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Epidemiology and the physiopathological link between depression and cardiovascular disease

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ABSTRACT

In the future, cardiovascular disease, together with depression, will be one of the leading causes of global disease in the Western World. It is well known that depression is independently associated with a poor prognosis in patients with ischemic heart disease.
Epidemiological studies suggest that in patients with coronary artery disease, depression symptoms identify patients with higher risk of adverse cardiovascular outcomes, other studies maintain that depression symptoms might influence the progression of coronary and peripheral atherosclerosis.
The defined pathophysiological pathways which link depression and cardiovascular outcomes are not well recognized although various mechanisms have been proposed to explain this association. Beyond traditional cardiovascular risk factors, autonomic nervous system, low grade of inflammation, platelet function, abnormal function of the hypothalamic–pituitary–adrenal axis and genetic factors can adversely impact the endothelium and arterial walls. Consequently, these mechanisms might be crucial factors in promoting and accelerating atherosclerosis and its complications due to plaque rupture and thrombosis. For these reasons, depression symptoms should be considered as a new cardiac risk factor in the general population and in patients with coronary artery disease.

"For some time, I do not know why, I lost all my mirth: I neglect my exercises …"

As William Shakespeare described a depressed Hamlet, in the same fashion we research the core aspects of depression: depressed mood, loss of interest and pleasure, and fatigue, all apparently belong to the purely psycho-social sphere, the correlations with the alteration of homeostasis and man/environment allostasis and their influence on the development of ischemic heart disease.

Scientific literature has abundantly shown how a percentage between 14% and 47% of patients with ischemic heart disease suffer from depressive symptoms, while the prevalence in the general population ranges from 4 to 7% [1], these data, however, do not fully explain the possible *consecutio temporum* between depression and coronary artery disease.

However, the latest scientific findings, which are crucial to the understanding of this etiological hypothesis, show how depression had been developing for a long time in many patients, and much earlier than the appearance of their acute coronary syndromes, so as to play a negative prognostic role in the cardiac disease itself [2,3] (Fig. 1).

1. Pathophysiology of depression and cardiovascular disease

Various pathophysiological processes have been suggested to link the depressive syndrome to an accelerated atherogenesis, that ultimately results in acute coronary syndromes. In addition to an unhealthy lifestyle, several biological pathways may be involved that include dysregulation of the hypothalamic–pituitary–adrenal, abnormal autonomic tone, modifications in platelet function, systemic immune activation and endothelial dysfunction (Table 1).

1.1. Dysfunction of the autonomic nervous system

Depression is implicated in the dysregulation of the autonomic nervous system which in turn is implicated in the development of ischemic heart disease.

In particular, from a clinical point of view, hyperactivity of the sympathetic nervous system is associated with arterial hypertension, a decreased heart rate variability, a decreased vagal tone and an increase in the recovery time after stress, all factors related to increased cardiovascular mortality.

There is a directly proportional association between increased sympathetic activity and the severity of depression.

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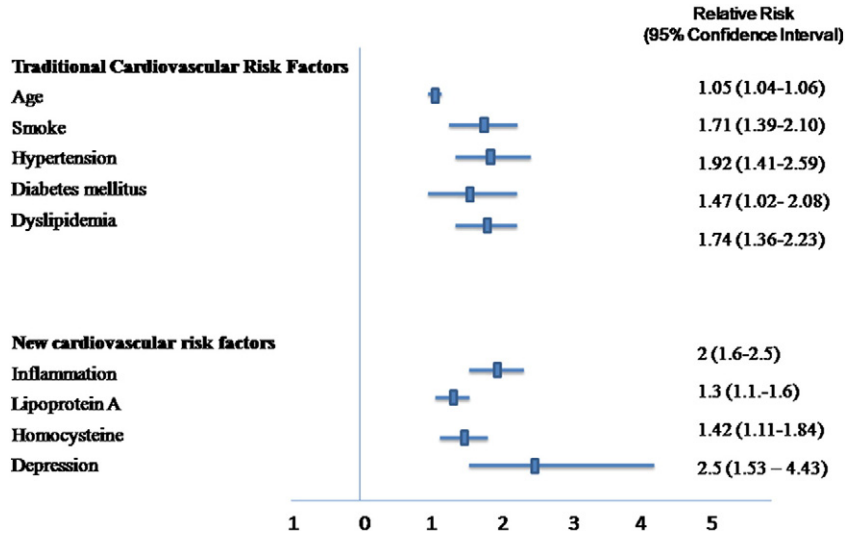

Fig. 1. Relative risk of traditional cardiovascular risk factors observed in the Framingham studies and relative danger of new cardiovascular risk factors from the data of the meta-analysis Traditional Cardiovascular Risk Factors.

The presence of depression in patients with ischemic heart disease determines a greater alteration in the sympatho-vagal balance compared with patients with only ischemic heart disease, suggesting that the effects of depression and ischemic heart disease are combined with the variability of the heartbeat [4].

1.2. Inflammation

Inflammatory cytokines play a key role in the genesis and evolution of atherosclerosis, unstable angina, acute myocardial infarction, ischemic heart disease and pathogenesis of chronic ischemic heart disease. Depression has been linked to increased levels of inflammatory cytokines (C-reactive protein, interleukin-1 and Inter china leu-6) [5,6]. This association has been documented in depressed patients with or without cardiovascular disease. The presence of inflammation in depressed patients predicts future cardiac events. However, it seems that inflammation plays a minor role in mediating the effects of depression on cardiovascular disease.

In fact, it has been proven that depression heralds cardiovascular mortality in healthy subjects or with ischemic heart disease; but this association was circa 20% lower if the values of inflammatory cytokines were added to the multivariate analysis [7].

A recent study provides further evidence as to how depression is associated with an increase in cardiovascular mortality by assuming the value of the most significant prognostic factor with respect to the levels of C-reactive protein in patients with stable coronary artery disease [8]. Several authors [9,10] have shown that depression is significantly associated with the metabolic syndrome, another risk factor for ischemic heart disease; inflammation and metabolic syndrome, may play a synergistic role in determining a higher incidence of coronary events through inflammatory cytokines.

Table 1
Pathoetiological correlations between depression and cardiovascular diseases.

Pathophysiological mechanisms
Autonomic nervous system alterations
Pro-inflammatory activation
Pro-coagulant factors activation
Endothelial dysfunction
Hypothalamic–pituitary–adrenal axis alterations
Genetic predisposition
Behavioral mechanisms
Smoking
Physical activity
Diet
Therapeutic adherence

1.3. Endothelial dysfunction

Endothelial dysfunction is involved in the altered control of vascular tone, proliferation of smooth vascular muscle cells, increased platelet aggregation, altered adhesive capacity of monocytes and leukocytes, decrease in the release of anti-inflammatory factors and decreased availability of nitric oxide.

All these factors account for the involvement of endothelial dysfunction in the clinical manifestations of atherosclerosis. Depression has been associated with impaired endothelial function in healthy subjects as well as in subjects with atherosclerosis, and in patients with ischemic heart disease. To confirm this correlation we have shown that treatment of depression with selective inhibitors of the serotonin re-uptake inhibitors (SSRIs) improves endothelial function in patients with ischemic heart disease and depression, providing further evidence that endothelial dysfunction is altered in depressed patients with ischemic heart disease [11].

1.4. Activity and increased platelet aggregation

Dysfunction and platelet aggregation activity are important factors in the genesis and evolution of acute coronary syndromes, atherosclerosis and thrombosis.

Alterations in the aggregation capacity and activity of platelets in patients with a major depression diagnosis are, hypothetically, related to an increase in morbidity and a decrease in survival compared to the general population.

Serotonin, an endogenous substance mainly involved in mood regulation and implicated in the pathogenesis of depression, can play a key role in the pathogenesis of myocardial ischemia through increased platelet aggregation.

The catecholamines bind to the platelet receptor (Alfa-2a) inducing an increase in the interplasmatic concentration of calcium, which in turn causes the de-granulation of alpha and beta granules. The de-granulation of alpha granules causes an increase in adhesion proteins and pro-inflammatory cytokines while the beta granules release serotonin, which leads to platelet aggregation and vasoconstriction [12].