EDITORIAL

Quantification of inflammation: Needs and challenges

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Introduction

Inflammation is a natural response against any external or internal stimuli that disturb the body homeostasis. Although inflammation was initially described in terms of simple clinical symptoms, it has evolved to define a more complex phenomenon. In spite of the advances in immunology, uncertainty prevails on the precise definition of inflammation.

The word inflammation is derived from the Latin term inflammare, which means 'to set on fire'. During the first century AD, Celsus described the four cardinal signs of inflammation: rubor, tumor, calore, and dolore (redness, swelling, heat, and pain).Two centuries later, Galen promoted the humoral view of inflammation, which considered pus production as a part of inflammation. In the year 1871, the fifth cardinal sign-function laesa (loss of function)-was introduced by Virchow, who reported it as inherently pathological, in contrast to Galen.[1, 2] In 1908, Metchnikoff, described the inflammatory reaction as a digestive process against the noxious agent. Lewis described inflammation as a triple response and a vascular event; this was the earliest description of neurogenic component of inflammation. Rocha e Silva, in 1974, described inflammation as a phenomenon associated with the appearance of multiple mediators at appropriate moments, increasing vascular permeability, attracting leucocytes, and producing pain, local edema and necrosis. This contributed to the development of biochemical definition of inflammation to injury.[3] Our recent understanding reveals that inflammation plays a key role in the genesis of morbidity and mortality in autoimmune diseases like RA, SLE, and vasculitis. Persisting chronic inflammation has been demonstrated to increase the risk of cardiovascular diseases like atherosclerosis.[4] There are a few extra-infection site manifestations like erythema nodosum and iridocyclitis secondary to infections. Quantifying inflammation and its impact become very critical for the management of these diseases. The appropriate quantification of a disease process is the key to implement suitable changes in medications and in monitoring the treatment outcome. Despite the need, a definition to measure the complex process of inflammation remains elusive. Nonetheless, current understanding of inflammation has helped us to appreciate its impact on health and its significant role in the development of disease.

Physiology of inflammation

Inflammation is an initial response to injury or a stimulus that threatens the body homeostasis. The response is physiological and expected to resolve after a set point of homeostasis is achieved. If not resolved, the inflammation may cause injury to the host and produce pathogenic effects. Thus, the impact of inflammation on an organism depends on many facets of inflammation, such as the type of inflammation (systemic or localized), the quantity of inflammatory response and the stimulus responsible for inflammation. It can be a short-lived response (an acute inflammation) or may be persisting in nature (chronic inflammation). The inflammation is either generalized or localized. In acute stage, it has a tendency to resolve after the inciting factor regresses; sometime it may be resolved even without the resolution of inciting stimuli. When such resolution does not happen, the inflammation becomes chronic (Figure 1). The inflammation can be classified based on different attributes like duration, distribution and nature as well as anatomical locations, as shown in table 1.

For instance, inflammation in a small furuncle is a localized response and its impact may be limited, whereas in pulmonary tuberculosis or sepsis, it is systemic and widespread. Similarly, iridocyclitis or chronic inflammation of an isolated eye is an example of localized inflammation. Multiple sclerosis involves localized recurring inflammation of the central nervous system, while rheumatoid arthritis

or systemic lupus erythematosus have multiple organ involvement and inflammation is more systemic in nature. Even with localized inflammation, there may be spill over as reflected by the systemic effect depicted in figure 2.

As a result, the impact of inflammation on the host depends on the pattern of inflammation, in addition to the cause of inflammation. The impact can be broadly categorized into resolution with or without scarring or persisting inflammation without resolution. Resolution of inflammation (with or without scarring) is a physiological need and it stabilizes the disturbed homeostasis. Persisting inflammation due to autoimmunity or an undetermined cause needs further evaluation. Epidemiological studies have revealed the association of many chronic diseases like diabetes mellitus and cerebrovascular diseases with persisting inflammation.[5] There is adequate evidence to suggest that chronic and persisting inflammation leads to accelerated senescence and promote development of malignancy.[6, 7] Moreover, the literature evidence indicate that reduction in inflammation using correct strategies will reduce the consequences of inflammation.[8] Therefore, it is important to know how much inflammation is beneficial for the host and factors regulating it.

Estimating inflammation

Inflammation becomes a harmful physiological response, when intense and dysregulated. It is a multi-step process with several dimensions.[9] Current measures of inflammation, such as ESR and CRP, are surrogate markers that measure only one dimension of this process. Consistent with the available evidence, inflammation is defined as a physiological response to inciting stimuli and occurs only on stimulation. Accordingly, the inflammation should be close to zero, in the absence of stimuli. This is an ideal circumstance, though it does not exist. Many external and internal stimuli can incite inflammation and are constantly activated under natural conditions. As long as the quality and quantity of inflammation remain within a permissible limit, it is protective to host. A deteriorating impact may occur, when it exceeds this threshold (Figure 1). The biggest challenge is to define the threshold, that is, how much of inflammation is natural and permissible. The permissible limit of inflammation (threshold) can be worked out only if we can measure the amount and determine when it crosses the threshold to potentially damage the host or organ. Quantifying inflammation becomes critical under these circumstances. There are many difficulties in estimating inflammation; some of the critical hurdles are detailed below.

Multiple stimuli: In a given clinical circumstances, patient may have more than one stimuli responsible for inflammation. However, the end inflammatory response is supposed to be stereotypic.

Difference in the nature and quantity: The major hurdle in quantifying inflammation is differing qualities of inflammation (Table 1). They are grouped based on timeline, organ involved, types of cells involved etc. The response and clinical implications, including therapeutic intervention required, are different. A measure of inflammation should qualify and quantify these attributes to assist in therapeutic decisions. However, currently there is no consensus on this aspect.

Differing Impact: The expected impact may vary, depending on the organ affected, location or the tissue zone, the type of inflammatory response, and other host factors. For instance, even subclinical inflammation of renal and central nervous system can be disastrous, while extensive skin involvement may not have an impact on other homeostatic functions. Currently, the treatment strategy for immune-suppression depends on the organ involved.[10]

Absence of markers: Specific and easily quantifiable markers of inflammation are not currently available.

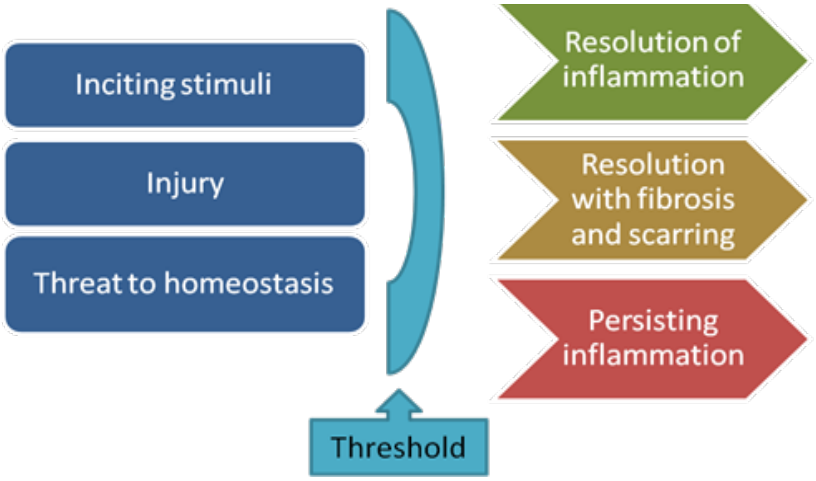
Measuring inflammation

Inflammation was initially described by the clinical features observed by physician. Subsequently, its biochemical and other biomarkers were described. Now it is clear that inflammation is not a monophasic stereotyped response, but it is dynamic and multifaceted. This has added to the complexity and raised the need for quantifying it from all possible dimensions. In order to effectively assess its impact, there is a need to intervene and quantify the effective change achieved by intervention. There are non-modifiable factors such as the duration of inflammation and the damage already incurred at the point of assessment. The other components are modifiable and are dynamic. Measuring a complex process of this nature needs to consider the influence of each factor, hence it may need a different approach. The studies with reference to RA have demonstrated that the joint damage is predictable, if estimated inflammation and duration are multiplied by individual constant factors. The relationship is better with integrated DAS score than time integrated CRP.[11] This observation suggests that if consideration is given to all the critical dimensions of the inflammatory

Table 1: Classification of inflammation based on different attributes

Duration	Distribution	Exudate/reaction	Anatomical
Hyper-acute Acute Sub-acute Chronic Chronic- active	Focal Multi-focal Coalescent Locally extensive Diffuse or systemic	Suppurative Fibrinous Sero-fibrinous Fibrinopurulent Necrotising Granulomatous Sclerosing	Intestitial Organ-specific Layer of tissue-specific

Fig. 1: Physiological process of inflammatory response

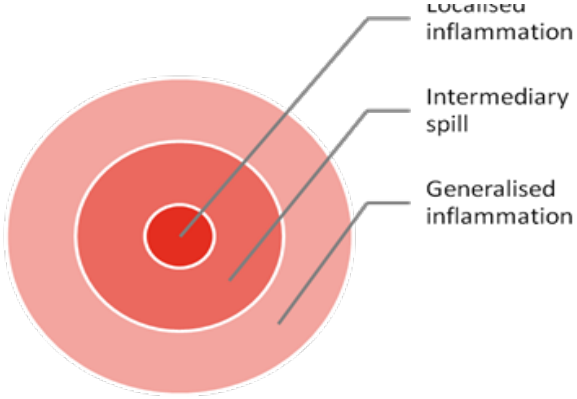


process, while measuring a complex process, there will be improvement in estimating its impact as well as utility. Here biologists need to utilize the experience and observations developed to quantify complex processes in social behavior and information technology, and evolve strategies to improve the estimation of inflammation. The experiences in these fields have suggested that the way the problem is approached (measurement) makes substantial difference in relating the measure to outcome.[12] Under the circumstances, the measure of inflammation should be viewed as a process with multi-dimensional constructs and multiple decisive and influencing variables.

The fact that a small change can lead to a shift from a physiological level to pathological status in inflammatory response, underlines the need for a more refined multi-dimensional approach rather than a simple, one point approach. We are often encouraged by single point measures like glycemic control in diabetes. In real clinical practice setting, using a multi-step construct may be difficult, especially to draft guidelines based on complex decision making process. However, a similar multi-step Disease Activity Score (DAS) is being used in rheumatoid arthritis. It has demonstrated success in assessing and monitoring the inflammatory disease of joints, but has many limitations, such as DAS being disease centric and does not consider inflammation as a primary measuring point.[13, 14]

Researchers in the fields of information technology as well as sociological science need to measure complex processes and have evolved strategies to quantify them. Utilization of these mathematical models and constructs in life science has been well appreciated.[15] Inflammation is a complex process and its outcome is influenced by many variables. The outcome in a given situation does not exhibit a simple linear relationship to a single measure. Studies on diseases where inflammation has been directly attributed to be responsible for damage have not shown any satisfactory relationship of the current way of measuring the inflammation and the disease process.[13, 14] In a complex process where both manifested and latent variables influence the outcome, the measurement needs to consider all of these variables. Misspecification of the measurement can cause interpretational error

Fig. 2: Area-wise possibility of inflammation



in decision making process as well as research.[12] The first step in measuring this type of process is to develop a 'construct' incorporating all the critical factors of the process. Measurement of a first-order (A first-order construct has observed variables (i.e., the items in its measure) as indicators of the construct) construct can be done using one of the following two methods: the reflective conceptualization and the formative conceptualization. The former assumes that the changes in the underlying construct are for the changes in the indicators; while latter considers that it is the measured items that cause changes to the construct rather than the other way round. Several studies have shown the importance of the choice of proper measurement conceptualization. Hence, measuring a complex phenomenon like inflammation in the host, and to monitor it for the purpose of intervention necessitates the development of suitable model that considers all the critical and significant factors.[16] Similarly, for the higher order multi-dimensional construct where there are primary or first order variables and their influence on second order variables have different manifestations in the construct i.e., the reflective conceptualization.[16] The construct model and the direction of cause-effect relationship between inflammation and damage are represented in figure 3.

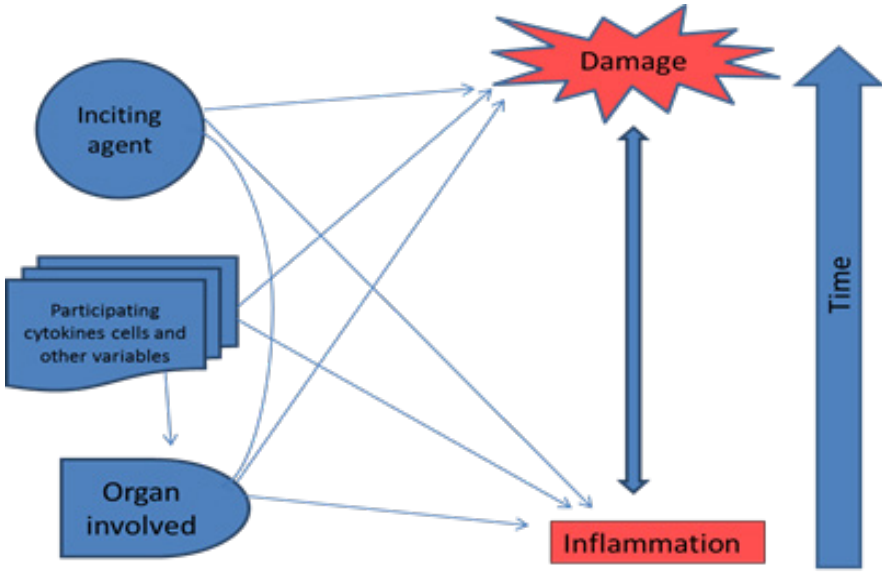
Quantified inflammation, if it has to be titrated against the expected damage, it should consider the following relationships. Several factors influence the damage incurred by the host, and the damage in turn depends on the inciting or triggering agent, type of immune response (determined by the cytokines and the cells responsible for inflammation), and the organ involved (the criticality of the organ as well as its capacity to regenerate). In addition to these factors, duration of exposure to inflammation also influences the outcome. Acute or chronic hepatic injury caused by hepatitis B infection provides a very good example of this scenario. When the immune response is mediated by Th 1, the deterioration is very fast, while inflammation mediated by IgG results in slow damage lasting several years.[17] The effect of inflammation on the host or on the organ depends on these factors required to assess the impact of inflammation.

Markers of inflammation – what can be measured?

Measuring inflammation as accurately as possible and to develop a model to improve its application in patient management is the need of the hour. Inflammation can be measured from different perspectives – the measures that quantify triggering factors, the chemicals or biomarkers participating in inflammation, surrogate markers of inflammation, and even the by-products of the inflammation process. Currently used markers of inflammation are acute phase reactants like CRP, ESR and serum amyloid A protein (SAA). They are the products of stimulation from the inflammatory mediators and some of them, CRP, SAA and fibrinogen, are consumed simultaneously in the process of inflammation. As a result, the markers do not completely reflect the process. These markers are not specific to trigger factors of inflammation; limiting their capacity to discriminate the cause for stimuli as well as the organs involved. Studies have failed to demonstrate the absolute correlation of these acute phase mediators with the outcome in many diseases.

The observable variables that can reflect inflammation can be broadly categorized into clinical variables and biological markers. The clinical variables are essential and assist in qualifying as well as quantifying the cause of inflammation. The biological markers employed represent different stages of inflammation. Possible

Fig. 3: Construct on the relationship of various measurable factors of inflammation and their impact. Quantified inflammation should consider the following relationships to titrate against the expected damage, it. Several factors influence the damage incurred by the host, and the damage, in turn, depends on the inciting agent, type of immune response (determined by the cytokines and the cells responsible for inflammation), and the organ involved (the criticality of the organ as well as its capacity to regenerate). In addition, duration of exposure to inflammation also influences the outcome.



ways of measuring inflammation are depicted in figure 4.

A measure of inflammation presumes that the quantity of inflammation reflects and depends on disease. However, this argument is arbitrary, considering the currently practiced immune modulatory and anti-inflammatory strategies. For instance, use of moderate dose of immune suppressant and immune modulatory agents in lupus, when the involvement is limited only to the musculoskeletal system. On the other hand, higher end immune suppression is used in case of renal involvement, even if inflammation is low.[10] There are limited immune modulators and anti-inflammatory strategies, and their implications for the management of inflammatory disorders (both of auto-immune nature and auto-inflammatory syndrome) are inadequate. However, studies indicate that the control of inflammation, as one

Fig. 4: Sources of potential biomarkers of inflammation

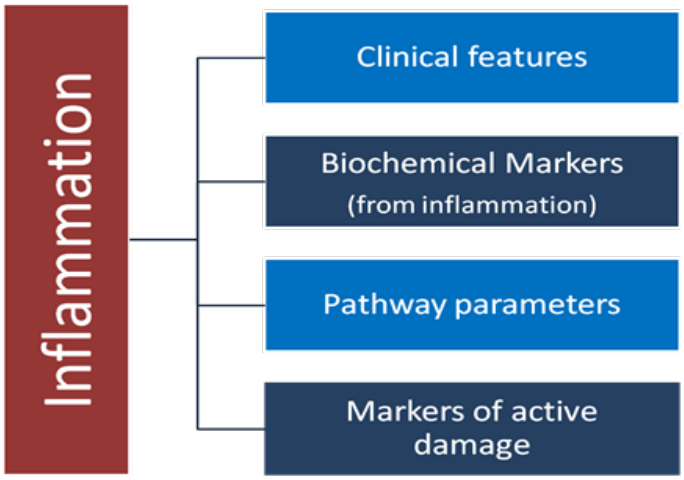
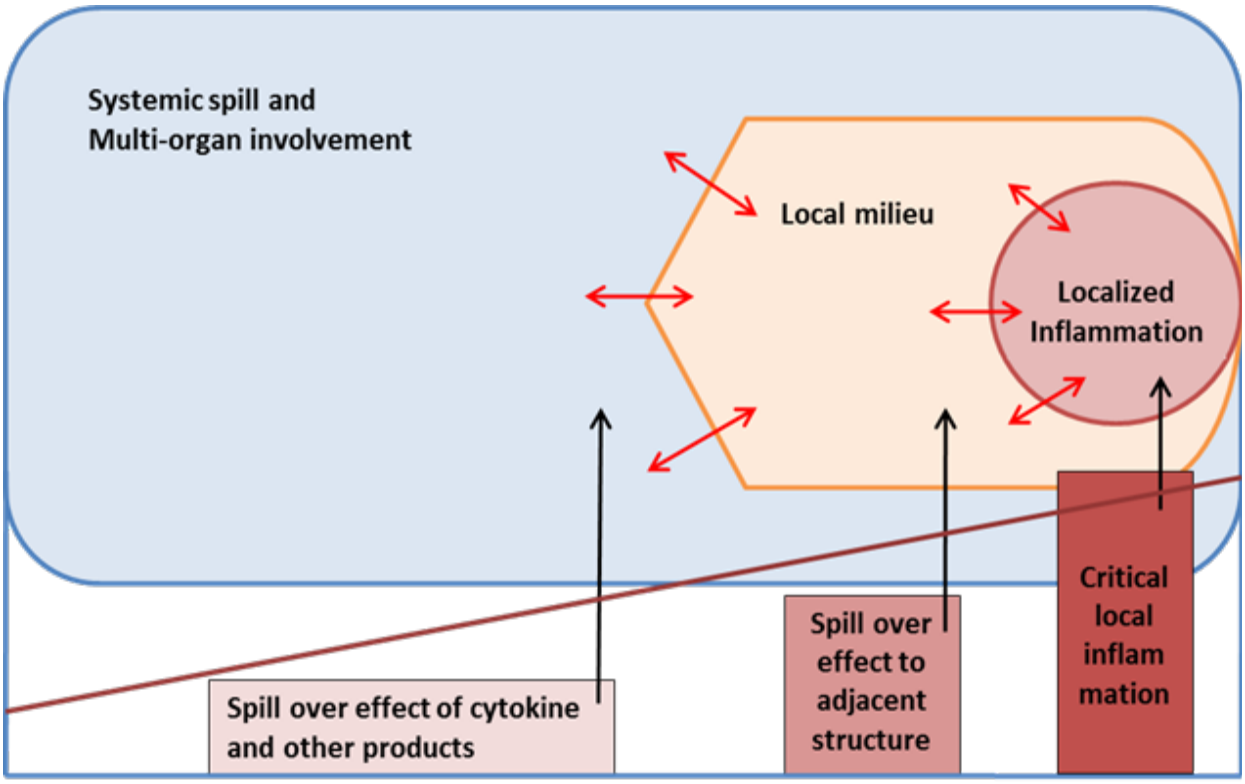


Fig. 5: Effect of inflammation at various levels and sites. The inflammation may be intense and localized and may spill over to the surrounding milieu. The spill may also be reflected in multiple organs in minimal to maximum effect. Therefore, a measure of inflammation should consider all these factors, while quantifying the effect. The markers of inflammation may represent different perspective of this spread. Acute-phase response from the liver for localized inflammation during organ infection (septic arthritis) suggests a systemic spill. This effect depends on quantum of spill rather than the intensity of inflammation.



of the primary targets of treatment, improves the outcome.

Biological markers of inflammation

The biological markers of an inflammation can be selected from three different areas (Figure 5). They may be at the site of intense inflammation as in synovium in RA, or skin and renal system in lupus nephritis. The inflammation, though localized to a specific site of the tissue, has a possibility of spill over to affect the neighboring area, for instance, to adjacent bone and cartilage in synovitis (This could be the second site). Systemic inflammation can occur as a consequence of systemic release of cytokines and other degradation products. This in turn stimulates the release of acute phase response as well as affects functioning of other organs (This can serve as third site or level).

The inflammation thus may be intense and localized and may spill over to the surrounding milieu. The spill may also be reflected in multiple organs with varied effects. Therefore, a measure of inflammation should consider all these factors while quantifying the effect. Thus markers of inflammation may represent different perspective of the process. For example, acute-phase response secreted from liver for an inflammation in localized organ infection (septic arthritis) suggests a systemic spill. This effect depends on quantum of the spill rather than the intensity of inflammation in the joint.

A biochemical, a clinical or a biological marker can be derived to represent these three sites. The secretion products, degradation products and other cell markers from the local site of inflammation, which can proportionately reflect the inflammation in local area, can assess the extent of inflammation on the target organ. The products from the neighboring tissue may evaluate the extent of involvement and this can be represented by both clinical and biomarkers, which can be quantified. The systemic spill and the release of cytokine may produce clinical features as well as the acute phase response.

Based on this brief survey of studies on quantifying

inflammation, there is a need for studies to analyze potential markers from different dimensions – clinical features, pathway of inflammation, damage, and localized vs. systemic spill over aspects – in inflammation are required. In the forthcoming years, directed research by biologists and statisticians, addressing these issues will help developing a clinically useful model for the measurement of inflammation.

Competing interests
The author declare that he has no competing interests.

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