



H63D Syndrome Research Consortium

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Modern Medicine

**The seductive temptation of ignorance:
how micro-inflammation can cause serious
diseases such as diabetes, obesity, heart
problems or cancer - and yet be ignored
because they are difficult to detect in the
laboratory.**

Abstract

Micro-inflammations are a phenomenon that has been attracting increasing attention from the scientific community in recent years. These small, persistent inflammatory responses that occur at a cellular level are thought to play a crucial role in the development and progression of many chronic diseases. Despite their importance, micro-inflammations are often ignored or overlooked in the clinical setting, and this can have serious consequences for patient health. In this paper, we will explore the mechanisms by which micro-inflammations occur, their impact on various health outcomes, and why it is dangerously wrong to ignore them. We will also discuss current approaches to managing micro-inflammations and the need for more comprehensive and targeted interventions to address this growing health concern.

Not everything that most doctors believe to be true is true.

Heart attacks, strokes, NAFLD, metabolic syndrome, NASH, diabetes type 2 and 3 diabetes, rheumatism, dementia(s) hypertension, chronic progressive heart failure, an uncountable number of autoimmune diseases, and even cancer. All of these serious and widespread 'common diseases', which often shorten life drastically, are the patient's own fault, many doctors still claim. Because of their diet, too little exercise, lifestyle and the like. While all of this may undeniably play a role, one important, if not the most important, driver of these widespread ailments is still being ignored by most physicians - and almost completely forgotten by researchers. The subject is micro-inflammations.^{1,4,8,21}

Which came first: the chicken or the egg?

Those affected often do not notice that they are suffering from any kind of chronic inflammation. However, treatment of hidden micro-inflammations could counteract diseases such as dementia or type 2 diabetes - or even cancer. The ailments that afflict people as they age are varied and often incurable. Some suffer a heart attack or stroke, others get cancer, are plagued by chronic heart failure, type 2 or 3 diabetes, develop kidney weakness, and still others will suffer from dementia at the end of their lives. However, more and more physicians believe that all these diseases could be due to a common cause, and they do so rightfully. These illnesses are thought to

be the result of a kind of small and undetected smoldering 'fires' that carry out their secret work of destruction in the organism over a period of years as a result of so called micro-inflammations. Inflammation as the cause of disease, is a concept that is convincing more and more scientists and is also becoming the focus of attention for pharmaceutical companies while younger clinicians have been aware of it for many years if not decades. However, almost nobody listens to these frontline doctors who are most commonly general practitioners or family doctors.

In general practice and family medicine it has long been accepted, for example, that atherosclerosis is not simply a clogging of the vessels with cholesterol and calcium, but an active inflammation of the vessel walls. A similar rethinking is beginning to take place in Alzheimer's research, and inflammatory processes are now known to play a significant role in type 2 and 3 diabetes and cancer. Everyone knows acute inflammation from their own experience, as painful swollen and reddened tissue. It is actually a beneficial facility of nature with which the body reacts to injuries and infections. Every wound attracts a colorful troop of busy immune cells that devour and break down destroyed tissue and invading bacteria. In addition, they secrete messenger substances that stimulate cell division and the growth of blood vessels. Over millions of years, this process has been perfected and honed by evolution, ensuring survival since the dawn of mankind. There is one thing, however, that evolution has not prepared humans for: a long life, one that extends far beyond the time it takes to have and raise children. Thanks to the game changing

invention of antibiotics, people countries die far less frequently from acute infections. But the more time passes in life, the more often the immune system seems to strike out everywhere in the body, even for no meaningful reason. "Inflammaging" - a strange compound of the English terms for inflammation and aging - is what now some scientists call the phenomenon that careful frontline physicians normally have been calling correctly 'micro-inflammations'. Scientists from the Center for Sleep Research at the University of California at Berkeley demonstrated a couple of years ago that frequent interruptions to night's rest cause inflammatory cells to circulate in the blood and drive atherosclerosis. Another major trigger of silent inflammation is obesity. However, the reason for obesity (high BMI) might in many cases be micro-inflammations, not the other way round. It has long been known that people who are overweight often have significantly elevated levels of inflammation. If a slim person will see his/her GP or family doctor with an infection, the physician can use inflammation markers in the blood to decide whether antibiotics are necessary. This is not so easy with a severely overweight patient, whose general inflammation levels may be chronically elevated, as if he/she had an acute infection.^{1,2,3,6,9,12,16,19,21,24}

Detecting micro-inflammations

C-reactive protein (CRP) and other standard inflammatory markers, such as erythrocyte sedimentation rate (ESR) and white blood cell (WBC) count, are commonly used to assess systemic inflammation in the body. However, these markers have limitations in detecting

micro-inflammations, which are low-grade, localized inflammations that occur in tissues such as the brain, heart, liver, kidneys, blood vessels, etc. The main reason that CRP and other standard inflammatory markers are unable to detect micro-inflammations is due to their systemic nature. CRP and ESR, for example, are produced in response to inflammation and are present in the bloodstream, but they do not reflect the localized and tissue-specific nature of micro-inflammations. Similarly, the WBC count measures the number of white blood cells in the bloodstream, but it does not provide information about the type or location of inflammation. Micro-inflammations are often associated with chronic diseases such as cardiovascular disease, neurodegenerative disorders, and metabolic disorders. To accurately assess micro-inflammations, more tissue-specific and sensitive markers are needed, such as the measurement of cytokines and other inflammatory mediators at the site of inflammation. In conclusion, CRP and other standard inflammatory markers are totally unable to detect micro-inflammations because they are systemic markers that do not reflect the localized and tissue-specific nature of low-grade inflammations. To accurately assess micro-inflammations, way more sensitive and tissue-specific markers are needed.⁴⁻¹⁰

The kynurenine pathway as an alarm system

The kynurenine pathway is a highly important but little known metabolic pathway that generates neurotransmitters and other molecules from tryptophan, an essential amino acid. In response to

inflammation, the levels of certain cytokines such as interferon-gamma increase, which activate the immune cells known as macrophages to produce an enzyme called indoleamine 2,3-dioxygenase (IDO). IDO then catalyzes the degradation of tryptophan into kynurenine.

The production of kynurenine and its subsequent metabolism by other enzymes provide a way to assess the levels of micro-inflammatory processes in humans. Elevated levels of kynurenine, combined with decreased levels of tryptophan, have been found to be associated with various inflammatory and autoimmune diseases, making the kynurenine pathway a useful and sensitive marker of inflammation. Such micro-inflammations occur in parenchymal tissue, abdominal fat, in the brain, or in the liver where they cause steatosis, NAFLD, or NASH. The tissue damage attracts immune cells that must clear out the dead tissue, as with any injury. How severe the damage is varies from person to person. Each person can only produce a limited amount of fat cells over the course of his or her lifetime from a supply of stem cells. Once that supply is used up and the patients continues to eat too much anyway, the fat cells become overloaded to a degree in which they cause liver function issues. Some people can have the problem with a BMI as low as 23, others have no issues with a BMI of 32. Most of the medical literature about metabolic syndrome, obesity, diabetes types 2 and 3 and many other illnesses have to be rewritten or updated sometime soon. Because it is all about micro inflammations causing these health problems and not the other way round.

Whether in abdominal fat, parenchyma, mineral channels (heart) or elsewhere, chronic inflammation can make a human very sick. For instance, inflammatory messengers interfere with signaling cascades in muscle and liver cells. The cells can then no longer respond as well to insulin and absorb sugar from the blood, and type 2 diabetes can develop. Although such correlations have been observed for a long time, it had not been proven for a far too long time whether inflammation is really the cause or only a concomitant of the diseases. Now research indicates that micro-inflammations happen before metabolic (and other) illnesses. To find out, it's crucial to curb chronic inflammation over a long period of time and see if people are less likely to die from diseases of old age as a result. Just a couple of years ago (a short period of time in medicine), a large-scale international study provided such evidence.

The American cardiologist Paul Ridker led the study, which involved more than 10,000 people who had already suffered a heart attack. Over a period of three to four years, some of the test subjects received an injection every three months with an anti-inflammatory agent, an antibody that binds specifically to a messenger substance and thus suppresses inflammatory reactions throughout the body. At the end of the study, fewer people in the group treated in this way had died from another heart attack or stroke than in the placebo group. Not only that, but there were also significantly fewer deaths from cancer, particularly lung cancer, in the group of treated subjects due to the dampened inflammation.

So, micro-inflammatory responses are a risk factor for many diseases, and by no means their concomitant.

Perhaps life can be prolonged in this way by targeting micro-inflammation before it causes permanent damage. In 2019, a group led by Jean-Claude Tardif of the Montréal Heart Institute published a paper in which patients who had suffered a heart attack were treated with a naturopathic anti-inflammatory that has been used for thousands of years to treat gout. Here, too, they saw a small but significant success. Fewer patients suffered from angina pectoris - pain caused by a lack of oxygen in the heart - or died from strokes. However, there were also more cases of pneumonia. Overall, the results were again not convincing for application, but support the thesis that silent inflammation promotes certain diseases.

However, many years will pass before this knowledge will be translated into common knowledge as medicine is a terrifying slow academic field when it comes to the transfer of the findings into daily medical practice. Under normal circumstances it takes at least one generation of physicians. Nevertheless, younger clinicians who have already worked with mild anti-inflammatory medications that are already on the market - but largely unknown - have seen actual success with their patients. Especially in countries like India where traditional folk medicine and its remedies are valued and being researched on. However, at the same time, some western researchers are also pursuing new and surprising approaches. It is now known, for example, that overweight people more often have inflammation in the

hypothalamus, a developmentally ancient brain region that controls energy metabolism and the feeling of satiety. For some time now, there has been growing evidence that such inflammation may precede obesity.

It is therefore possible that massive obesity is caused by inflammation in the first place - because people no longer feel when they are full. A genetic predisposition may contribute to the development of inflammation in the brain, but other factors may also play a role. Gastroenterologist-oriented researchers, meanwhile, are investigating a link with the gut flora and certain types of bacteria that promote inflammation beyond the gut. This could lead to combinations of gut bacteria in capsule form that prevent inflammation. Already, some clinicians are also using probiotics and report good results.^{1,2,5,6,7,8,21,22}

Conclusion

It is likely that the next generation of physicians will recommend a selection of entirely new anti-inflammatory therapies for patients with strikingly high BMI, NAFLD, hypertension, heart disease, etc., because there is growing evidence that these conditions are most likely related to chronic, low-grade inflammation (micro-inflammation), which is still ignored or even ridiculed in contemporary medicine. This kind of micro-inflammation can contribute to the development of several chronic diseases, such as type 2 diabetes, cardiovascular disease, and some types of cancer. Future novel anti-inflammatory medications (or those already available in the safe hands of experienced physicians) may help reduce micro-inflammations

and will most likely improve outcomes more effectively than anything we have available today as standard medication. However, it is still important for doctors to encourage lifestyle changes, such as regular exercise and healthy eating as this is a good idea - for everyone.

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Conflicts of interest

None declared.

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