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An insight into pathogenesis of cardiovascular diseases

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Abstract

This article presents additional data from most recent research work, which lends support to the hypotheses presented in my paper published recently [1].

The hypotheses highlight the role of chronic psychosocial stress in pathogenesis of cardiovascular diseases, and extends the concept of stress induced, lipid mediated vascular inflammation to disorders of tissues sub served by micro vascular circulation.

The studies presented, provide clinical data, which demonstrates role of increased psychosocial stress in increased cardiovascular morbidity and mortality, when associated with increased severity of co morbid micro vascular disorder –depression in this case.

Other two studies published recently provide evidence of subclinical atherosclerosis present in association with diseases of micro circulation i.e. rheumatoid arthritis and non alcoholic fatty liver disease, extending support to the hypothesis, that CVDs and disorders of micro vascular circulation present as co morbid conditions sharing common pathogenesis.

Abbreviations: HPA axis: Hypothalamus-pituitary-adrenal axis, SAM axis: sympathetic-adrenal-medullary axis, LDL: low density lipoprotein, oxLDL: oxidized low density lipoprotein, CVD: cardiovascular disease, SCORE: Systemic Coronary Risk Evaluation, RA: rheumatoid arthritis, NFALD: non fatty alcoholic liver disease, CAC: coronary artery calcium

The article 'Perfect Storm' of stress, depression may raise risk of death, heart attack for heart patients, published by American Heart Association as Rapid Access Journal Report, describes that combination of stress and heavy depression can significantly increase heart patients risk of death or heart attack.

The study examined the effects of high stress and high depression symptoms among nearly 5,000 heart patients. Researchers concluded that risk is amplified when both conditions are present, thus validating the concept of a "psychosocial perfect storm" Study participants included 4, 487 coronary heart disease patients 45 years and older, enrolled in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. About 6% reported both high stress and high depression. During an average six-year follow up 1,337 deaths or heart attacks occurred. Short term risk of death or heart attack increased 48% for those in high stress-high depression symptoms group compared with those in the low – stress depression symptoms group [2].

Discussion

This article demonstrates the role, high psychosocial stress plays in clinical progression in patients with coronary heart disease, when associated with high depression. These observations suggest that there is a strong link of psychosocial stress, to cardiovascular diseases. When there is high level of stress, it amplifies the stress response, which results in activation of innate immunity through hypothalamus-pituitary-adrenal (HPA) axis and sympathetic-adrenal-medullary (SAM) axis. This sets into motion a cascade of events among mobilization of free fatty acid and low density lipoprotein (LDL) release, reaching coronary arteries with conversion to oxidized LDL (ox LDL), which accelerates the inflammation/atherosclerosis already present (in the patient population in the study) with known coronary heart disease. It also at the same time progresses the symptoms of depression into high level, which might have been subclinical or mild with low level baseline stress. According to my hypothesis depression is present as a result of inflammation in the brain due to involvement of micro vascular circulation, which is ongoing in parallel with coronary heart disease. It is important to acknowledge that brain is also a target organ like heart and/or macro vascular circulation in coronary arteries.

The study has demonstrated significant increase in morbidity and mortality by 48% in the group with high stress – high depression. The association of diabetes with cardiovascular diseases has been shown to increase the morbidity and mortality from CVDs by 2-3 fold [3,4]. Similar trends have been observed with rheumatoid arthritis and cardiovascular diseases [5]. It appears that high depression when associated with coronary heart disease follows similar pattern that diabetes or rheumatoid arthritis have when associated with CVD, that is amplification of inflammatory burden with co- morbid conditions as a result of high level stress. This association has been described in one of the largest cross-sectional study, which demonstrated that adults who report permanent home/work stress and depression had 2-fold higher odds for a history of MI when compared with their never stressed and not depressed counterparts [5].

My second hypothesis is that cardiovascular diseases and diseases of micro vascular circulation share the same pathogenesis that is stress induced, lipid mediated tissue damage by systemic inflammation. There has been more recent work published which lends support to this hypothesis;

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The article published in Arthritis Research & Therapy 2015 describes that rheumatoid arthritis is a chronic inflammatory disease that enhances the risk of atherosclerotic cardiovascular event rates to a similar extent as type 2 diabetes. Traditional risk factors do not fully explain the increased cardiovascular (CVD) risk in RA. In fact traditional risk factors and disease characteristics, in particular high grade inflammation, associate overall additively and as strongly with atherosclerosis and incident CVD event rates in RA.

In this study a cohort of 144 women with an evaluated low risk of CVD (SCORE value of zero, Systemic Coronary Risk Evaluation (SCORE) model (often used in the Europe), was assembled amongst 550 consecutive patients with RA that underwent CVD risk factor recording and carotid artery ultrasound. Participants had no established CVD, moderate or severe chronic kidney disease or diabetes. They assessed carotid plaque (s) presence and its associated patient characteristics.

The study results demonstrated that carotid artery plaque was present in 35 (24.3%) of women with RA. Age, the number of synthetic disease modifying agents (DMARDs) and total cholesterol were independently associated with plaque in multivariate stepwise backward regression analysis. The results indicate that among women with RA, that are at low estimated risk according to the SCORE, consideration of age and total cholesterol concentration is useful in determining. Which of the patients experience high risk subclinical atherosclerosis? Indeed age >49.5 years and total cholesterol concentration of >5.4 mmol/L predicted plaque presence with a sensitivity and negative predictive value of 74% and 63% and 90% and 86% respectively.

The study concluded that approximately one-third of women with RA who experience a low SCORE value are aged >49.5 years/ and have a total cholesterol concentration of >5.4 mmol/L, experience high risk atherosclerosis, which required intensive CVD risk management [6].

The study published in Atherosclerosis April 2015 characterized the association of 3 metabolic conditions – obesity, metabolic syndrome and non alcoholic fatty liver disease (NAFLD)- with increased inflammation and subclinical atherosclerosis.

Cross sectional analysis was conducted in 3976 participants from Multi-Ethnic Study of Atherosclerosis (MESA) with adequate CT imaging to diagnose NAFLD.

Obesity was defined as BMI >30 kg/m^2, metabolic syndrome by AHA /NHLBI criteria and NFALD using non –contrast cardiac CT and liver/spleen attenuation ratio (L/S) <1. Increased inflammation was defined as high sensitivity C-reactive protein >2 mg/L and subclinical atherosclerosis as coronary artery calcium (CAC) >0. They studied the association of a stepwise increase in the number of the metabolic conditions (0-3) with increased inflammation and CAC, stratifying results by gender and ethnicity. Mean age of participants was 63 (+/-10) years.

The study concluded that NAFLD is associated with increased inflammation and CAC independent of traditional risk factors, obesity and metabolic syndrome. There is a graded association between obesity, metabolic syndrome and NAFLD with inflammation and CAC score [7].

Discussion

Above articles demonstrate that the diseases of micro vascular circulation *i.e.* rheumatoid arthritis has increased association with atherosclerosis, present as subclinical disease, demonstrated by plaque formation in carotid ultrasound. Non alcoholic fatty liver disease also has increased association with subclinical atherosclerosis as demonstrated by increased inflammation and CAC score.

These findings demonstrate that diseases of micro vascular circulation and cardiovascular diseases develop in parallel. The diseases which result due to organs affected by micro vascular circulation lend themselves more readily to diagnosis *i.e.* metabolic syndrome, diabetes, obesity, arthritis, NAFLD and so on. However CVDs remain subclinical until there is significant luminal stenosis to cause symptoms or there is sudden acceleration of inflammation from baseline mild /moderate level to severe degree due to changes in life style factors causing high level stress.

Organs sub served by micro vascular circulation, with onset of inflammation and even minor tissue damage as a result of oxidative stress express early as albuminuria in CKD, impaired glucose tolerance in diabetes, abnormal liver function tests in NAFLD, and elevated blood pressure on routine clinical examination. Atherosclerosis as described above even though developing in parallel with these conditions clinically presents late until advanced to cause luminal narrowing in large and medium sized arteries. This explains why the disorders developing as a result of inflammation of micro vascular circulation have been considered as risk factors for CVDs, as subclinical and clinical expression of these conditions preceded the clinical expression of CVDs which was generally devastating when manifesting as acute myocardial infarction, stroke, threatening limb ischemia or rupture of aortic aneurysm. This designation may be useful even today as presence of any indicator of even a single organ (risk factor) whether subclinical or clinical should immediately raise the concern for concomitant atherosclerosis process which may be at an early stage of inflammation causing tissue damage in the arteries. Carotid plaque, CAC score of >zero and ABI of <1.1 - >1.4 may identify subclinical disease but generally, it's already advanced, as these tests when abnormal predict high future events.

The concept of traditional risk factors, being diseases of inflammation of microcirculation, sharing the same pathogenesis as CVDs is important because, strategies to intervene early (*i.e.* Stress management, lipid lowering by life style changes and pharmacologic agents if necessary and anti –inflammatory pharmacologic drugs in addition to life style measures) need to be formulated.

As the research is advancing rapidly, providing more insight due to availability of laboratory tests and multiple other test modalities such as ultrasound and CT scans, we are able to find more diseases of micro vascular circulation, with strong co relation with CVDs. Depressions and chronic anxiety disorders have been described already. There are small studies indicating atrial fibrillation to have the same pathogenesis.1

There is extensive work on rheumatoid arthritis, having strong association with CVDs and to be considered as independent risk factor, and CHD risk equivalent as diabetes.

Extensive research data is pouring in for NAFLD as an independent risk factor for CVDs. Data presented in Vienna by European Association for the Study of the Liver (EASL) last week which reported that as the severity of non alcoholic fatty liver disease (NAFLD) increases, so does the risk for death and cardiovascular disease, according to data from a large population based study.

Heart failure, (HF), atrial fibrillation (AF), type 2 diabetes mellitus, and chronic kidney disease (CKD) rate was also increased with NAFLD compared with NASH or NASH cirrhosis. The meeting concluded with

remarks "It is therefore imperative that we identify people in the early stages of [the disease], so they can be treated through diet and life style interventions before their condition becomes potentially fatal".

There is extensive research work being produced in each sub specialty, demonstrating that several diseases, including traditional risk factors are associated with each other and with CVDs. They all have raised inflammatory markers pointing towards systemic inflammation like atherosclerosis and have evidence of oxidative stress and tissue damage.

Putting it together

It's time to put it all together. The disorders of micro vascular circulation and CVDs need to be identified early enough to prevent the damage from occurring. We need to develop strategies beyond clustering the diseases as risk factors, and subclinical presence of atherosclerosis, to even more sensitive assays. Inflammatory markers may be utilized more routinely to document the transition into inflammatory state.

Ox LDL levels in plasma may be useful, if present in spite of life style measures being implemented, consideration of lipid lowering with additional interventions earlier and more aggressively may be beneficial in preventing morbidity and mortality.

Conclusion

Chronic psychosocial stress plays a key role in the pathogenesis of vascular diseases (both cardiovascular diseases and disorders of micro vascular circulation), which when severe in intensity, accelerates the inflammation, increasing morbidity and mortality especially, when multiple conditions are present together such as depression, rheumatoid arthritis, NAFLD and several other disorders, including "traditional risk factors".

- Cardiovascular diseases and disorders of micro vascular circulation (*i.e.* rheumatoid arthritis and non alcoholic fatty liver disease) develop in parallel, lending support to the hypothesis that, they share a common pathophysiologic mechanism, which is stress induced, lipid mediated vascular inflammation.
- Disorders of micro vascular circulation generally precede in onset, while atherosclerosis may remain subclinical, until it encroaches the lumen, causing critical stenosis.

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