Low grade inflammatory response to obese and non-obese subjects, facts and promises.

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Abstract

- While researched the inflammatory response induced by diet, we have come across two terminologies that describe it. Generally, two most commonly used are as, chronic inflammation and Low-grade inflammation response, but the latter is more appropriate for conception and preferred.
- It is generally known that there is a greater presence of inflammatory elements in obese individuals, but how could be readouts in term of a ‘low grade of inflammation’ compered to non-obese subjects, we tried to find out in this study review.
- Many inflammatory mediators are released by adipose tissue, more expressed at obese subjects. Many of inflammatory markers are present at obese people in higher concentrations of lean people do. Infiltrations of macrophages in fatty tissue of the obese people seem to be a clear relation between obesity and pro inflammatory tendency. Therefore, it is believed that many of these mediators of inflammation are the trigger of many metabolic diseases, which begin as reactions at the cellular level and until the onset of metabolic syndrome where its insulin-resistance and the appearance of diabetes are at its center.
- Likewise, hours following the consumption of a meal, there is an elevation in the concentrations of inflammatory mediators in the bloodstream which is exaggerated in obese subjects and in type 2 diabetics although this is quite difficult to differentiate when other chronic inflammatory situations occur.

- Low grade inflammation response is induced mostly by high-fat, high-glucose meals and high meal content of advanced glycation end products (AGE), too. It has been proven that involvement of certain antioxidants or antioxidant-containing foods within the meal has greatly mitigated their adverse effects. The most known of healthy diet component are vegetables and fruits , whole grains , fish, PUFA(polyunsaturated fatty acids), especially long-chain n-3 PUFA, are all associated with lower inflammation or anti-inflammatory effects, while meal content AGE ,SFA(saturated fatty acids) ,trans-MUFA (monounsaturated fatty acids) are associated with inflammation and enhanced oxidative stress thus creating all the prerequisites for metabolic syndrome. The best monitoring of low grade inflammatory response is through pro-inflammatory and anti-inflammatory mediators concentrations, acute-phase proteins, pro-inflammatory cytokines,chemokines, soluble adhesion molecules, adipokines (TNF,Interleukines,MCP1 ,leptin,.),etc .It is generally accepted that a consider amount of these mediators produced are adipocytes and macrophages infiltrated therein.
- Main focus in this review was to analyze the literature regarding the presence of typical inflammatory mediators in obese and healthy individuals in some crossing-section studies, selected according to the purpose of this paper. We used sources in PubMed databases.
- In general, the low grade inflammation response, although being influenced by the type of diet and the modifiers of inflammatory markers, nevertheless of their mixed effects there is a clear trend of low grade inflammation, in obese versus non-obese subjects, this expressed through higher values of inflammatory mediators.
- Studies targeting the obese population group with a well-defined diet according to calorie and ingredients report also identifying or excluding of inflammatory modifiers, would be the best approaches to differentiate a diet with less inflammatory effect on the obese population.
- Such a diet would create all the prerequisites for obesity reduction as well as a reduction of low grade inflammatory response.

- Keywords: Obesity, Inflammation, Metabolic syndrome, Low-grade inflammation, Postprandial inflammatory response, Pro- and anti- inflammatory mediators, Pro- and anti- inflammatory diet.

Introduction

- **Inflammation** *is a normal host defense mechanism that protects the host from infection and other insults; it initiates pathogen killing, as well as tissue repair processes, and helps to restore homeostasis at infected or damaged sites 1[1].*
- *This whole process is followed by a series of mediators that initiate, regulate and terminate the inflammatory response.* The harmonization of these stages is done by pro and anti-inflammatory mediators and the inhibition of inflammatory signals, without which it would not be possible to disrupt the inflammatory response, thus leading to further tissue damage.
- Such mediators have local and systemic action too, giving systemic character to the disorders and the nature of the diseases themselves, as to obesity, the metabolic syndrome and CVD(cardiovascular disease).

- ***Acute inflammation*** is the initial response of the body to an infectious agent or another inflammatory trigger (e.g. tissue damage by wounding or irradiation) and is achieved by the increased movement of plasma and leucocytes (especially granulocytes) from the blood into the site of infection or injury.2 [2]

- ***Chronic inflammation***, involves a progressive shift in the type of cells present at the site of inflammation and simultaneous destruction and healing of

  the tissue due to the ongoing inflammatory process. 1[1]

- ***Chronic low-grade inflammation*** is a form of chronic inflammation with a low intensity and morbidity without giving specific clinical signs for a particular disease. Thus concentrations of inflammatory markers and of inflammatory cells in the systemic circulation is not as great as that seen in the chronic inflammatory conditions.

Table 1. Features of acute, chronic and low-grade chronic inflammation

	Acute inflammation	Chronic inflammation	Low-grade chronic inflammation
Trigger	Pathogens, injured tissues	Failure to resolve acute inflammation due to non-degradable pathogens, persistent foreign bodies or autoimmune reactions	Metabolic disturbance; some chronic infections
Major cells involved	Neutrophils and other granulocytes, mononuclear cells (monocytes, macrophages); T cells later	Mononuclear cells (monocytes, macrophages, T cells, B cells), neutrophils, fibroblasts	Mononuclear cells (monocytes, macrophages, T cells, B cells), neutrophils, adipocytes (if adipose tissue involved)
Primary mediators	Vasoactive amines, eicosanoids; chemokines and cytokines later	Cytokines, chemokines, eicosanoids, growth factors, reactive oxygen species, hydrolytic enzymes	Cytokines, chemokines, adipokines (if adipose tissue involved), eicosanoids, reactive oxygen species, hydrolytic enzymes
Onset	Immediate	Delayed	Delayed
Duration	A few days	Unlimited	Unlimited
Outcomes	Resolution, abscess formation, chronic inflammation	Tissue destruction, fibrosis, necrosis	No overt pathology, tissue (vascular) damage, increased insulin resistance, intracellular lipid accumulation

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Mediators of inflammation.

Inflammatory mediators are protein compounds, arise at the site of inflammation to give systemic effects. The markers of inflammation are many. In order to classify them, some typical characteristics are derived based on their circulation ability, biological nature, mechanism of action, etc.

Table 1. A concise overview of inflammatory markers.

Inflammatory markers	cells/organs producer	biological functions
Cytokines/chemokines: IL-1B, IL-6, IL-10, IL-12, IL-18,IFN-G,TNF, MCP-1.	Immune cells, bone, epithelial cells, Adipocytes, muscle cells	Fever, acute phase protein synthesis, granulocites, macrophage, lymphocites, NK-cells activation,chemoattractant protein ect.
Acute-phase protein: CRP,a-1-Antitrypsin, Serum amyloid A, a-1-Antichymotrypsin, Complement C3^C4,	Liver,Adipocytes, endothelial cells,	opsonisation and complement activation, protease inhibitor
Adhesions markers: VCAM1,ICAM1,E&P selectin	endothelial cells,platlets	Adhesion of leucocytes to endothelialcells.Expression stimulated by pro-inflammatory cytokines (IL-1 and TNF) as well as IL-4. Chemotactic properties
Other : Leptin,autoantibodies	Adipocytes,B cells	Appetite,adipose tissue regulation,cell destruction

Obesity and low grade inflammation.

- Systemic concentrations of pro-inflammatory mediators are higher in obese (BMI .30 kg/m2) than in normal-weight persons 4[4] However, there is a positive relationship between BMI and other measures of obesity such as waist circumference and circulating concentrations of CRP and other inflammatory markers 5 [5]
- A mechanistic link between obesity and low-grade inflammation was first proposed by Hotamisligil et al. who showed that white adipose tissueproduce and releases the pro-inflammatory cytokine TNF-a. The expression of TNF-a is elevated in adipocytes of obese and insulin-resistant mice, while insulin sensitivity is improved following administration of anti-TNF-a antibodies.
- Based on these data, it was suggested that adipose tissue plays an important immune role and may be a major low-grade chronic inflammation source through pro-inflammatory mediators,inducing chronic inflammation, insulin resistance and atherosclerosis, all of which are characteristics of the metabolic deregulation, associated with obesity. 6[6]
- The discovery of *leptin* modified the view of adipose tissue as being an ‘inert’ energy store to being the largest endocrine gland in the body. Leptin is produced and secreted by white adipose tissue. Thus introduced the concept of ‘adipocytokines’ or ‘adipokines’, substances produced by adipose tissue and which circulate in the bloodstream, so exerting systemic effects as hormones 7 [7]

- Some adipokines are produced within adipose tissue exclusively by adipocytes (leptin, adiponectin, serum amyloid A [SAA]), while others are produced by both adipocytes and other cell types therein adipose tissue. It is now recognized that macrophages accumulate in the adipose tissue in obesity 8[8] (Fig.2) making them major contributors of adipokines production9[9].

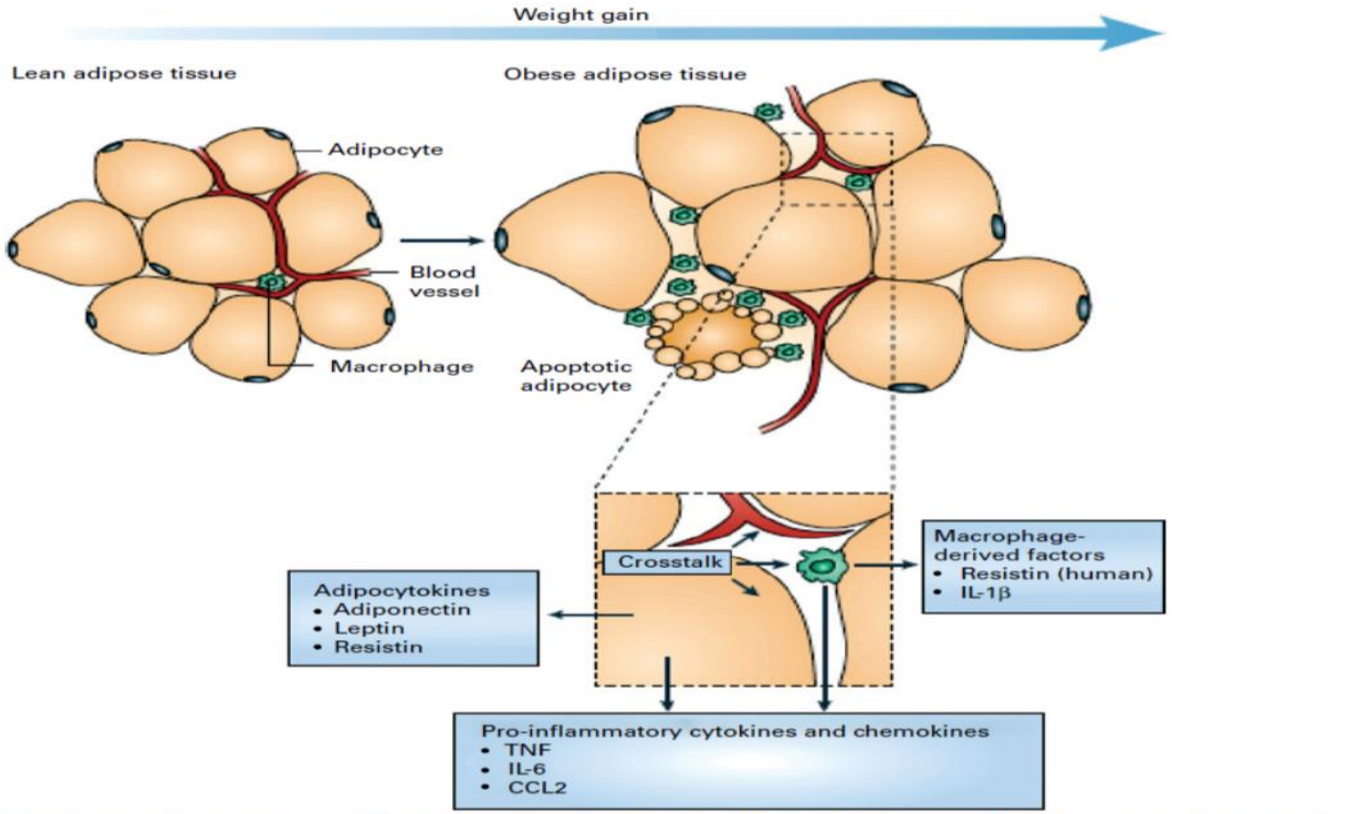

Fig. 1. Schematic representation of the interaction between adipocytes and macrophages showing some of the molecules released. Expansion of adipose tissue during weight gain leads to the recruitment of macrophages through various signals (e.g. chemokines such as chemokine (C–C motif) ligand 2 (CCL2)) released by adipocytes. Macrophages accumulate around apoptotic adipocytes. Mediators synthesised by adipocytes and resident macrophages contribute to local and systemic inflammation. Reproduced with permission from Tilg & Moschen[10].

Fig.3 Schematic representation of the interaction between adipocytes and macrophages showing some of the molecules released.

- Macrophage accumulation is more abundant in the abdominal adipose tissue than in the subcutaneous tissue, and this could explain some of the risks associated with the accumulation of intra-abdominal fat. Hence, abdominal adipose tissue infiltrated by macrophages with hepatic inflammation and fibrosis has been reported 10. [10]

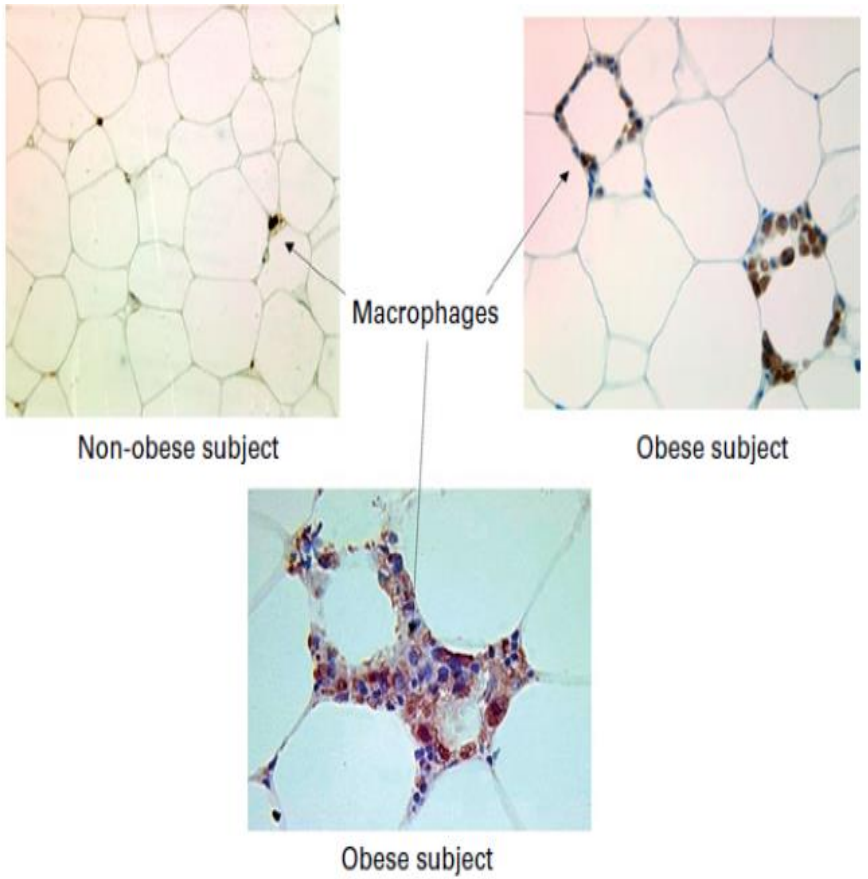

Fig. 2. Adipose tissue from non-obese and obese human subjects showing macrophage infiltration. Macrophages are stained with HAM56 antibody. Reproduced with permission from Cancello *et al.*[65].

Fig.4 Adipose tissue from non-obese and obese human subjects showing macrophage infiltration.

Obesity as a trigger of inflamatory mediators.

- Several acute-phase proteins are elevated in overweight and obese subjects. For example, the circulating concentration of CRP is higher in obese persons, and decreased levels after they lost weight is shown .11[11]
- A meta-analysis showed a strong association between Body Mass Index (BMI) and serum amyloid A concentration 12 [12] Elevated levels of soluble adhesion molecules, such as VCAM-1(vascular celullar adhesion molecule or CD106), ICAM-1(intercelullar adhesion molecule or CD54), E-selectin and P-selectin, are found in obese individuals compared with normal-weight subjects 13 [13]
- Although these studies focused on obesity per se, the distribution of adipose tissue appears to be important for its inflammatory burden. Visceral adipose tissue has a greater production of inflammatory mediators such as cytokines than subcutaneous adipose tissue, although the precise contribution of each to the circulating pool is not clear 14 [14]

Obesity has been described as a low grade inflammatory condition, contributing with its both aspects of inflamatory,cellular and secretion. Current evidence suggests that overnutrition leads to adipocyte hypertrophy, followed by cell death, which may act as a stimulus for immune cell infiltration into the tissue. 15 [15]

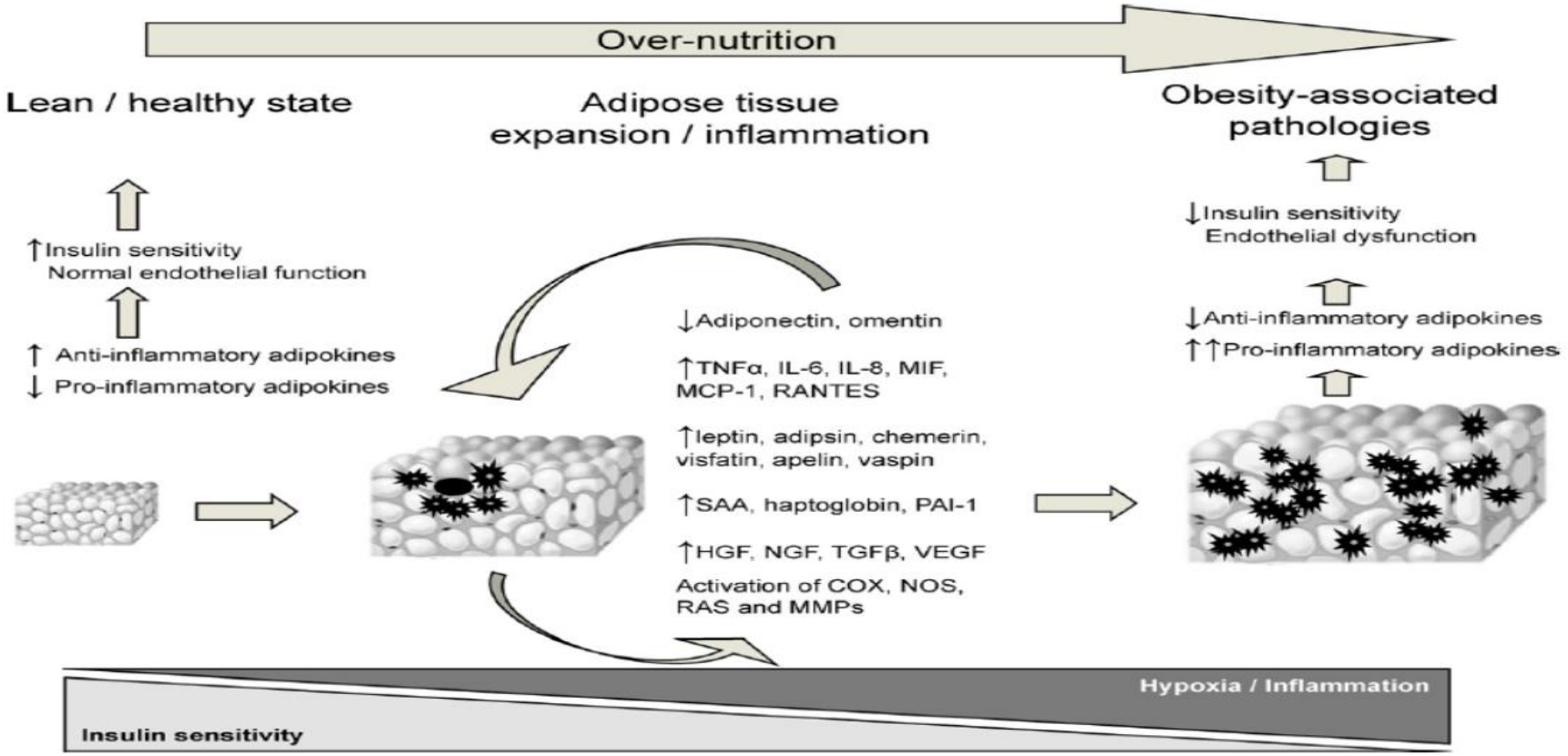

Fig. 1. A schematic representation of the alterations in adipose tissue that accompany body weight gain. In the lean state the tissue secretes elevated levels of adiponectin and other anti-inflammatory adipokines and is insulin responsive. Increased energy intake is followed by adipocyte hypertrophy/death and chemotactic adipokine release (e.g. MCP-1). This facilitates macrophage infiltration into the tissue and exacerbates the inflammatory response. These secretory changes are accompanied by local insulin resistance and hypoxia. Many of the adipokines released by this inflamed adipose tissue cause insulin resistance and endothelial dysfunction, precursors to many metabolic diseases. (●) Dead adipocyte and (✹) infiltrating macrophages.

Methods

- We collected articles through a search into Pubmed/Medline NLM databases, some of the terms are also given through MeSH(Medical Subject Headings). The terms used for searching are : Obesity, non-obese, Inflammation, Metabolic syndrome, Low-grade inflammation, pro and anti-inflammatory mediators. Selected studies are focused on comparing different mediators of inflammation in obese and non-obese individuals.
- We considered only those studies who provided statistical significance ($p<0.05$) for inflammatory parameters between two groups (obese/non obese).Obesity as BMI-based values >25 kg/m2. Without evidence for chronic inflammatory diseases. Different studies models included: case studies, cross sectional studies and follow-up studies.

Results

- The following table presents the relationship of inflammatory parameters between groups: non-obese compered to obese obtained in different studies. Almost all pro-inflammatory parameters cytokines and chemokines such as: TNF(tumor necrosis factor),IL-1,IL-6,IL-8,and MCP-1(Monocyte chemoattractant protein-1) in obese subjects compared with normal-weight subjects(non obese) have been found with higher concentrations 17 [17].
- Also several acute-phase proteins are elevated in overweight and obese subjects. An interesting study present decreased CRP concentration at obese subjects after they lost weight ,thus highlighting even CRP feature as inflammatory marker induced by obese condition 18 [18]
- Adhesion molecules, such as VCAM-1, ICAM-1, E-selectin and P-selectin, are found in obese individuals higher compared to normal-weight subjects,19 [19].
- Inverse relations are between adiponectin and leptin. Low adiponectin / high leptin concentrations obese group ,vice versa at healthy subjects. 20 [20].

TABLE 1.

Mediator	Healthy subjects	Overweight /Obese	References
TNF	0·75–5 mg/L	↑	21 [21] 22 [22] 23[23]
IL6	0.4-1.4 g/L	↑	24 [24] 25 [25]
IL1	200-500 mg/L	↑	26 [26]
IL8	2-10 mg/L	↑/↔	27 [27] 28 [28] 29 [29]
IFN-γ	1–5 mg/L	↑	30 [30]
CRP	0.1–10 mg/L	↑	31 [31] 32 [32] 33 [33] 34 [34]
SSA	15-35 mg/L	↑	35 [35] 36 [36]
Fibrinogjen	1.5-4.0 g/L	↑	37 [37]
V.Willibrand factor	5-15 mg/L	↑	38 [38]
C3	1-3 mg/L	↑	39 [39]
VCAM 1	500 mg/L	↑	40 [40]
ICAM 1	175-200 mg/mL	↑	41 [41] 42 [42]
E-Selectin	43-80 mg/mL	↑	43 [43] 44 [44]
P-Selectin	50-60 mg/mL	↑	45 [45] 46 [46]
Leptin	10 mg/mL	↑	47 [47] 48 [48]d 49 [49]
Adiponectin	5-15 mg/mL	↓	50 [50]d 51 [51] 52 [52]

Discussion

- The data obtained in this study created a more complete profile of mediators correlated in a low grade inflammatory response.
- From the researches and datas comparisons of these studies, the biggest challenge is the specificity of the mediators of inflammation associated with the low grade inflammation response. This makes it difficult to exclude the effect of modifying factors such as: increasing age, physical activity, genetics, smoking, gut microbiota and medication use. Thus, there is little scale of inflammation that responds only to an inflammatory condition without being influenced by other modifying factors. 53 [53].
- Of all the inflammatory modifying factors, nutrition seems to be very important and at the same time very challenging in terms of monitoring many pro- and anti-inflammatory effects it provides.
- As this review did not include the study with main focus on food ingredients and their effect on inflammation we are only giving some general considerations which have been reflected by some of studies about nutrition.

Low grade inflammation response is induced mostly by high-fat, high-glucose meals and high meal content of advanced glycation end-products (AGE), too. It has been proven that involvement of certain antioxidants or antioxidant-containing foods within the meal has greatly mitigated their adverse effects. The most known of healthy diet component are vegetables and fruits , whole grains , fish, PUFA(polyunsaturated fatty acids), especially long-chain n-3 PUFA, are all associated with lower inflammation or anti-inflammatory effects, while meal content AGE ,SFA(saturated fatty acids) ,trans-MUFA (monounsaturated fatty acids) are associated with inflammation and enhanced oxidative stress 54 [54] .

- In some studies infiltration of inflammatory elements, like macrofages,activated different leukocytes, in adipose tissue has been explored, resulting with a lot of inflammatory mediators in circulation,conseguently LGI-response with the metabolic syndrome ones such : CVD, which further strengthens their correlation 55 [55].
- Exposure of adipose tissue to oxidative and hypoxic elements is very important data regarding the initiation of an inflammatory process in adipose tissue itself, a condition that is subsequently followed by macrophage infiltration and secretion of many inflammatory mediators and exacerbates the inflammatory response. These secretory changes are accompanied by local insulin resistance and hypoxia. Many of the adipokines released by this inflamed adipose tissue cause insulin resistance and endothelial dysfunction, precursors to many metabolic diseases. 57 [57]

Conclusion

- Low grade inflammation is an abnormal physiological response, including chemokines, cytokines, acute-phase proteins and adhesion molecules and other blood cellular markers, although being influenced by inflammatory modifiers, lead to a metabolic syndrome, that often precedes a well-defined disease.
- Many inflammatory mediators belong to all stages of inflammation (initiation and solvation of acute and chronic inflammation) making it difficult to consider as group specific for the low grade Inflammation condition.
- The presence of endogenous and exogenous modifiers of inflammation such as age, nutrition, sex, overweight, genetics, drugs, etc. yield numerous variations between individuals, making them difficult to compare as equivalent element of studies.
- From all studies done with different models at subjects with obesity versus non-obesity, there is a clear tendency of pro-inflammatory expression at obese subjects, despite of the mixed effects of modifiers of inflammation .
- Advancing evaluation of *low grade inflammation response* in relation to a disease or health condition, as in our case at obesity, two main aspects would be in account:

a) further consideration of the modifiers factors of inflammation at the subjects studied,

b) standardization of studies according to the correlation of the specific inflammatory markers for low grade inflammation.

Thank you!

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