Local Inflammatory Diseases Are at Risk of Developing Myocardial Infarction, Stroke, Renal Failure and Cancer via Chronic Systemic Inflammation

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Inflammatory diseases at various anatomic sites, regardless how mild it appears, should not be taken lightly. If not treated, the chronic inflammation associated with the local inflammatory disease can lead to further development of fatal diseases such as myocardial infarction (MI), stroke, renal failure, cancer and even chronic obstructive pulmonary disease. Inflammatory mediators generated from the local inflammation reaction will spread systemically and attack on cells of other organs and tissues. More than one target of cells may be attacked at the same time leading to the onset of new, multiple inflammatory diseases. Because inflammation is also known to play an important role in the pathogenesis and diseases progression of all fatal degenerative diseases, it is conceivable why patients with mild local inflammatory diseases are at risk of developing MI, stroke, renal failure and cancer.

Key words: Inflammatory disease, risk, MI, stroke, renal failure, cancer, chronic systemic inflammation

Introduction

Multiple risk factors are known to exist today, as we have summarized in our earlier report [1] that will attack on cells in various organs and tissues eliciting inflammation. When the risk factor(s) continues to exist, chronic inflammation will develop. The continuous exposure to the risk factor(s) will generate inflammatory mediators (most of them are cytokines), which will transport systemically and attack on cells at various sites of the body producing new inflammation sites. When endothelial cells lining the blood vessel are under attack, the new inflammation will result in atherosclerosis which may lead to myocardial infarction (MI) and stroke etc. The new site may also be epithelial cells in the kidney, and results in the development of renal dysfunction and progresses to fatal end stage renal disease (ESRD). It should be noted that inflammatory mediators can be derived from any inflammatory diseases including those fatal degenerative diseases. Therefore, it is not surprising to find cardiovascular disease (CVD) and MI developed from patients with cancer, also via chronic systemic inflammation.

In this review efforts have been made to remind the public not to treat any of the seemingly mild chronic inflammatory diseases lightly. It is important to identify and eliminate (avoid) risk factor(s) causing chronic inflammation as well as reducing inflammation associated with the disease in order to avoid the risk of developing MI, stroke, renal failure and cancer.

We also try to emphasize in this review that most of us may not be aware of the fact that inflammation exist widely. It involves in the pathogenesis (onset) and progression of most clinical disorders known to us today, which takes place in almost every organ and tissue. Therefore, any local inflammation may lead to a simultaneously development of multiple inflammations at distant anatomic sites and results in clinical manifestations such as cardiac vascular disease (CVD) and renal...
Risk of fatal diseases...dysfunction, etc. Below are our collection of publications from the recent literature, which have reported their findings regarding the development of MI, renal dysfunction and cancer from local inflammatory diseases and vise versa, as the result of the chronic systemic inflammation.

**Presence of Wide Spread Inflammatory Diseases**

Rheumatoid arthritis, inflammatory bowel diseases including Crohn’s disease and ulcerative colitis, osteoarthritis and various forms of thyroiditis are probably the most well-known inflammatory diseases. Recent findings have pointed out that inflammation also play a critical role contributing to the onset and disease progression of a long list of diseases such as type 2 diabetes (T2DM), various autoimmune diseases, asthma, chronic obstructive pulmonary disease (COPD), calculus, bacterial and viral infection, etc. It is important to note that all degenerative fatal diseases such as cardiovascular disease, stroke, ESRD and cancer also involve inflammation in their pathogenesis and progression.

We now have begun to realize that the persistent attack of risk factor(s) on cells at various organs is most likely the major cause of the onset of local inflammatory diseases. For example, there is rheumatoid arthritis taking place at the connective tissue, inflammatory bowel disease (IBD) in the digestive system, asthma and COPD in the lung, cirrhosis in the liver, Systemic Lupus Erythematosus (SLE) in the kidney and psoriasis with the skin. It appears that one can almost detect inflammatory disease in every organ and tissue.

**The Central Role of Chronic Systemic Inflammation**

When individuals are exposed continuously to the risk factor(s), such as visceral fat, hyperglycemia, hypercholesterolemia or infection etc. [1], chronic inflammation will develop leading eventually to the pathogenesis (onset) of multiple inflammatory diseases. In diagram 1 we have outlined simplified pathways depicting how does the local inflammatory disease lead to the development of various fatal diseases via chronic systemic inflammation. The diagram is our attempt to show that it is the proinflammatory mediators generated from the chronic inflammation, in association with the local inflammatory disease that travel to various distant sites and induce the onset of other inflammatory diseases. However, it should also be noted that none of these paths is one directional. In fact, local inflammatory diseases can also be derived from atherosclerosis, renal dysfunction and cancer via chronic systemic inflammation.

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**Diagram 1. The central role played by the chronic systemic inflammation. Development of stroke, MI, renal dysfunction, cancer and other inflammatory diseases from a primary local inflammatory disease is mediated through proinflammatory mediators generated from the chronic systemic inflammation.**
Risk of CVD

Development of atherosclerosis and CVD has been found most frequently from various local inflammatory diseases in the literature. This may have to do with the wide spread of blood vessel throughout the body and also may be because that the blood vessel being the major route for transporting proinflammatory mediators. Apparently the frequent risk for atherosclerosis is also due to the fact that endothelial cells layer, lining inside the blood vessel, are most accessible to the attack by proinflammatory mediators.

Moreover, the increased cardiovascular risk has been found to be derived from inflammatory diseases at almost every anatomic site involving various organs and tissues. Risk for CVD has been found in rheumatoid arthritis involving the joint [2], in Crohn’s disease involving the large bowel [3], in asthma and COPD involving the lung [4, 5], in Psoriasis involving the skin [6] and in benign prostate hyperplasia (BPH) [7] involving the prostate. However, development of CVD has also been reported from inflammatory diseases less specifically associated with certain cells such as type 2 diabetes [8], autoimmune disease [9], ESRD [10] and cancer [11, 12].

Recently several reports have indicated that risk of cardiovascular disease could be found in patients with periodontitis, a very common chronic infection of the tissue surrounding the teeth [13]. Therefore, this finding strongly suggest again that none of the local inflammatory diseases, regardless how mild it may appear, can lead to severe consequence and not be overlooked.

Risk of Renal Failure

It is now recognized that chronic inflammation and oxidative stress are closely associated with the development and progression of ESRD [14, 15]. The risk of chronic renal disease and eventually the development of fatal ESRD (if not treated or treated unsuccessfully) from local inflammatory diseases have also been reported to be due to the presence of chronic systemic inflammation. For example, renal failure can be developed from asthma [16]. On the other hand, patients with ESRD are also at risk of developing asthma [17].

Risk of Cancer

Increasing evidences have suggested that cancer is an inflammatory disease [18]. As pointed out by Shaacter et al. that chronic inflammation can predispose an individual to cancer [19]. It should be noted that tumorigenesis and carcinogenesis take place one-step further beyond chronic inflammation, which involve multiple mutations of genes associated with the regulation of growth [20]. However, it is the chronic inflammation and the proinflammatory mediators generated that promote tumorigenesis. They contribute to neoplasia by inhibiting the normal function of suppressor genes, such as p53, and suppressing apoptosis and promoting proliferation and angiogenesis [21], events that help the development of malignant disease.

It appears that many tumors tend to develop at or close to the site of inflammation. It is very likely that cells close to the site of inflammation are more susceptible to mutation. For example, ESRD has been found as a risk factor for developing renal cell carcinoma (RCC) [22]. Ovarian and uterine tumors have been found to be developed in patients with benign gynecologic inflammatory diseases including endometriosis and uterine leiomyomas [23]. The association of urinary bladder cancer with Schistosoma haematobium infection, the risk of pancreatic malignancies in patients with autoimmune pancreatitis [24], the progression from precancerous (adenomatous) colon polyps to malignant colorectal cancer [25] and the significantly increased long term risk of anal cancer in patients with inflammatory benign anal lesions [26] all suggest the fact that tumorigenesis is more readily to take place at or close to the site of inflammation.

Again it should be noted that the risk of developing cancer is not one directional. Because of the association of chronic systemic inflammation with all inflammatory diseases, cancer patients are also at risk of developing other life-threatening inflammatory diseases such as myocardial infarction, stroke and ESRD [27, 28] and vice versa.

Apparentely the development of tumor is not limited entirely to the site of inflammation. Many clinical disorders such as obesity, type 2 diabetes, are also found to be associated with an increased incidence for a number of cancers, including those of the colon, prostate, and pancreas [29].

Multiple Inflammatory Diseases

It is important to emphasize that chronic systemic inflammation derived from a local primary inflammatory disease will lead to the development not a single but, in most cases, multiple inflammatory diseases simultaneously at many different sites involving many organ systems. As observed by Bernstein et al. [30] that a cluster-
ing of several chronic inflammatory diseases could be found in patients with inflammatory bowel disease (IBD). They found that patients with either ulcerative colitis (UC) or Crohn’s disease had a significantly greater likelihood of also developing arthritis, asthma, bronchitis, psoriasis, and pericarditis at the same time. An increased risk for chronic renal disease and multiple sclerosis has also been noted in UC patients by Bernstein et al. [30].

References

局部發炎疾病造成的慢性發炎會導致心肌梗塞、中風、腎臟衰竭與癌症發展的風險

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身體各個組織都可能發生局部的發炎疾病，就算是最輕微的發炎疾病也不可等閒視之。急性炎症若不即時治療轉為慢性炎症，會影響到心肌梗塞、中風、腎衰竭、癌症與慢性阻塞性肺病等嚴重疾病的發生。由局部癥炎所產生的炎症介質，可經由血液循環擴散到全身並攻擊其他器官與組織的細胞，會同時產生許多新的發炎疾病。由於發炎反應在所有嚴重退化性疾病的發病與病程發展中也扮演一個重要角色，所以可以了解為何局部發炎疾病會增加心肌梗塞、中風、腎衰竭與癌症等疾病的發生。

關鍵詞：發炎疾病、風險因子、心肌梗塞、中風、腎衰竭、癌症、慢性系統性發炎

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