Finding the source of chronic inflammation with laboratory testing

Introduction

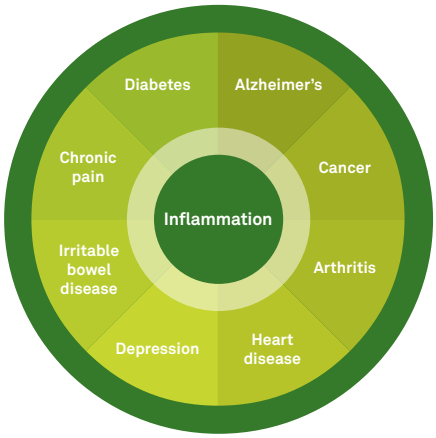
Inflammation is part of the body's crucial healing process, acting as a protection system and alerting the immune system to attack foreign invaders such as viruses when they enter the body. In this way, acute inflammation is vital to health. However, problems arise when inflammation becomes chronic, deploying a constant onslaught of inflammatory cytokines that can damage not only foreign threats but also the body's own cells. This internal war can have a myriad of effects including the disruption of hormone balance,[1] increased insulin resistance, degraded gut health, mental health issues, and even impaired reproduction in women.[2] Unfortunately, these inflammation-associated diseases are anticipated to increase persistently for the next 30 years in the United States.[1]

Chronic inflammation, or dysregulation of the immune system, is difficult to diagnose as patients often present with a complex tangle of symptoms. For example, many people with chronic inflammation experience lipotoxicity, which can cause weight gain. The ability of fat tissue to store excess energy is limited and free fatty acids are released directly into the bloodstream, posing a threat of organ damage and fat necrosis. In response to this cell death, signaling molecules known as cytokines are released to eliminate the dead fat tissue.[3] Ultimately, the patient becomes trapped in a vicious cycle, in which toxic fatty acids accumulate, lead to more inflammation, and so on.

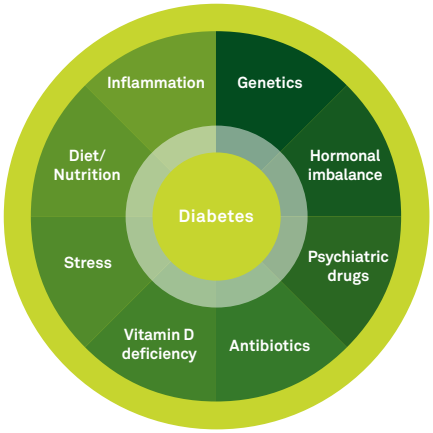
These cycles make it difficult to discern where chronic inflammation ends and chronic diseases begin, thus chronic inflammatory diseases are recognized as the most significant cause of death in the world.[1] When you understand how chronic low-level inflammation contributes to heart disease, cancer, chronic lower respiratory disease, stroke, Alzheimer's, diabetes, obesity, and nephritis,[4] you come to realize the gravity of this complex condition. Fortunately, there is growing research on the topic and an expansive menu of laboratory tests that can help medical professionals efficiently and accurately identify the underlying causes of inflammation, break the vicious cycle, and restore normal immune response.

Inflammation is an underlying cause of many common diseases including diabetes, which is a condition driven by many different factors.

One cause, multiple conditions



One condition, multiple causes



What causes inflammation?

Chronic inflammation can persist for years, making it difficult to understand if inflammation is a symptom of other conditions or the underlying cause of those conditions. In some cases, chronic inflammation is a response to acute inflammation caused by diseases such as tuberculosis and rheumatoid arthritis.[1] But more commonly, chronic inflammation is triggered by one of these recognized risk factors:

Aging

As we age, we experience increasing levels of inflammatory molecules due to mitochondrial dysfunction, the accumulation of free radicals, and other factors like an increase in visceral body fat.

Nutritional deficiencies

Individuals who consume foods rich in saturated fats, trans fats, or refined sugar may have higher production of proinflammatory molecules, especially if they have diabetes or are overweight. Studies have shown that the body mass index of an individual correlates with the amount of proinflammatory cytokines secreted.[1]

Smoking

Cigarette smoking is associated with reduced production of anti-inflammatory molecules, leading to increased inflammation. Metals present in tobacco smoke may cause a pro-oxidant/antioxidant imbalance through the direct generation of free radicals which can activate an inflammatory response.[5]

Low sex hormones

Studies show that sex hormones can suppress the production of proinflammatory markers, such that maintaining sex hormone levels may reduce the risk of several inflammatory diseases.[6]

Stress & sleep disorders

Stress is its own form of toxin which causes the body to release inflammatory cytokines which are damaging at high levels.[7] Through the stress response, psychological trauma has been tied to chronic inflammation in the digestive system.[8] Sleep disorders are also associated with inflammation. Individuals with irregular sleep schedules are more likely to have chronic inflammation than consistent sleepers.[9]

Chronic infections

Some chronic infections such as Lyme disease trigger the immune system to launch a serious inflammatory response. While antibiotic treatments can destroy the bacteria, these drugs do little to quell the inflammatory response waged against these microbes. Over time, Lyme-induced inflammation can damage cells, tissues, and organs, causing widespread bodily dysfunction.[10] *Mycoplasma pneumoniae* is another infectious invader against which the body releases proinflammatory cytokines that initiate an excessive immune response leading to the development of pneumonia.[11] Viruses, yeasts, fungi, and even parasites exhibit similar associations with whole-body inflammatory response.

Environmental toxicants

It is known that inflammation plays a role in tobacco-related tumor development.[12] In fact, the presence of inflammatory cells commonly precedes tumor development.[13] Another common toxin is mold which can cause brain inflammation in the hippocampus, the area of the brain that is responsible for memory, learning, and the sleep cycle.[14] Environmental exposure to pesticides and herbicides can also induce changes in the immune system leading to serious inflammation-related disorders.[15] Likewise, there are 2 chemicals ubiquitously used in the production of plastic that pose a threat. Phthalate chemicals used to make plastics more durable increase levels of chronic low-grade inflammatory biomarkers[16] and bisphenol A (BPA), an endocrine disruptor, impacts adipose tissue, the immune system, and the intestine.[17]

Effects of chronic inflammation across body systems

Digestive system

Throughout the history of human evolution, the gut microbiota has shaped the development and function of the immune, metabolic, and nervous systems.[18] Therefore, a dysbiotic gut microbiome can affect the immune system and create a cascade of events leading to a host of symptoms and medical conditions including inflammatory bowel disease (IBD), a group of chronic inflammatory disorders of the digestive tract. It can develop as ulcerative colitis or Crohn's disease.[19] Additionally, inflammation is associated with tumor growth, making IBD an important risk factor for the development of colon cancer.[20] Inflammation of the mouth such as gingivitis and periodontal disease is also linked to the initiation and progression of systemic diseases (eg, atherosclerosis).[21]

Neurology & mental health

Experts believe that chronic inflammation contributes to neurodegenerative disorders, cognitive decline, and mental health illnesses, such as depression, post-traumatic stress disorder, and schizophrenia.[22] Specifically, there is a well-documented correlation between the inflammation of the gastrointestinal tract that causes IBD and anxiety- and depression-related symptoms. Psychological symptoms are more prevalent during active disease including IBD, Crohn's disease, and ulcerative colitis.[23] Furthermore, there is a growing body of evidence that links post-traumatic stress disorder

and immune dysregulation resulting in metabolic syndrome, atherosclerotic cardiovascular disease, and autoimmune diseases.[24]

Hormone regulation & reproduction

There is a theory that the risk of chronic diseases is increased with early-life exposure to endocrine-disrupting chemicals (EDCs), which can lead to misregulated inflammation.[25] Also, the reduction in hormone levels as one ages increases the risk of cardiovascular mortality since inflammation in the body may initiate atherosclerosis.[26] This risk extends to pregnant women for whom inflammation may increase the chance of cardiovascular events like pre-eclampsia[27] or gestational diabetes.[28] Polycystic ovary syndrome (PCOS) is another hormonal condition that is linked to a proinflammatory state. Research suggests that chronic low-grade inflammation underpins the development of ovarian dysfunction, hyperandrogenism, and insulin resistance.[29]

Dermatology

Many dermatological conditions are associated with dyslipidemia, a disorder of lipoprotein metabolism. These chronic inflammatory diseases that are activated by the secretion of proinflammatory cytokines include psoriasis, lichen planus, pemphigus, granuloma annulare, histiocytosis, and connective tissues diseases like lupus erythematosus.[30]

Rheumatology

Inflammation of joints and bones such as is seen with arthritis and osteoporosis affect approximately 43 million people in the United States or almost 20% of the population. This number was expected to exceed 60 million by 2020.[1] It is now known that systemic inflammation and autoimmunity begin in rheumatoid arthritis patients years before the onset of detectable joint inflammation.[31]

Pulmonary system

Chronic obstructive pulmonary disease (COPD) was the third most common cause of death in the United States in 2014, with nearly 15.7 million Americans diagnosed. Asthma affects more than 24 million Americans and allergies sicken more than 50 million Americans each year.[1] Inflammation is a critical driver of these and other common respiratory diseases, including bronchiectasis, acute respiratory distress syndrome (ARDS), and sarcoidosis.[32]

Laboratory testing to support inflammatory diagnosis

Inflammation markers & tests

Beyond specific body system complications, individuals with chronic inflammation often experience body pain, frequent infections, weight gain, constant fatigue, insomnia, depression, anxiety, and mood disorders. Indeed, chronic inflammation is a complex process associated with a wide range of diseases. For this reason, obtaining a thorough medical history, physical examination, and leveraging the full complement of laboratory tests can confirm or rule out most of the differential diagnoses and shorten the time to optimal treatment.

When a significant amount of certain proteins are released into the bloodstream during inflammation, they can be used as systemic inflammatory markers. Although there are many inflammatory markers, those most commonly measured in clinical practice are:

- **C-reactive protein (CRP)** is a protein produced by the liver. A CRP level between 1 and 3 milligrams per liter of blood often signals a low, yet chronic, level of inflammation[3]
- **Erythrocyte sedimentation rate (ESR)** is an indirect measurement of plasma protein concentrations. The test is especially useful in the diagnosis of select conditions such as bone lesions and osteomyelitis.[33] Normal ESR values are specific to age and sex
- **Procalcitonin (PCT)** is released into the blood in cases of bacterial infection, severe viral infection, pancreatitis, tissue trauma, and with some autoimmune disorders.[34] In particular, increased PCT levels have a high positive predictive value for sepsis[35]

Other inflammatory markers that can be tested for are serum amyloid A (SAA) and proinflammatory cytokines like tumor necrosis factor-alpha (TNF-alpha), interleukin-1 beta (IL-1beta), interleukin-6 (IL-6), and interleukin-8 (IL-8). However, these are expensive methods and should only be used when appropriate.

While CRP, ESR, and PCT are nonspecific and therefore cannot be used to diagnose any particular condition, they can assist in identifying an inflammatory state in conjunction with other tests that may lead to a differential diagnosis.

Examples of combined testing methods for diagnosis

Multiple markers (fecal calprotectin, ESR, CRP, platelets, hemoglobin, and albumin) as a single test can lead to more definitive IBD risk classification in symptomatic pediatric patients by correctly classifying them in the low-and high-risk groups more often, rather than the ambiguous intermediate group.

Holtman GA, Lisman-van Leeuwen Y, Day AS, et al. Use of laboratory markers in addition to symptoms for diagnosis of inflammatory bowel disease in children: a meta-analysis of individual patient data. *JAMA Pediatr.* 2017;171(10):984–991. doi:10.1001/jamapediatrics.2017.1736

CRP/albumin ratio was shown to be a more effective predictor of PCOS compared to classical correlates such as Free Androgen Index and insulin resistance for all body mass index categories. Using this marker can be especially valuable for treating a complex disease like PCOS that is difficult to diagnose, given how symptoms often differ between each patient.

Kalyan S, Goshtesabi A, Sarray S, et al. Assessing C reactive protein/albumin ratio as a new biomarker for polycystic ovary syndrome: a case-control study of women from Bahraini medical clinics. *BMJ Open.* 2018;8(10):e021860. doi:10.1136/bmjopen-2018-021860

Clinical application of ESR, CRP and PCT

When applied to a patient's overall clinical condition, testing for inflammatory markers can help to diagnose suspected inflammatory disorders. The tests may also help to distinguish between inflammatory and noninflammatory diseases as in the case of inflammatory bowel disease versus irritable bowel syndrome. Both CRP and PCT can aid in the management of antibiotic therapies by signaling the appropriate time to end antimicrobial therapy[36] while PCT is capable of predicting 28-day cumulative mortality risk for patients diagnosed with sepsis.[37]

Because the inflammatory markers discussed above lack sensitivity or specificity, they should not be used exclusively for diagnosis. However, they are helpful in diagnosing and monitoring inflammatory conditions (see Table 1).

Table 1. Conditions associated with changes in inflammatory markers

Conditions associated with a rise in CRP	Conditions associated with a rise in ESR	Conditions associated with a rise in PCT
• Active inflammation*	• Malignancy*	• Bacterial infection (sepsis)
• Severe bacterial infection*	• Temporal arteritis*	• Severe viral infection
• Burns*	• Renal disease*	• Pancreatitis
• Viral infections	• Collagen vascular diseases*	• Tissue trauma
• Mucosal infections	• Increasing age	• Autoimmune disorders
» Periodontitis	• Female gender	
» Stomatitis	• Pregnancy	
» Sinusitis	• Anemia	
» Vaginitis	• Red blood cell abnormalities (including macrocytosis)	
» Intestinal hyperpermeability	• Elevated fibrinogen level	
» Bacterial translocation	» Inflammation	
• Noninfectious causes of mild inflammation	» Infection	
» Obesity	» Malignancy	
» Insulin resistance	» Diabetes	
» Pancreatitis	» Renal disease	
» Smoking	» Heart disease	
» Uremia	» Collagen vascular diseases	
» Cardia ischemia		
» Oral hormone replacement therapy		
» Sleep disturbance		
» Chronic fatigue		
» Mild alcohol consumption		
» Increasing age		
» Depression		

*Indicates associations with a major rise in the marker.
Table adapted from Bray C, Bell LN, Liang H, et al. Erythrocyte sedimentation rate and C-reactive protein measurements and their relevance in clinical medicine. *WMJ.* 2016;115(6):317-321.

Conclusion

Chronic inflammation is a powerful reminder that finding the root cause of dysregulation is essential to both prevent illness and create lasting improvements in health. Knowing that systemic inflammation may be lurking below the surface of many common conditions, it is prudent to leverage appropriate biomarker laboratory tests to confirm or rule out differential diagnoses and speed time to effective treatment. When we are aware of the impact of chronic inflammation, lifestyle, dietary and environmental changes, appropriate supplemental and therapeutic measures may be employed to improve and preserve health.

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