Acute and Chronic Inflammation: Effect of the Risk Factor(s) on the Progression of the Early Inflammatory Response to the Oxidative and Nitrosative Stress

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Multiple risk factors are known to exist that will attack cells at various parts of the body eliciting new inflammation sites hence new inflammatory diseases. Acute inflammation usually takes place first in response to the attack of the risk factor (s). As soon as the risk factor (s) is removed, the acute inflammatory response will stop. Conceivably, acute inflammation does not lead to oxidative and nitrosative stress or any serious adverse effect. However, when the risk factor (s) continues to exist, the acute inflammation will progress to chronic inflammation. It is the chronic inflammation that plays the major role in the pathogenesis of all inflammatory diseases. By monitoring soluble markers corresponding to the sequential events of both acute and chronic inflammation it is possible not only to determine whether an individual is currently exposed to risk factor (s) of inflammation but also the extent of overall inflammation reaction.

Key words: Acute inflammation, chronic systemic inflammation, risk factor, oxidative stress, biomarkers

Introduction

As we have reported earlier [1-2] that numerous risk factors, in addition to hypercholesterolemia, have been identified which will attack cells at various parts of the body and elicit new inflammatory sites and hence new inflammatory diseases. Increasing number of reports in the literature have emphasized the fact that inflammation, especially the chronic inflammation, plays an important role in the pathogenesis and progression of all inflammatory diseases including the life-threatening degenerative diseases such as cancer, cardiovascular disease (CVD), stroke, renal failure and chronic obstructive pulmonary disease (COPD)[2].

However, we now have also realized that when cells are exposed to the risk factor (s) it is the acute inflammation that takes place first. Cells response acutely to the attack of risk factor (s) by producing acute phase reactants [3]. If the risk factor (s) continues to exist and is not removed, acute inflammation will then progress and extend to chronic inflammation [1]. Exactly how long it takes to advance from acute to chronic inflammation is not clear. It is also not clear whether the speed of progression is actually dependent on the type of risk factor, and whether it is also dose dependent. In our experience, the transition from acute to chronic inflammation will most likely take weeks or even months. It is most important to understand that acute inflammation always occurs first in response to the risk factor (s), however, whether the chronic inflammation will also take place is largely depending on the continuing presence or absence of the risk factor (s).

In our liposuction study on normal women [4] we could detect the elevation of not only acute phase reactants such as C-reactive protein (CRP), serum amyloid protein A (SAA) and fibrinogen but also proinflammatory cytokines including interleukin 6 (IL-6) and tumor
necrosis factor-alpha (TNF-\(\alpha\)) in day-one following liposuction in the blood circulation. According to our liposuction study [4] the acute inflammatory response or the acute inflammation appears to exist only transiently. In the liposuction study the risk factor causing acute inflammation was the surgical procedure of liposuction, which no longer existed upon completion of the surgery. All elevated markers of acute inflammatory response were found to return to the previous baseline. Since all subjects participated in the liposuction study were normal women, therefore, all elevated acute inflammatory markers returned to the normal levels following the completion of liposuction surgery. The transient nature of acute inflammatory response is also supported by the study of patients with dental infection by Tonetti et al. [5]. They found that elevated acute inflammatory markers detected in patients with periodontitis also returned to normal following the successful treatment of dental infection. In this study periodontitis was the risk factor eliciting acute inflammation. Removal of the risk factor in the periodontitis study was carried out by the successful treatment, which brought to an end of the acute inflammatory response. In both the liposuction and periodontitis studies no oxidative and nitrosative stress were found and no cell damage and adverse effects were detected. In other words, the removal of the risk factor (s), either by elimination or by treatment, will end not only the acute inflammation but also the extension of acute inflammation into chronic inflammation [5].

**Chronic Inflammation**

Individuals suffering from hypercholesterolemia, abdominal obesity, hyperglycemia, or bacterial or viral infection, or exposing to pollutant chronically tend to produce both acute inflammatory response [1] and chronic inflammation. The major difference between short-lived liposuction and the above-mentioned inflammatory risk factors is the length of time of exposure. Individuals suffering from abdominal obesity, hypercholesterolemia, etc. are usually exposed for a relatively long time. In other words, individuals suffering, for example, from abdominal obesity are usually bombarded by adipocytokines from fat cells persistently that elicit both acute and chronic inflammation. Apparently the prolonged attack by inflammatory adipocytokines provides sufficiently time for acute inflammation to progress to chronic inflammation. In other words, the continuous presence of risk factor (s) allows the sequence of inflammatory events to continue beyond the acute inflammatory response. From the result of our liposuction study we believe that chronic inflammation most likely begin with cell damage such as the endothelial dysfunction in the blood vessel, or airway inflammation in asthma and COPD and then followed by the recruitment of leukocytes to the injured site, and subsequent inflammatory events.

Conceivably the persistent existence of the risk factor is the key to the onset of chronic inflammation. We learned from the liposuction study that chronic inflammation would not take place if the risk factor were being removed. We now know that it is the progression of chronic inflammation that eventually leads to oxidative and nitrosative stress, to renal failure and to lipid peroxidation. Apparently the time of exposure to the risk factor (s) plays a critical role. It appears that a prolonged exposure to the risk factor (s) is the major reason for the onset of inflammatory events such as recruitment of leukocytes, the release of oxidizing enzyme such as MPO and ROS from activated leukocytes, lipid peroxidation, appearance of microalbuminuria, and the subsequent oxidative and nitrosative stress.

It should be noted that chronic inflammation tends to be systemic. During the prolonged exposure to the risk factor (s) the onset of chronic systemic inflammation generates proinflammatory mediators from the primary site of inflammation, travels via blood vessel to various distant sites of the body, attacks cells at distant organs and tissues creating new inflammation sites and new inflammatory diseases [2].

**Associated Markers**

Soluble markers corresponding to the sequential individual events of the overall inflammation reaction for atherogenesis have been described [1]. They are listed in Table 1. These soluble markers can be monitored to identify whether the acute inflammation, chronic inflammation, lipid peroxidation and oxidative and nitrosative stress are present or not. Measurement of these markers will also let us know whether an individual is currently exposed to the risk factor (s), whether chronic inflammation has begun. It will also inform us as to how extensively the chronic inflammation has progressed and whether oxidative and nitrosative stresses are present.

In our liposuction study we have learned what markers in the blood circulation corresponding to acute inflammatory response. In addition to acute phase reactants and proinflammatory cytokines we have also
detected elevation in chemokine such as monocyte chemoattractant protein (MCP-1). We also have detected a decline in nitric oxide (NO) [4]. Apparently even during acute inflammation, cells may suffer a slight damage. Conceivably all these markers are useful to indicate whether the risk factor (s) is present or not. Returning of these marker to normal concentration is a sign indicating the success of removing the risk factor (s).

It should be noted that the removal of the risk factor (s) would lead to an end of both acute and chronic inflammation and a decline of circulating concentration of all corresponding markers. However, the rate of decline of the concentration of these markers is expected to be slow. Some markers, once become elevated, their concentration may no longer impacted directly by the presence and absence of the risk factor (s). It is not only because that the rate of decline may be dependent on the half-life of these markers in circulation, there is an additional factor needs to be considered. There have been reports about the existence of a vicious circle for some of the products of inflammation. These products, once formed, may stimulate or enhance inflammation forming a vicious circle. Many inflammatory products such as CRP and oxidized LDL have been found to continue to enhance inflammation independent of the risk factor (s) [6,7].

### Clinical Impact

To summarize, it is important to know that acute inflammation does not lead to oxidative and nitrosative stress and severe adverse effects. However, acute inflammation can proceed and progress onto chronic inflammation if the risk factor (s) exist persistently. Conceivably it is also important to know whether an individual is currently exposed to the risk factor (s), and effort should be made to remove the risk factor (s) in order to prevent the progression of acute to chronic inflammation.

We now also realize that most damages and adverse effects associated with inflammation are caused by chronic inflammation. Continued progression of chronic inflammation not only leads to lipid peroxidation, oxidative and nitrosative stress but also renal failure. In fact, as we have found in patients with atherosclerosis and with type 2 diabetes (T2DM), inflammation may continue to intensify during the course of these diseases [8,9]. Most likely it is the chronic inflammation that continues to intensify which accounts for the progression of these clinical disorders to their advanced stage and to the development of additional clinical complications [10]. It is most likely that the existence of the inflammatory risk factor (s) and the presence of a vicious circle both contribute to the disease progression. Conceivably removing the risk factor (s) and reducing inflammation are both important for early intervention and prevention.

Conceivably it is important to monitor both acute and chronic inflammation by measuring markers listed in Table 1. The reason of monitoring is not only for the assessment of the presence of the risk factor (s) but also for any individual suffering from inflammatory diseases to further develop complications such as myocardial infarction, stroke, renal failure and cancer.

### References

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急性及慢性發炎：
危險因子所引發的氧化與硝酸化壓力對發炎反應進展的影響

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許多年的危險因子會引起發炎反應，危険因子會侵襲身體各部份的細胞，造成新的傷害及新的發炎疾病。細胞對於危險因子的最早反應為急性發炎，當危險因子不再存在，急性發炎反應也會立即停止，而不會繼續導致氧化與硝酸化壓力或其他不良結果。如果危險因子繼續存在，急性發炎將發展為慢性發炎。慢性發炎才是形成許多發炎疾病的主要原因。如果可以測量血液或尿液中急性與慢性發炎的指標，不僅可以獲知個體當時是否受危險因子的侵襲，而且可判斷其發炎的嚴重度。

關鍵詞：急性發炎、慢性系統性發炎、危險因子、氧化壓力、指標