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THE PIVOTAL ROLE OF STRESS IN CORONARY ARTERY DISEASE. OVER THE CHOLESTEROL PARADIGM.

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L'aterosclerosi oggi non è più considerata un semplice processo di stoccaggio lipidico, bensì un processo infiammatorio. L'infiammazione è una risposta normale ad un insulto fisico od infettivo. Quando la risposta infiammatoria è alterata o prolungata, può effettivamente causare maggiori danni rispetto al patogeno stesso. Ora è ampiamente riconosciuto che l'infiammazione cronica svolge un ruolo in molte malattie tra cui l'asma, l'artrite, il diabete, l'obesità e l'aterosclerosi. Le citochine svolgono un ruolo centrale nel sistema immunitario e nella risposta infiammatoria; Quelle molecole coordinano le funzioni delle cellule; quelle che aumentano o regolano l'infiammazione soeno indicate come proinfiammatorie, mentre quelle che regolano l'infiammazione sono chiamate anti-infiammatorie. Le citochine proinfiammatorie IL-1, interleuchina-6 (IL-6) e TNF-α, coordinano una varietà di funzioni cellulari che stimolano e controllano l'infiammazione.

Esistono in letteratura prove sostanziali che lo stress psicologico può causare un notevole aumento dell'attività infiammatoria. Stati di infiammazione possono a loro volta provocare profondi cambiamenti nel comportamento, che includono la comparsa di sintomi depressivi come l'umore triste, l'anedonia, la stanchezza, il ritardo psicomotorio e il ritiro sociale-comportamentale.

Alcuni tipi di stress possono regolare i processi infiammatori in un modo che favorisce la depressione.

Avversità socio-ambientali sono in grado di attivare programmi di trascrizione proinfiammatori attraverso due meccanisi fisiologici. Il primo percorso comprende il sistema nervoso simpatico (SNS) e il secondo percorso comprende l'asse ipotalamico-ipofisi-adrenale (HPA). Il sistema nervoso parasimpatico influenza la risposta immunitaria a livello locale attraverso fibre efferenti e afferenti del nervo vago, consentendo così di modulare il processo infiammatorio.

Il SNS regola la produzione di citochine proinfiammatorie rilasciando il neurotrasmettitore noradrenalina nei tessuti periferici, negli organi linfoidi primari e secondari e in molti altri organi, inclusi i tessuti vascolari e perivascolari. Una volta liberata, la noradrenalina, mediante la stimolazione dei recettori β-adrenergici, modula la trascrizione dei geni IL1, TNF e IL6 della risposta immunitaria proinfiammatoria, incrementando l'attività infiammatoria sistemica.

C'è uno stretto legame tra lo stress psicologico e la malattia cardiovascolare.

Esempi di stress acuti come i terremoti e situazioni croniche o situazioni di stress lavorativo, l'infelicità matrimoniale e l'assistenza a familiari affetti da malattie croniche, sono connessi con un aumento dell'incidenza di malattie cardiovascolari, tra cui morte improvvisa, infarto miocardico, ischemia del miocardio e deficit segmentari di contrattilita'. E' comunque chiaro che lo stress abbia effetti deleteri sul sistema cardiovascolare e che fattori di vulnerabilità e di resilienza svolgono un ruolo di amplificazione o di smorzamento di tali effetti. Sono disponibili numerosi approcci per la gestione dello stress che possono ridurre la sofferenza dei pazienti e migliorare la loro qualità di vita

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Nowday atherosclerosis is no more considered a simple lipid storage process but an inflammatory one. Inflammation is a typical and normal response to physical injury or infection. When the inflammatory response is altered or prolonged, it can actually cause more damage to a host than the pathogen itself. It is now widely recognized that chronic inflammation plays a role in several major diseases including asthma, arthritis, diabetes, obesity, and atherosclerosis. Cytokines play a central role in immune system and inflammatory response; those molecules coordinate cell functions; those that increase or up-regulate inflammation are referred to as proinflammatory, whereas those that down-regulate inflammation are called anti-inflammatory; the proinflammatory cytokines IL-1, interleukin-6 (IL-6), and TNF-α, coordinate a variety of cell functions that stimulate and enhance inflammation.

There is now substantial evidence that psychological stress can trigger significant increases in inflammatory activity. Increases in inflammation can in turn elicit profound changes in behavior, which include the initiation of depressive symptoms such as sad mood, anhedonia, fatigue, psychomotor retardation, and social-behavioral withdrawal.

Certain types of stress may up-regulate inflammatory processes in a way that promotes depression.

Two physiological pathways are responsible for converting social-environmental adversity into broad proinflammatory transcriptional programs. The first pathway involves the sympathetic nervous system (SNS), and the second pathway involves the hypothalamic–pituitary–adrenal (HPA) axis. Additional evidence suggests that the parasympathetic nervous system modulates immune responses at a regional level through both the efferent and afferent fibers of the vagus nerve, enabling it to prevent excessive inflammation.

The SNS regulates proinflammatory cytokine production by releasing the neurotransmitter norepinephrine into peripheral tissues, primary and secondary lymphoid organs, and all other major organ systems including the vasculature and perivascular tissues. Once released, norepinephrine modulates immune response gene transcription via stimulation of β-adrenergic receptors, although α-adrenergic signaling has also been implicated. This adrenergic signaling cascade suppresses transcription of antiviral type I IFN genes and up-regulates transcription of the proinflammatory immune response genes IL1, TNF, and IL6, leading to increases in systemic inflammatory activity.

There is a link between psychological stress and cardiovascular disease.

Examples of acute stressor studies such as earthquakes and chronic situations like job stress, marital unhappiness, and burden of caregiving are connected with an increase in incidence of cardiovascular diseasesincluding sudden death, myocardial infarction, myocardial ischemia, and wall motion abnormalities, as well as to alterations in cardiac regulation as indexed by changes in sympathetic nervous system activity and hemostasis. Although stressors trigger events,it is less clear that stress “causes” the events. There is nonetheless overwhelming evidence both for the deleterious effects of stress on the heart and for the fact that vulnerability and resilience factors play a role in amplifying or dampening those effects. Numerous approaches are available for stress management that can decrease patients’ suffering and enhance their quality of life.

THE PSYCHOLOGY IN THE TREATMENT OF METABOLIC DISEASES

The weight of psycho-behavioral factors

An international study on the needs of people with diabetes in the Italian population shows that negative psychological conditions - psychological discomfort (50%), high stress (40%), depression (18%) - affect many PCDs and result in a significant decrease in the quality of life (QdV) (Nicolucci et al., 2013, Lazzari 2015). High levels of distress (PAID-5> 49) emerge in two-thirds of subjects with DM1 and DM2 treated with insulin and in half those with DM2 not treated pharmacologically or with insulin.

As for QdV, according to the PCD, the greatest impact of diabetes is on physical health, followed by psychological well-being: half of the PCDs (54% with DM1 and 49% with DM2) state that diabetes has a very or moderate impact Negative on their psychological well-being.

12% of PCD family members treated with insulin and 6% of untreated ones consider their QdV very poor, one fifth has depressive symptoms. According to family members, the greatest impact of diabetes is on psychological well-being (55%), Families feel very involved but one in three feels frustrated because they want to have more tools to play their role better.

On the one hand, literature has highlighted the role of chronic stress as a risk factor for metabolic syndrome and type 2 diabetes (Nicolaides et al., 2015; Bottaccioli 2012, Kyrou et al 2006). On the other hand, a state of illness, which requires and involves adaptive changes, is in itself a source of stress. The person (and family) who has to deal with and manage this situation can structure appropriate and functional changes or, conversely, dysfunctional situations that amplify the weight of the disease. Therefore, there is a risk of a kind of "short circuit" between past and present conditions, between person's attitudes and the actual pathology management.

Looking at the person rather than the disease is not an option but a necessity, strengthened by the role the subjective aspects have on the complexity of disease management: adherence, complications, QdV, costs (Lazzari 2011, Naylor et al 2012)

An operational integration model

Addressing psychological aspects in an operational integration model has been and is the challenge of these years. We worked in two directions: a) Develop a reading and evaluation model that takes into account the literature and validates it (Lazzari 2009, 2017) and b) Develops a generalizable and sustainable intervention model. The indications that emerge for future implementations include:

- The promotion of a comprehensive vision of the PCD through knowledge of the weight and interactions of the various factors (doctors, psycho-behavioral, relational) in the treatment and management of the disease. The spread of functional training to this integrated vision, which is able to share common knowledge and effectively integrate the various professional skills. It takes a strategic point in this context to consider the set of behavior of the PCDs and Fs (what they feel, think and do in relation to the MD) within an autoregolatory explanatory model.

- The development of intervention models that improve the performance of the system in this field, by optimizing the interaction between information, educational and psychological interventions - and their specific contributions - and declining them in relation to emerging needs from evaluation (validated, generalizable and Sustainable) of non-medical aspects of PCDs.