased plasminogen activator inhibitor 1
Increased viscosity

Inflammatory markers

Increased white blood cell count
Increased interleukin 6
Increased tumor necrosis factor
Increased resistin
Increased C-reactive protein
Decreased adiponectin

Vascular

Microalbuminuria
Increased asymmetric dimethylarginine
Increased uric acid
Increased homocysteine

Adapted from Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet* 2005;365:1420.

Relationship of metabolic syndrome with cardiovascular disease, type 2 diabetes, and depression

The metabolic syndrome is associated with an increased risk of both diabetes and cardiovascular disease. This association is not surprising because the definition of the syndrome comprises established risk factors for diabetes and cardiovascular disease. For cardiovascular disease, the relative hazard ratios range from 2 to 5 [1]. The risk of diabetes is substantial also. The cumulative incidence of diabetes in subjects with impaired glucose tolerance (and obesity) who participated in the diabetes prevention studies was approximately 30% after 3 years of follow-up [4].

A large body of evidence supports an association between type 2 diabetes, cardiovascular disease, and, recently, metabolic syndrome and the occurrence of depression. Individuals who have diabetes are twice as likely to develop depression as individuals who do not have diabetes. Interestingly, one study indicated an increased risk of depression in type 2 diabetes only when comorbid cardiovascular diseases were present [5]. The prevalence of metabolic syndrome among women who have a history of depression is twice as high as that among women who have no history of depression [6]. If one accepts obesity as a surrogate marker of the metabolic syndrome, a potential gender difference may exist. In women in the United States, obesity increases the risk of being diagnosed with major depression by 37%, whereas obese men have a 37% lower risk of depression than men of normal weight [7]. Conversely, depression is associated with an increased incidence of diabetes, which in turn seems to be mediated largely through central adiposity [8]. When depression complicates diabetes, it is significantly associated with nonadherence to medication and self-care recommendations, poor metabolic control, and, thus, increased odds of having diabetic and cardiovascular complications (see the article by Egede in this issue).

Depressed patients who do not have overt diabetes also have an increased relative risk for developing cardiovascular complications that varies between 1.5 and 2.7 depending on the magnitude of depressive symptoms [9]. Notably, also in the absence of predefined psychiatric diagnoses as major depression, psychologic factors (especially when occurring in combination) result in an increased risk for cardiovascular complications are to the risks associated with hypercholesterolemia, hypertension, and other major risk factors [10,11].

Others have postulated that there might exist a subtype of vascular depression in which cerebrovascular disease predisposes, precipitates, or perpetuates a depressive syndrome [12].

A life-course approach

The aforementioned relationships are derived largely from conventional epidemiologic studies that merely studied classic disease models (eg, smoking or obesity) as exponents of adult lifestyle that turned out to be

modifiable risk factors for cardiovascular disease and diabetes. This epidemiologic approach, however, does not acknowledge many other observations that do not fit such a simple disease model. Throughout life various biologic, psychologic, and social factors act independently, cumulatively, and interactively on health and disease in adult life (Fig. 1). In a life-course epidemiologic approach the risk of disease is related to physical and social exposures during gestation, childhood, and adolescence as well as during later adult life [13].

The importance of the temporal relationships between these exposures is underscored by the existence of so-called “critical periods.” For example, studies have shown that poor growth in utero relates to cardiovascular disease, type 2 diabetes, and insulin resistance in adult life. Moreover, this relationship is particularly strong or is observed only in subjects who become obese in childhood, adulthood, or both [14–16]. This finding suggests that fetal exposure may alter the metabolic system permanently but is still under influence of exposures acting later in life. Likewise, a relationship between low birth weight and psychologic distress in adult life has been documented [17].

The life-course approach also incorporates and integrates social risk processes. Socially patterned exposures during childhood, adolescence, and early adult life have been shown to influence adult disease risk and socioeconomic status (SES) [18]. SES is characterized as a composite of factors such as occupational status, economic resources, education, and social status. Longitudinal studies have indicated a strong inverse gradient between SES level and adverse cardiac events. Low SES is accompanied by poorer health habits and higher frequencies of coronary risk factors and, as would be

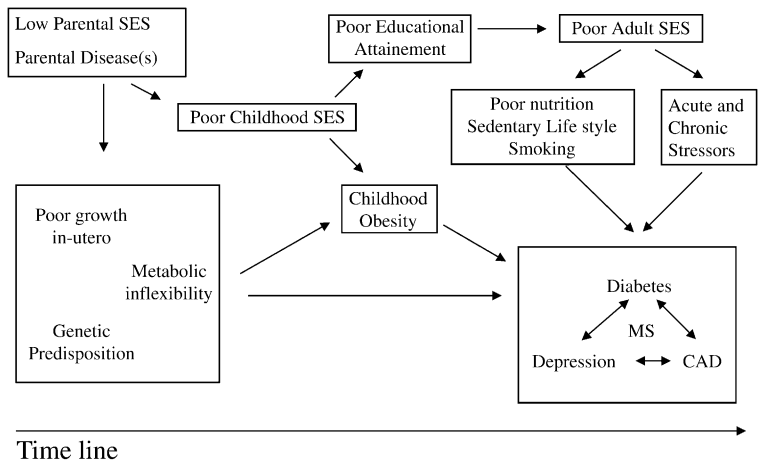


Fig. 1. Biologic and psychosocial exposures across the life timeline that influence the metabolic syndrome. CAD, coronary artery disease; MS, Metabolic Syndrome; SES, socioeconomic status.

expected, is associated with an increased prevalence of the metabolic syndrome [19,20]. At the same time, low SES is considered a chronic stressor, and persons who have low SES also have higher frequencies of mental disorders (ie, anxiety and depression) [21].

Accumulation of risk is another concept that plays a pivotal role in the life-course model of chronic diseases. More than 80 years ago Selye [22] recognized that the physiologic systems activated by stress can protect and restore but also can damage the body. To understand this paradox, the concept of allostasis has been introduced [23]. Allostasis is defined as the ability to achieve stability through change. The price of this accommodation to stress has been defined as the allostatic load [23]. It follows that acute stress (eg, the “fright, flight or fight” response or major life events) and chronic stress (the cumulative load of minor, day-to-day stresses) can add to the allostatic load and have long-term consequences. Subacute stress is defined as an accumulation of stressful life events over a duration of months and includes emotional factors such as hostility and anger as well as affective disorders such as major depression and anxiety disorders. Chronic stressors include factors such as low social support, low SES, work stress, marital stress, and caregiver strain and present as feelings of fatigue, lack of energy, irritability, and demoralization. The life-course approach is complementary to this concept and argues that factors that raise the risk of disease or promote good health may accumulate gradually over the life course, although their effects may have greater impact on later health at specific developmental periods than at other times [13].

Pathophysiologic mechanisms

To integrate biologic and psychosocial pathways, the life-course approach requires understanding the natural history and physiologic trajectory of normal biologic systems, including the brain, and how these systems are affected by chronic exposure to disease risks.

Normal stress response

As stated previously, the response of the body to maintain its stability in the face of a challenge (eg, infection or an instable social situation) comprises the allostatic response. The brain plays a pivotal role in the maintenance of body homeostasis [23]. For this purpose the brain has two avenues of communication: hormones and neurons. The sensory organs inform the brain about the external environment. The state of the internal environment is reported to the spinal cord and brain stem through feedback from virtually all organs [24]. In addition, the brain integrates information about circulating hormone and substrate availability through receptors located in areas where the blood–brain barrier allows this information to be passed to the brain. Processing of internal and external stress stimuli results

in responses of the autonomic nervous system, the hypothalamus-pituitary-adrenal (HPA) axis, and the cardiovascular, metabolic, and immune systems.

The immune system is characterized by two components, the innate and the acquired immune systems. In general, the innate and the acquired immune systems react to pathogens and other antigens with an inflammatory response that, if severe enough, may include an acute-phase response as well as the formation of an immunologic memory. Fever is an example of the neuroendocrine changes that characterize the acute-phase response. Other clinical manifestations reflect complex interactions among cytokines, the HPA axis, and other components of the neuroendocrine system. The behavioral changes that often accompany this response (eg, anorexia, somnolence, lethargy, irritability, depressed mood, and social withdrawal) also reflect responses to cytokines. The HPA axis and the autonomic nervous system contain the acute-phase response and dampen cellular immunity. In addition, inflammatory input to the hypothalamus activates a reflexive, fast, and subconscious anti-inflammatory response (which until recently was unknown) through the efferent vagal nerve [25]. Vagal cholinergic activation directly inhibits the activation of macrophages and the release of cytokines at the site of injury. It serves to localize invasive events from several local sites, mobilizes defenses, and creates memory to improve chances for survival. At the same time it prevents spillage of inflammatory products into the circulation.

When the threat is gone, these systems must be shut off. In the setting of repeated hits from multiple stressors, lack of adaptation with repeated exposure, a delayed shutdown, or an inadequate response that leads to compensatory hyperactivity of other mediators (eg, impaired counter-regulation of cytokines [inflammatory state] caused by inadequate secretion of glucocorticoids) results in wear and tear from chronic overactivity or underactivity of these allostatic systems (allostatic load).

Insulin resistance

The most accepted and unifying hypothesis to describe the pathophysiology of the metabolic syndrome is insulin resistance, although quantification of insulin action in vivo is not always strongly related to the presence of the syndrome [26]. Alterations that are not included in the diagnostic criteria for the metabolic syndrome but have been reported in association with insulin resistance are depicted in Box 1. Several studies have reported an association between insulin resistance and depressive disorder, although the association is not seen universally [27–30].

Insulin resistance and major depression share several disturbances in the aforementioned physiologic systems that include the HPA axis, the autonomic nervous system, the immune system, platelets, and endothelial function.

Activation of the hypothalamus-pituitary-adrenal axis

Depression is often accompanied by hypercortisolemia. Associated findings include attenuation of the corticotropin response to the administration of corticotrophin-releasing factor and nonsuppression of cortisol secretion after dexamethasone administration. Hypercortisolemia in association with blunted growth and sex hormones promotes central obesity and contributes to increased insulin resistance and diabetes among depressed subjects [31]. The presence of hypercortisolemia in insulin resistance has been documented in some, but not all, studies. A small case-control study has shown some evidence for increased cortisol production in the metabolic syndrome as well [32]. Notably, a contributory role for cortisol metabolism in the pathogenesis of the metabolic syndrome has been postulated. Deregulation of 11 betahydroxysteroiddehydrogenase, an enzyme that converts cortisol into cortison (which cannot activate the glucocorticoid receptor), may result in excess cortisol exposure at the tissue level and induce visceral adiposity [33].

Autonomic nervous system imbalance

In healthy persons the autonomic balance in the body varies depending on the activity it performs. The sympathetic nervous system is predominant in the active (“fight, fright, and flight”) period, whereas the parasympathetic nervous system rules the body in the inactive (“rest and digest”) period. With physical activity in the active period, the movement apparatus requires blood, and the digestive apparatus slows down; the opposite holds for the inactive period. Thus, blood vessels in these different regions must receive different autonomic signals depending on the time of the day. Recently, neuroanatomic studies have shown the existence of compartmentalization of autonomic motor neurons, thus providing a basis for selective changes of the sympatho-parasympathetic balance in different compartments of the body [34]. Parasympathetic input to fat tissue has been shown to enhance insulin sensitivity and fat accumulation.

Abnormalities in autonomic nervous system activity are consistent findings in depression, insulin resistance, and, more recently, the metabolic syndrome. Impaired autonomic function previously has been associated with elevated concentrations of serum insulin and decreased insulin sensitivity (markers of insulin resistance), independent of glucose levels [35,36]. Depressed patients commonly manifest higher resting heart rates than healthy controls and exhibit autonomic nervous system dysfunction, including diminished heart rate variability (HRV), baroreflex dysfunction, and increased QT variability, all of which have been linked to increased cardiac mortality, including sudden death [37].

Decreased HRV seems to be predictive of diabetes. HRV reflects fluctuations in autonomic inputs to the heart and comprises both parasympathetic

and sympathetic inputs. In the Atherosclerosis Risk in Communities study, subjects who had reduced HRV in the low-frequency (LF) range (a marker of decreased parasympathetic input) and high resting heart rate (a global marker of poor autonomic nervous system modulation) were at increased risk for developing type 2 diabetes, and low levels of physical activity and central adiposity played a large role in this association [38]. Persons who have low HRV and correspondingly low LF power presumably have considerable resting sympathetic input. Increased sympathetic activation leads to enhanced catecholamine release and consequent increases in circulating free fatty acids and thus increased insulin resistance.

It has been postulated that in the metabolic syndrome the sympathetic branch prevails in the thorax (heart and large vessels) and movement compartment (skeletal muscles), leading to high blood pressure and impaired glucose uptake by the muscle (ie, insulin resistance). In the intra-abdominal compartment, however, the autonomic nervous system balance is shifted in favor of the parasympathetic branch, resulting in increased insulin secretion and growth of intra-abdominal fat tissue [34]. Cardiac sympathetic predominance and increased catecholamine output has recently been shown in subjects who have metabolic syndrome [32]. Notably, psychosocial factors seemed to explain a considerable part of this association.

Endothelial dysfunction

The endothelium is a critical determinant of vascular tone, reactivity, inflammation, vascular remodeling, maintenance of vascular patency, and blood fluidity. In the healthy state the normal homeostatic properties of the endothelium favors vasodilatation, low permeability, anticoagulation, and poor adhesiveness with respect to leukocytes and platelets. Different forms of injury (eg, hyperlipidemia, diabetes, hypertension, and smoking) increase the vasomotor tone and the vasomotor response of arteries to various stimuli, including mental stress, increase the adhesiveness and permeability of the endothelium, and induce a procoagulant state as a result of the formation of vasoactive molecules, cytokines, and growth factors. The concomitant and ongoing inflammatory response at the tissue as well as systemic level supposedly propagates tissue injury and results in progressive atherosclerosis [39].

Depression is associated with a heightened incidence of endothelial dysfunction (ie, impaired flow-mediated vasodilation) among various cohorts, including young and otherwise healthy depressed patients [40]. Impaired endothelial function is a putative mechanism that links insulin resistance and cardiovascular disease, including hypertension [41–43]. It comes as no surprise that endothelial function is found to be impaired in the metabolic syndrome as well [44].

Thus far, the putative mechanisms behind the association between endothelial dysfunction and depression are largely unknown but may involve stimulation of the HPA axis, activation of the sympathetic nervous system,

endothelial dysfunction, and also potential synergy induced by peripheral effects. One such mechanism in the presence of the metabolic syndrome has recently been postulated as vasocrine signaling from perivascular fat that inhibits insulin-mediated capillary recruitment through the release of the adipocytokine tumor necrosis factor [45].

Platelets

Insulin resistance is associated with changes in platelets (and fibrinolysis and coagulation) that favor a prothrombotic state [46]. Depressed patients also may develop significant impairments in platelet function. In the presence of concomitant risk factors for coronary artery disease, enhanced platelet reactivity and release of platelet products such as platelet factor 4 and b-thromboglobulin, increased concentration of functional glycoprotein IIb/IIIa receptors, and a hyperactive 5-hydroxytryptamine transporter2A receptor signal transduction system and related increased responsiveness of platelets to serotonin have been shown [47]. Whatever its cause, enhanced platelet reactivity may contribute to cardiovascular complications in the setting of atherosclerotic disease. For this reason a cardioprotective effect of selective serotonin reuptake inhibitors has been postulated but remains to be proven [48].

Inflammation

Lately, much attention has been directed to inflammation as the central feature of atherosclerosis. The balance between inflammatory and anti-inflammatory activity in the vessel wall governs the progression of atherosclerosis, in close interactions with various metabolic factors of which lipid and products of lipid peroxidation are the most prominent [49]. Activated immune cells in the atherosclerotic plaque produce inflammatory cytokines (interferon-gamma, interleukin-1, and tumor necrosis factor) that induce the production of substantial amounts of interleukin-6. When these cytokines spill into the systemic circulation, interleukin-6 stimulates the production of large amounts of acute-phase reactants, including C-reactive protein, serum amyloid A, and fibrinogen, especially in the liver. The inflammatory process in the atherosclerotic artery thus may lead to increased blood levels of inflammatory cytokines and other acute-phase reactants. A moderately elevated C-reactive protein level on a highly sensitive immunoassay has been shown to be an independent risk factor for coronary artery disease in a healthy population [43]. Levels of C-reactive protein and interleukin-6 are elevated in patients who have unstable angina and myocardial infarction, with higher levels predicting worse prognosis [50]. Visceral adipose tissue has turned out to be another major production site of these cytokines and thus may contribute to this inflammatory burden in persons who have the metabolic syndrome.

Depression has also been found to be associated with increases in C-reactive protein, interleukin-6, tumor necrosis factor, and other inflammatory proteins [51,52]. The possibility of insufficient dampening of the inflammatory response related to diminished glucocorticoid sensitivity in depression has been suggested [52]. Whether this reduced sensitivity relates to increased cardiovascular risk has yet not been studied.

The significance of psychosocial stress

It follows from the previous sections that psychosocial factors, such as a physical threat, may induce an allostatic response and thus have profound effects on the integrity of the body and add to the wear and tear on tissues and organs. Excessive weight gain, for example, is a physical threat that, in turn, may be the outcome of a complex interaction between an adverse life style caused by psychosocial factors in the setting of a genetic predisposition to metabolic inflexibility [53] and complex cross-talk between the brain and the gut. In this section, the effect of psychosocial factors on the cardiovascular system and some new insight on the relationship between psychosocial factors and food intake are addressed.

Wear and tear on the cardiovascular system

Semiacute psychosocial stress is associated with increased cardiovascular morbidity and mortality. The incidence of sudden death increases directly after a major disaster [54]. Also, reversible cardiac failure caused by sudden emotional distress has been reported [55]. A major role in the pathogenesis of these complications has been ascribed to activation of the HPA axis. Evidence of neurohumoral arousal and elevation of arterial blood pressure has been noted in situations associated with acute and subacute stress [56,57]. Exaggerated physiologic responses to acute stressors also have been shown in depressed, hostile, and low-SES subjects [37,58,59]. Chronic stress and hostility have been linked to increased reactivity of the fibrinogen system and of platelets, both of which increase the risk of myocardial infarction [60,61]. Also, tension and anxiety over a more prolonged period of time have been observed to be independent risk factors of incident coronary heart disease, atrial fibrillation, and mortality [62]. This notion is corroborated by animal studies among *Cynomolgus* monkeys that have reported an association between social isolation and hypercortisolemia and reversible increases in resting heart rates, suggesting that social factors promote atherogenesis through activation of the HPA axis and the autonomic nervous system [63,64].

Recently, the increased mortality of elderly people in the year following the hospital admittance of a spouse has been demonstrated [65]. Notably, the hospitalization of a spouse was associated with a risk of death for the partner within the first 30 days that was almost as great as the risk associated with the death of a spouse. Although factors related to harmful

behavior by the partner who has been left behind cannot be ruled out in the latter study, the time frame is such that a direct stress-mediated effect is suggested.

Other studies have linked sympathetic hyperresponsivity to the induction of myocardial ischemia during exercise and mental stress and to predictions of the future development of hypertension and progression of atherosclerosis [66–72]. Increased systemic vascular resistance during mental stress testing is the most significant hemodynamic factor associated with mental stress-induced myocardial ischemia and most likely is the result of peripheral endothelial dysfunction [73]. Inhibition of cortisol production has been shown to prevent mental stress-induced endothelial dysfunction and baroreflex impairment, again pointing to a significant role of the HPA axis [74]. Interestingly, endothelial dysfunction after mental stress has been shown in hypertensive subjects but not in patients who have hypercholesterolemia [75]. This finding is noteworthy because both hypertension and hypercholesterolemia are risk factors for atherosclerosis and cardiovascular disease, and endothelial dysfunction is a distinct feature of both diseases. These findings suggest different underlying mechanisms for endothelial dysfunction to account for the observed difference. When a similar stressor exerts a distinct response in subjects that, depending on the disease, that makes them more susceptible to atherosclerosis, the question is raised whether different stressors might likewise evoke different pathophysiologic mechanisms and, possibly, different atherosclerotic manifestations. The latter possibility is supported by animal data. Exposure of Watanabe heritable hyperlipidemic rabbits to two different chronic stressors (ie, an unstable social environment or social isolation) resulted in more atherosclerosis than seen in a control group, but the two stressed groups exhibited different metabolic consequences and patterns of accrued atherosclerosis [76]. Animals that were socially isolated were relatively sedentary, gained more body weight, and developed more profound hyperinsulinemia than the socially unstable group. They exhibited no stressful behaviors, such as cowering, vocalizations, or sleep or feeding disturbances, and had low corticosterone levels compared with the socially unstable group. At the same time they had higher resting heart rates and more pronounced abdominal aortic atherosclerosis.

The extent to which psychosocial factors affect the cardiovascular system through its interaction with the immune system has not been widely investigated thus far, but its potential significance is suggested by studies that have documented increased severity of the common cold related to psychologic stress and lack of social support [77,78]. As in depression, insufficient dampening of the inflammatory response related to diminished glucocorticoid sensitivity might be of importance [52]. Whether facilitation of sustained expression of inflammatory mediators under the influence of psychosocial factors might foster cardiovascular complications remains speculative.

Food, stress, and reward

The limbic system is a complex set of structures that includes the hypothalamus, the hippocampus, the amygdala, and several nearby areas. It seems to be primarily responsible for emotional life and the formation of memories. As described earlier, the hypothalamus is mainly responsible for homeostasis and thereby regulates heart rate, blood pressure, breathing, and gastrointestinal motility and also regulates behavior and arousal in response to hunger, thirst, and emotional circumstances (eg, pain, pleasure, sex, fear, or hostility).

Repeated stress especially affects the hippocampus, which participates in verbal memory and is particularly important for the memory of context, that is, the time and place of events that have a strong emotional bias [23]. Moreover, glucocorticoids are involved in remembering the context in which an emotionally laden event took place. The hippocampus also regulates the stress response and acts to inhibit the response of the HPA axis to stress.

The hypothalamus, especially the arcuate nucleus, is relatively accessible to circulating factors and receives inputs from other areas of the brain, including the tractus solitarius and the area postrema [79]. The hypothalamus receives signals that relate to total energy stores in fat and to immediate changes in energy availability, including insulin, leptin, and nutrients within the gut. Afferent signals from the gut to the brain are carried in vagal and splanchnic nerve pathways. The gut also releases several hormones that have incretin- (GLP-1, GIP), hunger- (Ghrelin), and satiety-stimulating (PYY, GLP-1, OXM) actions [79]. In addition, major afferent input originates from the adipose tissue. The adipocyte is now recognized as a bona fide endocrine cell. Adipocyte hormones such as adiponectin, resistin, and visfatin influence appetite, glucose homeostasis and insulin sensitivity, and vascular function, among other functions [80].

The hypothalamus integrates these peripheral and central signals and exerts homeostatic control over food intake, levels of physical activity, basal energy expenditure, and endocrine systems.

There is no doubt that food intake in humans is influenced by emotional factors, social cues, and learned behavior. Functional neuroimaging techniques have provided the first insight in the response of the brain to nutritional stimuli. Differences regarding both the need to eat and the pleasure of eating between obese and lean individuals have been noted [81].

In obese individuals the decrease in hypothalamic activity following a meal is significantly reduced compared with lean individuals. Importantly, the neural substrates of the sensory perception of food overlap extensively with the brain representation of reward. Dopamine is the neurotransmitter that plays a central role in mediating the anticipation of reward. Abnormalities in dopaminergic transmission can be evidenced in obese individuals [82]. A decreased D2 receptor function in this same reward area of the brain has been shown, varying inversely with body mass index.

Various other data suggest that the link between chronic psychologic distress and adverse behavior such as overeating may be centrally mediated [83,84]. Normally, glucocorticoids help end acute stress responses by exerting negative feedback on the HPA axis. In contrast, it has been shown in a rat model that glucocorticoids occupy central glucocorticoid receptors during chronic stress, with resultant activation of the chronic stress response network, including continued glucocorticoid production [85]. This combination of chronic stress and high glucocorticoid levels seems to stimulate a preferential desire to ingest sweet and fatty foods, presumably by affecting dopaminergic transmission in areas of the brain associated with motivation and reward [86]. Similar to observations in obese individuals, diminished dopamine D2-binding potential within midbrain systems under conditions of chronic stress has been shown by positron-emission tomography scanning in the Cynomolgus monkey [87]. It has been demonstrated that in humans this area is involved specifically in food motivation [88].

Recent evidence also links brain areas associated with reward with those that sense physical pain. It is common notion that chronic pain can cause depression, and depression can increase pain. Most patients who have depression also present with mainly physical symptoms [89]. Studies using functional MRI have shown that social rejection lights up brain areas that are also key regions in the response to physical pain. The area of the anterior cingulate cortex that is activated by visceral pain also is activated in cases of social rejection [90]. The importance of these brain areas is underscored by the observation that the right ventral prefrontal cortex that mitigates emotional distress caused by pain is activated when placebo administration relieves pain [91].

These stress-induced changes (ie, allostatic load) are not without consequences. MRI has shown that stress-related disorders such as recurrent depressive illness or posttraumatic stress disorder are associated with atrophy of the hippocampus [92,93]. Impairment of the hippocampus decreases the reliability and accuracy of contextual memories. This decrement may exacerbate stress by preventing access to the information needed to decide that a situation is not an emotional or physical threat. Also, the suppression of routine sensory input from the body that normally occurs might, under these circumstances, be felt as discomfort or pain. There is evidence that antidepressants can reverse these changes [94].

Integrative approach to treatment

From the previous discussion, it has become clear that some parts of the pathophysiologic basis for the association between depression, cardiovascular diseases, and the metabolic syndrome are gradually becoming clearer, but these associations are complex and should be modeled over the lifetime. Because exposure to various disease risks (ie, physical, psychosocial stress,

and behavioral stressors) in humans changes over time, and risks cluster together in variable fashion, it is evident that a simple cause-and-effect approach does not fit the individual patient. One must define the chain of risk (as discussed later) with its mediating and modifying factors that have played and still play a role. For this reason an integrated approach with close attention to the history and actual needs and expectations of the individual patient in both the biologic and psychosocial domains is necessary.

It is not necessary to identify with certainty or to address every component cause or risk to prevent or avoid further deterioration of a disease. To understand this notion, one needs to address the issue of causation once more. When one defines a cause of a disease as an event, condition, or characteristic that preceded the disease and without which the disease either would not have occurred at all or would not have occurred until some later time, it follows that no specific event, condition, or characteristic is sufficient by itself to produce disease [95]. A sufficient cause can be defined as a set of minimal conditions and events that over time inevitably produce disease. A minimal cause implies that all of the conditions or events are necessary for disease occurrence. For a disease to occur, a multitude of component causes are needed that act over time in a chain of risk that in turn involves mediating and modifying factors. The importance of this notion is that most identified causes are neither necessary nor sufficient to produce disease. Vice-versa, a cause need not be either necessary or sufficient for its removal to result in disease prevention in some individuals. Because each individual has a unique chain of risks over time, it should come as no surprise that until now it has been difficult to prove that treatment for depression benefits the cardiovascular outcome after myocardial infarction [96].

This lack of proof, however, does not preclude the possibility that some subjects do benefit in this respect. Although the therapeutic advice in this context should be based on the overall outcome of such intervention studies,

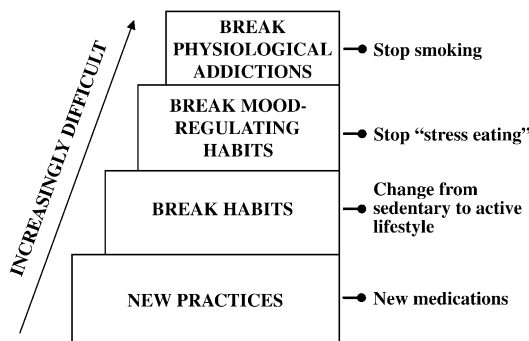


Fig. 2. Hierarchy of interventions relative to their complexity. (From Rozanski A. Integrating psychologic approaches into the behavioral management of cardiac patients. *Psychosom Med* 2005;67(Suppl 1):S68; with permission.)

it is important to pay proper attention to all three biopsychosocial domains, and thus the individual situation of a patient, and to act as one deems necessary for the general health of the patient. This approach is, at the same time, the most difficult, because inducing patients to make behavioral changes is much more difficult than prescribing some medication (Fig. 2) [97]. Such an approach, however, will best address the patients' physical, emotional, and social well being and, importantly, create a trusting patient-doctor relationship. It is evident that current medical services, which by definition act upon simple cause-and-effect disease models, do not suffice to provide this kind of patient-tailored therapy.

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