Sveriges lantbruksuniversitet
Swedish University of Agricultural Sciences

Faculty of Natural Resources and Agricultural Sciences
Department of Food Science

How nutritional aspects can affect immune mediated inflammatory diseases

Hur nutritionella aspekter kan påverka inflammatoriska sjukdomar

Sohail Ehsanzamir

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Abstract

Low- grade inflammation is a state where the immune system is chronically active and it is a major cause of various diseases such as type 1 diabetes, schizophrenia, different cardiovascular diseases and cancers. The diet, what we eat and the load of it plays an important role in the prevalence of those disease. This is proven by many studies that have been conducted on how foods affect certain biomarkers for inflammation, such as C- reactive protein, different cytokines and eicosanoids.

A high omega- 6 consumption compared to omega- 3 is one of many nutritional aspects which raises levels of biomarkers. Consuming more trans fatty acids, gluten and sugars have also been proved to heighten levels of such biomarkers meanwhile an energy restricted diet among overweight people and an increased intake of fruit and vegetables have lowered such levels significantly.

Keywords: chronic, inflammation, omega- 6, trans fatty acids, gluten, obesity, casein, biomarker, dairy, flavonoid, fruits, vegetables, carbohydrate.

Abstrakt

Kronisk inflammation är ett tillstånd då immunsystemet är aktivt under en längre period. Detta är orsaken till många sjukdomar som; typ 1 diabetes mellitus, schizofreni, kardiovaskulära sjukdomar och cancer. Kosten, vad vi äter och hur mycket, spelar en stor roll i förekomsten av sådana sjukdomar. Många olika studier påvisar hur mat påverkar biomarkörer för inflammation efter konsumtion. C-reaktivt protein, olika cytokiner och eikasanoider är några få av alla kända biomarkörer. En hög omega -6 konsumtion jämfört med omega- 3 är en av många nutritionella aspekter som höjer nivåer av biomarkörer för inflammation. Större konsumtion av transfetter, gluten och socker har hos många också associerats med förhöjda nivåer medans en kaloribegränsad diet och ett större intag av frukt och grönsaker sänkt dessa.

Keywords: inflammation, omega- 6, transfetter, gluten, fetma, kasein, biomarkör.

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Abbreviations

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LTB4	Leukotriene B4
BHB	β- Hydroxybutyrate
CD	Celiac Disease
CRP	C- reactive protein
CVD	Cardio vascular disease
BCM7	β- casomorphin 7
IL	Interleukin
IMID	Immune- mediated inflammatory disease
MCP- 1	Monocyte chemoattractant protein- 1
MPO	Myeloperoxidase
NCGS	Non coeliac gluten sensitivity
TNF	Tumor necrosis factor

1 Introduction

Low- grade inflammation, also known as chronic inflammation, is the cause of many medical and psychiatric diseases e.g. arthritis, diabetes, psoriasis, cancer, schizophrenia and depression. The western life style, characterized by limited exercise and consumption of refined foods is likely one of the reasons of this state. Chronic inflammation is a state, where the immune system is constantly activated and attacks the host. Approximately 5-7 % of the western society is suffering from an immune- mediated inflammatory disease (IMID) (El-Gabalawy et al., 2010). In type 1 diabetes, the pancreas is not able to produce insulin because of an autoimmune reaction which attacks the insulin producing cells. Glucose can therefore not be transported in to the cells (Cnop et al., 2005). When suffering from rheumatoid arthritis the immune system attacks and breaks down cartilage, bones and close arteries. This leads to pain and loss of mobility (McInnes and Schett, 2011). In psoriasis, the immune system is chronically activated which leads to extreme cell proliferation and differentiation of skin cells (Gudjonsson et al., 2004). These are just few examples of how inflammation mediates various diseases. The treatments against IMIDs are often not directed towards the disease but the symptoms. Patients are frequently prescribed medications with anti-inflammatory properties which cause serious side effects in the long run. Since most of the cells that are involved in the immune system is located in the gut, researchers are looking for answers in the diet (Vighi et al., 2008). Also, many patients who suffer from an inflammatory disease have experienced major improvement of their symptoms after changing their diet.

1. 1 Aim

The aim of this study was to investigate how nutritional aspects may interfere with immune- mediated inflammatory diseases. Moreover, the study should enlighten patients suffering from such condition about the possibility of their diet's involvement in the progression of these disease.

1. 2 Method

The study was based on literature reviews and studies published on PubMed and Web of science. Searches were conducted using MeSH terms such as "omega -6" and "inflammation". The results were limited to studies published in Swedish and English.

2 Literature review

2. 1 The mechanism of inflammation

Inflammation is a vital part of the body's immune system. It is a response to harmful stimuli like damaged cells, pathogens or irritants. The aim of an inflammatory response is to recruit leukocytes to help fight off the infected or damaged tissue. During an acute response, the first step is to increase the blood flow to the area and activate endothelial cells, which causes adhesion of leukocytes. The next step is to increase vascular permeability so that macrophages and other cells can migrate from the blood stream into the tissue. Macrophages produce factors like prostaglandin and cytokines which signals to the other cells of the immune defense (Wood, 2011).

If exposed to a pathogen, irritant or even a self- antigen for a longer time, the acute inflammation can develop to chronic inflammation (Murakami and Hirano, 2012).

The typical symptoms of acute inflammation are redness, swelling, pain, heat and loss of function. A chronic inflammation is on the other hand less noticeable, but is occurring during a longer time (Libby, 2007). An acute response can many times lead to a prolonged one, even after the threat is eliminated. This could be due to the fact that some pathogens may share similar antigens as our own self-antigens, which leads to the attack on our own tissues. This is called an autoimmune reaction (Vighi et al., 2008). Environmental factors like stress can also lead to activation of T helper cells (T_h cells), which main purpose is to aid in the recognition of pathogens. Activation of T_h- cells leads to production of cytokines and further activation of macrophages (Wood, 2011).

2. 2 Biomarkers of inflammation

Nothing can tell us for sure that someone will suffer from an IMID beforehand. However, we can measure the levels of certain proteins or cells in the blood, which have a task in the inflammatory response to evaluate the risk. These cells and proteins are biomarkers of inflammation and are used to detect ongoing reactions. Most studies on foods involvement in inflammatory processes compares levels of biomarkers before and after consumption. To make conclusions about the results, reliable biomarkers must be used.

2. 2. 1 C- Reactive Protein

C- Reactive Protein (CRP) is an acute phase protein which means that its levels increase during an inflammation. When the patient is healthy again, the CRP levels in the blood lowers. Intensive workout, pregnancy and visceral fat can also raise CRP levels.

It was shown in a study that, women with the highest levels of CRP had four times higher risk suffer by heart attack or stroke than women with the lowest. CRP was also a better marker than cholesterol at predicting heart diseases. Inflammation of the arteries is linked to an increased risk of cardio vascular diseases (CVD). Therefore the presence of higher CRP levels, indicate an increased risk for CVD (Zakynthinos and Pappa, 2009).

2. 2. 2 Cytokines

Cytokines are important signal molecules which are produced by cells involved in the immune system. They are secreted as an answer to infection or tissue damages. Through binding to specific receptors they stimulate production and differentiation of lymphocytes and hence regulates biological processes like growth, inflammation and wound healing. Examples of cytokines, which are used as biomarkers for chronic inflammation are IL- 1B, IL- 6, IL- 12, TNF-a and MCP- 1 (Zakynthinos and Pappa, 2009).

Monocyte Chemoattractant Protein- 1 (MCP-1) or its synonym CCL2 is one of the key cytokine that regulate migration and infiltration of macrophages from the bloodstream to the damaged tissue during inflammation. MCP-1 and its receptor CCR2 are linked to various IMIDs such as multiple sclerosis (MS), rheumatoid arthritis, atherosclerosis, psoriasis and type 2 diabetes (Deshmane et al., 2009).

Tumor Necrosis Factors (TNF or TNF- α) is a glycoprotein that is produced mostly by macrophages and T- lymphocytes. In healthy patients, TNF- α is normally not detectable but elevated levels are found in patients with

inflammatory and infectious diseases. TNF- α is a key regulator of inflammation and also linked to multiple IMIDs (Bradley, 2008).

2. 2. 3 Myeloperoxidase

Myeloperoxidase (MPO) is an enzyme, which is most abundant in neutrophils in the artery wall and it is released in response to inflammation. They generate reactive oxygen species that contributes to the removal of pathogens (Zakynthinos and Pappa, 2009). In clinical studies, patients with coronary artery disease had elevated levels of MPO. Most studies made on MPO have been conducted on patients with established cardiovascular disease but a prospective study in 2007 were the first to show that MPO is predictive of future cardiac events in healthy individuals. It is an independent biomarker indicating risk even in those with normal low- density lipoprotein (LDL), high- density lipoprotein (HDL) and CRP levels (Loria et al., 2008).

2. 2. 4 Leukotrienes and prostaglandines

Leukotrienes and prostaglandins are metabolites of arachidonic acid synthesized by enzymatic break down. They are subfamilies of lipid- derived hormones called eicosanoids and their main purpose is to act as signaling hormones (Bäck et al., 2015). Leukotriene B4 (LTB4) is produced by leukocytes and induces recruitment and activation of neutrophils in various inflammatory diseases (Bray, 1986).

2. 3 Obesity and chronic inflammation

Obesity is a growing concern all over the world. In 2014 more than 1.9 billion people were classified as overweight and 600 millions of these were obese in definition as a body mass index (BMI) of 30 or more (WHO, 2015). Between year 2004 and 2013 the percentage of obese people rose from 11 to 14, in Sweden (Folkhälsomyndigheten, 2014). This is a major concern since obesity significantly lowers life expectancy and is directly linked to various coronary diseases and diabetes.

A lot of people that are suffering from an IMID are overweight. It is now clear that obesity is associated with low- grade inflammation of adipose tissues which is a result of chronic activation of the immune system. This can lead to diabetes and cardiovascular diseases. It is specifically the visceral obesity which is a major problem since it is a predominant cardiovascular risk factor (Nishimura et al., 2009). One of the first discoveries of low- grade inflammation among obese

people was revealed after a study on mice, where obese mice had increased levels of the cytokine TNF-a. Several following studies approached the same issue and concluded that there was a rise in many other cytokines too such as IL- 6 and IL-1B (Gregor and Hotamisligil, 2011).

Adipose tissue is considered to be an endocrine organ that secretes various pro-inflammatory factors and the inflammation is not limited to the tissues but also affects the liver, pancreas and brain.

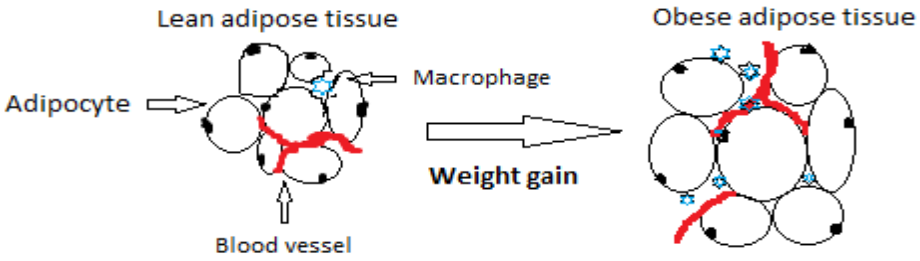

Figure 1. Weight gain leads to expansion of adipose tissues and the infiltration of macrophages through various signals. Macrophages produce factors such as IL-1β and resistin, which is a pro-inflammatory hormone (Sohail Ehsanzamir, 2016)

A range of pathways in the metabolic cells may be the cause of an uprising inflammation due to excess nutrient intake. One of the features is an increased infiltration of macrophages into the adipose tissue which raises cytokine production (Figure 1). The exact mechanism of how adipose tissue attracts macrophages is not clear but it appeared that isolated bone marrow cells migrated to cultured medium conditioned by adipose explants from obese animals (Nishimura et al., 2009).

The inflammation discovered in obese animals has also been reported in humans. Therefore, overweight patients who suffer from an inflammatory disease may benefit from energy restricted diet (Sears and Ricordi, 2011).

2. 4 Dairy products

Milk and dairy products in general are in most western households consumed every day because it is a source of proteins, minerals and vitamins. Sweden is one of the top consumers of milk; approximately 86 liters per person each year.

In recent years a lot of suspicions have aroused about milk but most of the claims have been made without clinical studies to confirm them. However, some studies lately have been able to associate a certain type of casein with IMIDs.

Caseins are a group of phosphorus proteins, occurring in different variants. They are abundant in milk and other dairy products. β- Casein B, A1 and A2 are three caseins from the protein family. The levels of these in milk differs depending on the lactation stage and breed of the cow (Kamiński et al., 2007).

An epidemiological study from New Zealand compared type 1 diabetes incidence among children in 10 different countries and their β- casein A1 consumption. Only countries, which could provide reliable data about the β-casein variation and had low dairy import was included in the study. The results showed strong positive relationship between countries consuming milk with high A1 and B levels and prevalence of diabetes. Countries consuming milk with higher A2 levels had lower incidence of such diseases (Elliott et al., 1999). Although there is a strong relationship between high A1 consumption and certain diseases, these kinds of studies are controversial and difficult to interpret because many factors plays a role.

Another study performed in mice provided a mechanism of the pathogeneses of β- casein A1. It proved that this variant of caseins yield the bioactive peptide β-casomorphin- 7 (BCM7) after digestion, which A2 did not (Nguyen et al., 2015). BCM7 increased levels of inflammatory molecules MPO, MCP- 1, IL-4 and histamine and induced inflammatory immune response in mice gut through T_h2 pathway[1] (Haq et al., 2014). It also increased the infiltration of leukocytes in the intestinal of mice. However, most studies were conducted by injecting BCM7 directly into the mice gut which may have other effects than if taken orally. Therefore, further studies on BCM7 are warranted.

2. 4 The ratio between omega- 6 and 3

The omega- 6 and 3 fatty acids (FA) are polyunsaturated with either a double bond on the 6th or 3rd carbon from the methyl end. Hence a wide range of fatty acids can be categorized as omega -6 or 3. In our diet, omega -6 is most abundant in cereals, vegetable oils, nuts and dairy products meanwhile omega -3 can be found in fish and in livestock fed on grass (Simopoulos, 2008). Only small quantities of both fatty acids are needed but the ratio between them is important.

[1] Th2 pathway is the anti-body mediated defense, meanwhile Th1 includes the innate immune-system.

Many sources suggests that the ratio between intake of omega -6 and 3 was 1:1 or 2:1 when humans were evolving and the genes were set. However, over the past 150 years, rapid changes in our diet have occurred and today in western diets the ratio is estimated to be 15:1. This depends on the mass consumption of cereals and vegetable oils (Simopoulos, 2002).

A recommended ratio is said to be between 1:1 and 4:1 based on studies suggesting that a ratio of 4:1 is associated with 70 % lower mortality and a ratio of 2.5 : 1 lowered cell proliferation in colon cancer and also lowered inflammation levels in arthritis (de Lorgeril et al., 1994, James et al., 1997).

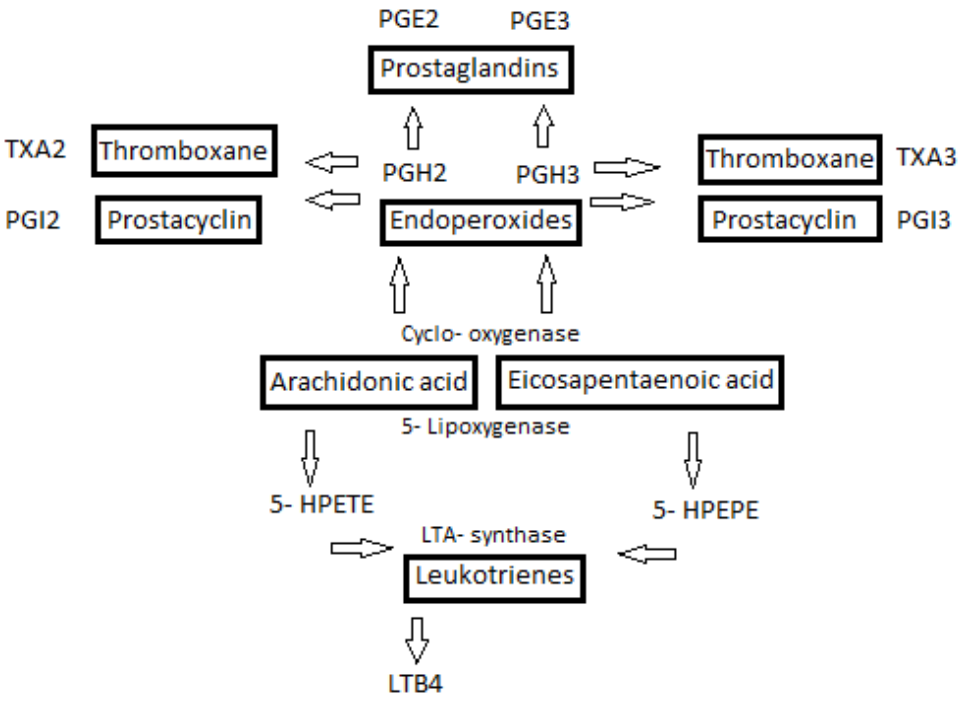

Figure 2. Arachidonic acid and Eicosopentaenoic acid compete for the same enzymes to produce hormones with opposing functions (Sohail Ehsanzamir, modified from Simopoulos, 2002).

In the human body, omega -6 and 3 are rearranged to prostaglandins and leukotrienes, hormones commonly known as eicasanoids. Both type of FA compete for the same enzymes to produce similar hormones but with opposing functions (Figure 2). Since they compete for the same enzymes, a western diet characterized by a high omega -6 consumption will mostly yield hormones with properties belonging to omega- 6 eicosanoids which are known to be pro-inflammatory meanwhile derivatives of omega- 3 are anti- inflammatory.

Biomarkers thromboxane A2 (TXA2), LTB4, IL-1β, IL-6, TNF- α, and C-reactive protein are all associated to many chronic conditions and positively related to increased intake of omega -6 in oppose to omega- 3 (Simopoulos, 2002).

2. 5 Carbohydrates

Many patients suffering from an IMID have improved a lot by changing to a low carbohydrate diet. Is this a result from the possible weight change or are carbohydrates in today's amount actually pro- inflammatory? Studies point to both. A research which was published in Nature Medicine has shown that a diet low in carbohydrates can lower inflammation (Youm et al., 2015). Mice which had autoimmune diseases, were treated successfully with specific ketone bodies called B- Hydroxybutarate (BHB). The ketone bodies are synthesized in the liver when glucose levels are low. The amount of BHB rises when going on a low carbohydrate diet, during fasting or intensive work out (2015).

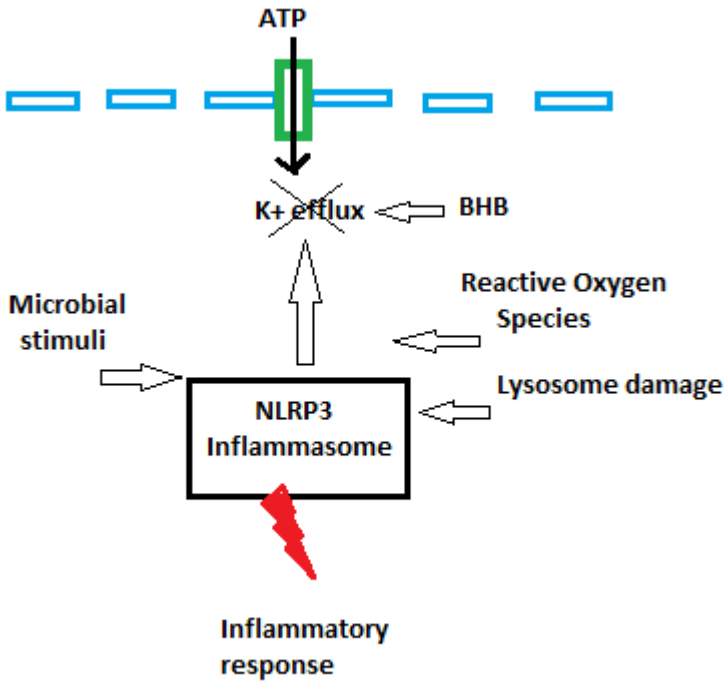

Figure 3. The NLRP3 inflammasome can be triggered by three mechanisms; lysosyme damage, reactive oxygen species and microbial molecules. As an answer to these stimuli, potassium ions are pumped out of the cell which activates the inflammasome. BHB inhibits the potassium efflux and thereby the inflammatory reaction (Sohail Ehsanzamir, modified from Chen and Pedra, 2009).

BHB inhibits the activation of the inflammasome NLRP3, which is a receptor or a sensor that regulates the inflammation process. NLRP3 activates when potassium ions are pumped out but BHB inhibits this out flow, which suppresses an inflammasome- mediated response (Figure 4). In humans, BHB reduces IL- 1B and IL- 18 production in monocytes (Youm et al., 2015).

Evidence also introduces another pathway. Dickinson *et al.*(2008) observed that carbohydrates with high glycemic index (GI) activates NF-kb, which is a protein complex that regulates the transcription of many genes related to the immune system. It is persistently active in a number of diseases, including rheumatoid arthritis, cancer, asthma and neurodegenerative diseases. Consistent with this epidemiological studies shows that dietary fiber also lowers CRP levels in normotensive[2] subjects. Furthermore diets low in glycemic load and high in dietary fiber have a protective effect against low- grade inflammation in diabetic patients (de Punder and Pruimboom, 2013).

[2] Having normal blood pressure.

Taken together, low carbohydrate diets can lower inflammation in mice and also in human monocytes[3] by increasing BHB production. But more importantly, there seems to be a positive correlation between the GI of the carbohydrate and low-grade inflammation.

2. 6 Gluten

Wheat and other cereals are an important part of the human diet. Along the consumption of these, celiac disease (CD) is a problem for approximately 1 % of the world's population.

It is an autoimmune disorder where people with CD have antibodies against the gluten structure found in wheat, barley and rye. When eating products from these, it triggers an autoimmune response which damages the small intestine. This often leads to abdominal pain and diarrhea (Troncone and Jabri, 2011).

Specially in patients suffering from psoriasis, there seems to be a connection between the disease and gluten sensitivity. In an interventional study in Uppsala, psoriatic patients, both with and without antibodies against gluten, were given a gluten free diet during three months and returned to the normal diet thereafter. The results were that all psoriatic patients with antibodies against gluten improved radically during the gluten free diet meanwhile the others expressed no changes. The symptoms got worse when they returned to the original diet (Michaëlsson et al., 2000). This was a continuing on a previous study which demonstrated that out of 302 patients, 16 % had antibodies against gliadin[4]. There is clearly a heighten association between gluten intolerance and patients suffering from psoriasis (Michaëlsson et al., 2000).

However, the last few years, many studies have shown that gluten intolerance can also affect people, who does not suffer from celiac disease or wheat allergy. The new syndrome was in 2012 called non -celiac gluten disease- sensitivity (NCGS).

[3] A type of leukocyte that is produced in the bone marrow and later matured into macrophage.

[4] Gluten consists of two types of proteins; prolamins and glutelines. The prolamins found in wheat are called gliadins, in rye; secalin and in barley; hordein. They have a sequence of peptides in common, which the body can see as pathogens. Therefore, those who have antibodies toward gliadin, also react in the presence of secalin and hordein.

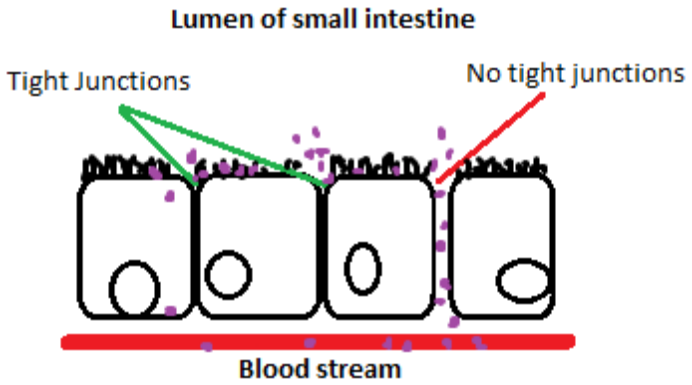

Figure 4. Zonulin causes intestinal junctions in the lumen of the small intestine to loosen up, which leads to undesired infiltration of larger molecules (Sohail Ehsanzamir, modified from Demarcus Briers, 2012).

According to Dr. Fasano, gluten fragments, which, cannot be degraded can induce enterocytes[5] to release a protein called zonulin which loosens intestinal tight junctions. This allows larger molecules to leak out to the blood stream and trigger an immunological reaction because the immune system sees them as pathogens (Figure 4). This is referred to as "leaking gut" and may be the cause of symptoms expressed in other parts of the body (Fasano, 2012). NCGS is yet not fully understood and the diagnosis is set after seeing improvements in symptoms when CD and wheat allergy have been ruled out.

2. 7 Trans fatty acids

Trans fatty acids (TFA) are a group of unsaturated fats with at least one double bound in the trans configuration. Trans fatty acids in our diet are largely coming from partially hydrogenated vegetable oils aimed for use in margarine, food manufacturing and frying (Ganguly and Pierce, 2012). The National Food Agency recommends that the consumption of TFA should be as low as possible (Livsmedelsverket, 2015).

The pathogenesis of excessive consumption of trans fats is well known. Studies have associated trans fatty acid with the development of cardiovascular diseases and type 2 diabetes. The association is only partially a cause of raised LDL

[5] Enterocytes are epithelial cells in the gut that absorbs nutrients on the surface of the small intestinal villus.

cholesterol, lowered HDL cholesterol and increased plasma triglyceride levels (Ganguly and Pierce, 2012). The effect of TFA on systemic inflammation is however less established.

A recent study examined the intake of TFA in relation to plasma concentration of biomarkers of inflammation in healthy women, including CRP and IL-6. They concluded that subjects with the highest intake of trans fatty acids had 73% higher levels of CRP compared with the lowest intake meanwhile levels of IL-6 were 17% higher (Mozaffarian et al., 2004). Another separate study concluded that the association between intake of TFA and low- grade inflammation were specifically for the intake of trans isomers of oleic acid (C18:1) and linoleic acid (C18:2) and not palmitoleic acid (C16:1) (Mozaffarian, 2006).

2. 8 Fruits and vegetables

Fruits and vegetables are vital components of a healthy diet and their presence on the plate could help prevent IMIDs like CVDs, diabetes and certain cancers. According to the World Health Organization (WHO) 2.8 percent (1.7 million) of deaths worldwide are attributable to low fruit- and vegetable consumption.

The Swedish National Food Agency (Livsmedelsverket) recommends a daily intake of 500 g fruits and vegetables to prevent such diseases but only one in every eight women and one in twenty men in Sweden, follows the recommendation.

Intake of fruits and vegetables may affect different risk factors of CVD and diabetes. One is that it has potential to aid in weight management due to high dietary fiber concentration. Another is that intake of fruits and vegetables have been shown to decrease LDL cholesterol concentrations in humans. It also help to reduce blood pressure in normotensive subjects (Djoussé et al., 2004).

Many nutrients and components as fibers, potassium, folate and antioxidants in fruits and vegetables may be responsible for the protective effect of developing IMIDs. Recently also flavonoids have received further attention.

Flavonoids are chemical compounds found in onions, apples and grapes that act as antioxidants. It is generally found in colorful food, in particular yellow food (Terahara, 2015).

An increased intake of flavonoids has been associated with slower rates of cognitive decline among elderly people. Furthermore, many studies but in particularly one large involving more than 8300 men and women concluded that dietary intake of flavonoids reduced plasma concentrations of CRP with 25- 30 % compared to a control group (Chun et al., 2008). Additional studies have also

shown reduced levels of other biomarkers such as IL- 1B, IL-6 and TNF- α among test groups (Landberg et al., 2011).

The effects of dietary intake of flavonoids were thought to be an attribute of antioxidants but it is now clear that levels of flavonoids in biological tissues may not be sufficient to act in this manner. But instead they are active in other pathways. Flavonoids may mediate inflammatory processes in the central nerve system (CNS) by inhibiting release of cytokines such as IL- 1B and TNF- α from activated microglia, the immune cells of the CNS which is believed to play an important role in many neurodegenerative diseases including Alzheimer's disease and MS (Schroeter et al., 2001).

3 Discussion

The immune system involves millions of cells. Most of them are understandably located in the gut because we constantly introduce foreign substances with the food. Therefore chronic activation of the immune system is likely a consequence of events in the gut. When activated, a vast number of cells and proteins are involved and these are often used as biomarkers for an ongoing inflammation. There is no consensus as to which biomarker best represents chronic inflammation and can best distinguish between acute and chronic inflammation. Therefore many different markers are used to provide better insight. However, there are few concerns about using these as determinants of low- grade inflammation. First they are non- specific and does not represent metabolic low- grade inflammation alone. Second, many factors can affect the concentration of inflammatory markers in an individual at a given time, such as age, body fat, fitness and genetics.

Body fat of individuals are often a concern in these studies since people with more adipose tissue can show a greater rise of inflammatory markers than others after consumption. This also speaks for the benefits of energy restricted diet in overweight individuals suffering from an IMID.

The association between β- casein A1 consumption and prevalence of diabetes is very interesting because there is no correlation between protein intake and the disease but only this casein form. However the European Food Safety Authority reviewed all literature and laboratory studies made on BCM7 and published a report in 2009. They concluded that there were no relationship between drinking A1 milk and chronic diseases. In almost all studies made on BCM7, the substance was injected directly into the animal instead of taken orally as humans would be exposed to it. Even though there have been reported cases where patients improved after excluding milk, it is impossible to determine exactly what component may be responsible. This is a case where personal experience seems to be more reliable than science and therefore it may be a solution to try excluding dairy products from the diet if suffering from chronic inflammation.

The pathogenesis of TFA is however more established in science than dairy products. Although it can be argued if all TFA are linked to CVDs, it is clear that an overall total consumption is positively associated to those by increasing the bad cholesterol, plasma triglycerides and CRP in the blood. Therefore, it should be avoided as much as possible.

The omega- 6 and 3 ratio should also be lowered according to mechanistic evidence and intervention studies. The optimal ratio is understood to be between 1:1 and 4:1 depending on the disease in matter but a lower ratio also lowers metabolic inflammation in healthy subjects. One can either increase the intake of omega -3 or decrease omega- 6 intake. A standard should be to first follow the recommendations of the Swedish National Food Agency regarding fish, which is to consume it three times a week and then decrease omega- 6 intake accordingly.

The conclusion of this literature review is that the consumption of more fruits and vegetables, avoidance of trans fatty acids, decreased ratio between omega- 6 and 3, lowered glycemic index and limited energy intake, can lower inflammation and therefore improve symptoms in patients suffering from an immune- mediated inflammatory disease. Gluten and dairy products are also possible triggers of inflammation in certain people.

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