Turkish Journal of Endocrinology and Metabolism, (2004) 3 : 85-89 **REVIEW**

Inflammation and Metabolic Syndrome

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The relationship among inflammatory markers: C-reactive protein (CRP), fibrinogen, white blood cells count and metabolic syndrome has been observed in experimental, clinical and epidemiological studies. High levels of inflammatory markers are related to increased body mass index (BMI), increased serum lipoproteins, high blood glucose, hyperinsulinemia and insulin resistance. Probably the chronic inflammation triggers insulin resistance and type 2 diabetes mellitus. In genetically and metabolically predisposed persons different stimuli (overnutrition, increased hypothalamus-hypophyseal activity) can cause pro-inflammatory cytokine oversecretion and provoke insulin resistance and diabetes. The increased acute phase protein levels can be related to decreased insulin sensitivity of hepatocytes. Insulin exerted selective effects on liver protein synthesis with increased albumin synthesis and decreased fibrinogen and CRP production. Insulin resistance leads to increased synthesis of fibrinogen and CRP. The level of inflammatory markers is predictive of the development of cardiovascular diseases. CRP is pointed out as the most perspective marker for chronic subclinical inflammation, participating in metabolic syndrome. The evidences for the role of inflammation in the genesis of metabolic syndrome is still not well defined. Additional population based, clinical and basic investigations are needed to confirm this relation. Future studies will help to estimate the efficiency of inflammatory marker detection in the prophylaxis and treatment of cardiovascular diseases.

Keywords: Inflammatory markers, metabolic syndrome, cardiovascular risk, diabetes mellitus, obesity

Introduction

Inflammation is a process in response to tissue or organ damage from exogenous and endogenous factors, aiming at the restoration of impaired homeostasis. The main components of the inflammatory process are: White blood cells (macrophages, lymphocytes, granulocytes), connective tissue cells (fibroblasts), smooth muscle cells, mesangial cells, extracellular matrix (collagen, elastin, fibronectin, proteoglycans), cytokines (interleukins, hemokines) and growth factors.

In different tissues and organs the inflammation possesses specific characteristics (Table 1). In arthritis rheumatoides the granulocytes are the main representative of white blood cells. In glomerulonephritis the main representatives of connective tissue are mesangial cells. The matrix is usually presented by different collagen types (1).

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Inflammation and Atherosclerosis

Atherosclerosis is a chronic inflammatory process with the following characteristics: lipid accumulation, calcification, thrombotic potential. The atherosclerotic lesions are highly specific cell and molecular disturbances that can be defined as in inflammatory disease. From pathological point of view all stages of the atherosclerotic process – the initiation of the lesion, plaque growth, fibrous cap formation and plaque complications can be described as an inflammatory response to injury. The damaging factors can be mechanical (high blood pressure), endocrine (diabetes, modified lipoproteins) toxic (nicotine), genetic (homocysteinemia) infections (chlamydia pneumoniae, herpes simplex virus). The injury leads to endothelial dysfunction, which in combination with the inflammatory reaction and lipid accumulation causes low-grade chronic inflammation. Hence, there is no regression of the initial lesion and the atherosclerotic plaque continuos its formation (2).

Inflammatory Cascade and Inflammatory Markers

After a tissue injury of different origin (mechanical, toxic, infection) cytokine synthesis begins on the

Table 1. Cell and tissue components participating in different inflammatory diseases

Diseases	White Blood Cells	Connective Tissue	Matrix	Cytokines
Arthritis Rheumatoides	Monocytes Lymphocytes Granulocytes	Synovial fibroblasts	Collagen type 1 and 3 Fibronectin Proteoglycans	IL-8 *ENA-78* MIP-1
Glomerulo nephritis	Monocytes Lymphocytes	Mesangial cells	Collagen type 1 and 4 Fibronectin	IL-10 RANTES MIP-1
Pulmonary fibrosis	Monocytes Lymphocytes Granulocytes	Smooth muscule cells Fibroblasts	Collagen type 3 and 4 Fibronectin	IL-8, IL-10 ENA-78 RANTES
Cirrhosis	Monocytes Lymphocytes	Fibroblasts Ito cells	Collagen type 1 and 3	IL-8 MCP-1 MIP-1
Athero sclerosis	Monocytes Macrophages Lymphocytes	Smooth muscle cells	Collagen type 1, 3, 4 Elastin Fibronectin	IL-1, IL-10 MCP-1

IL-1: Interleukin 1, IL-6: Interleukin 6, IL-8: Interleukin 8: IL-10: Interleukin 10: ENA-78: Extractable nuclear antigen-78, MIP-1: macrophage inflammatory protein-1, MCP: monocyte chemoattractant protein, RANTES: chemotactic cytokine, (Regulated upon Activation Normal T-cell Expressed and Secreted)

spot. Interleukin-1 (IL- 1) and Tumor Necrotizing factor-alpha (TNF-α) are the most common cytokines present. They posses local and systemic effects. The local effect is connected with increased expression of adhesion cell molecules such as Intracellular adhesion Molecule-1 (ICAM-1), selectins and heat-shock proteins. The systemic effect is mediated by Interleukin-6 (IL-6) that stimulates acute phase protein synthesis by the liver. The acute phase reactants - C-reactive protein (CRP), serum amiloid A, fibrinogen, α-1 antitripsin, haptoglobin, ceruloplasmin, α-2 macro-globulin - are included in old phylogenetic phenomena concerning the innate immune defense. Examining the inflammatory cascade the following groups of inflammatory markers are described in Table 2.

Table 2. Inflammatory markers

Proinflammatory cytokines	IL-1, TNF-α
Adhesion cell molecules	ICAM-1, selectins
Inflammatory stimuli with hepatic effects	IL-6
Products of hepatic stimulation	CRP, SAA, fibrinogen
Other inflammatory indicators	WBC, ESR

IL-1: Interleukin 1, IL-6: Interleukin 6, TNF-α : Tumor Necrosis factor- α, CRP: C-reactive protein, SAA: Sera amyloid A, WBC: White blood cells count, ICAM-1: Intracellular adhesion molecule, ESR: Erythrocyte sedimentation rate

Inflammation and Metabolic Syndrome

The main features of metabolic syndrome are abdominal obesity, dyslipidemia, abnormal glucose tolerance, hypertension and prothrombotic state. The concentration of the metabolic disturbances amplifies the risk of atherosclerosis development (3).

Recent investigations established a correlation among different components of metabolic syndrome and the most common markers of inflammation. The highest correlation between CRP and body mass index (BMI) was found, followed by the indexes of insulin resistance – fasting insulin and insulin sensitivity (Table 3) (4).

Table 3. Correlation among inflammatory markers and components of metabolic syndrome

Index	CRP (r)	WBC (r)	Fibrinogen (r)
BMI	0,40	0,17	0,22
Waist circumference	0,43	0,18	0,27
SBP	0,20	0,08	0,11
FBG	0,18	0,13	0,07
Fasting insulin	0,33	0,24	0,18
Insulin sensitivity	-0,37	-0,24	-0,18

CRP: C-reactive protein, WBC: White blood cell count, BMI: Body mass index, SBP:Systolic blood pressure, FBG: Fasting blood glucose

In obese children compared with non-obese CRP, TNF-α and TNF-α receptors were significantly increased (5). In obese adults higher levels of CRP, TNF-α were found in comparison with the non-obese (6). A decrease in inflammatory markers was observed in both children and adults during weight reduction (3).

The abdominal fat tissue produces IL-6 and TNF-α (7). Furthermore it synthesizes hormones such as leptin and adiponectin. It was found that leptin possesses proinflamatory properties because it induces adipocites to produce inflammatory cytokines. On the contrary, adiponectin suppresses proinflammatory cytokine production (8). Macrophage accumulation in abdominal fat in the obese was pointed out as a marker of low-grade chronic inflammation. It is considered that chronic inflammation of fat tissue plays a major role in obesity related insulin resistance (9, 10).

Proinflammatory cytocine production in hypothalamus is under control of dopamine, serotonin and acetylcholine. The increased production of proinflammatory cytokines (TNF-α, CRP) in the hypothalamus leads to neuronal cell death. Most often the neurons detecting satiety and appetite as well as the neurons controlling the level of blood glucose are damaged. It is concluded that the neuronal cell death is one of the factors increasing appetite, causing obesity and impaired glucose tolerance in patients with the metabolic syndrome (11, 12).

In some ethnic groups – Pima Indians, Indian Asians living in the U.K - the morbidity from type 2 diabetes and cardiovascular disease is very high. In the same group it was found that the increased level of IL-6 and CRP significantly correlated with insulin resistance (13, 14). It was established that in persons with higher levels of CRP the possibility of diabetes to develop for the period of 3-4 years is greater than those with normal values for CRP (15, 16).

Insulin can be determined as a modulator of acute phase protein synthesis in liver. Hepatocytes with unimpaired insulin sensitivity the major protein synthesized is albumin. In the insulin resistance state the protein synthesis shifts to acute phase protein production (4).

In adipose tissue hyperglycemia can influence TNF-α synthesis. In young subjects hyperglycemia does not stimulate TNF-α production. In the elderly hyperglycemia is a powerful inductor of TNF-α synthesis. Probably these age-related disturbances in the control of TNF-α production could play a role in the development of type 2 diabetes (17).

Low-grade systemic inflammation plays role in development of hypertension. High systolic and diastolic blood pressure positively correlates with IL-6 level (18, 19). High level of CRP predicts the risk for transient ischemic attack and ischemic stroke (20).

Prothrombotic state is an element of metabolic syndrome. Coagulation (fibrinogen, factor VII, factor VIII, Von Villebrand factor) and fibrinolitic factors (t-PA, plasminogen) are both defective. Disturbances in the control of haemoststic mechanisms [plasminogen activator inhibitor-1(PAI-1), protein C, antitrombin III] are also related to metabolic syndrome. Many of the components of hemostasis are the elements of the inflammatory cascade – fibrinogen, von Willebrand factor, PAI-1. The coagulation and the inflammatory cascade share many common steps, common mediators and cytokines related to their homeostatic function for preserving the steady state in the organism (21).

Clinical Use of Inflammatory Markers

The implementation of inflammatory markers in the medical practice needs analysis for clinical significance of a given marker and evaluation for the quality and stability of laboratory methods used. It is necessary to estimate the precision of laboratory tests evaluated by their coefficient of variation (CV%) (Table 4).

Estimating different characteristics of inflammatory markers, CRP is accepted as the most promising marker with the best clinical and laboratory advantages (22).

C-reactive protein and serum amyloid A belong to the pentraxin plasma protein family. CRP possesses a typical pentamer disk-like structure. Its main characteristic is binding to phosphocholine residues leading to aggregation and precipitation of cell structures. Endogenous ligands for CRP are native and modified plasma lipoproteins, damaged cell membranes, small nuclear fragments, apoptotic cells. Exogenous ligands are capsules and somatic components of bacteria, fungi and parasites. During CRP binding activation of complement cascade is triggered (23).

Table 4. Inflammatory markers for potential clinical use

Analyte	Stability	Assay Availability	WHO Standards Availability	Interassay Precision
Soluble adhesion molecules– P-selectins, E –selectins ICAM-1 VCAM-1	Unstabale (unless frozen)	Limited	No	CV<15 %
Cytokines IL-1, IL-6, IL-10, TNF-α	Unstable (unless frozen)	Few	Yes	CV<15 %
Acute-phase reactants				
Fibrinogen	Unstable (unless frozen)	Many	Yes	CV<8%
SAA	*Stable*	One	Yes	CV<9%
hs-CRP	Stable	*Many*	Yes	CV<10%
WBC count	Stable	*Many*	Yes	CV<3%

IL-1: Interleukin 1, IL-6: Interleukin 6, TNF-α: tumor necrosis factor-α, hs-CRP: high sensitive C-reactive protein, SAA: Sera amyloid A, WBC: White blood cell count, ICAM-1: Intracellular adhesion molecule, ESR: Erythrocyte sedimentation rate

CV % - coefficient of variation %

After acute phase signal stimuli TNF-α, IL-1, and CRP concentrations can increase from 50 μg/l to 500 mg/l (ten thousand fold). CRP production is under Il-6 transcriptional control. De novo CRP synthesis begins very rapidly, on the sixth hour increases over 5 mg/l and achieves its maximum in 48 hours (24). CRP level does not change postprandially. There were differences in the basal concentrations related to the genetic polymorphism for IL-1, Il-6, as for CRP itself (25).

Table 5. Conditions associated with increased or decreased hs-CRP levels

Increased levels	Decreased levels
Elevated body mass index	Moderate alcochol consumption
Elevated blood pressure	Increased physical activity
Cigarette smoking	Weight loss
Diabetes mellitus	Medications
Hypertriglyceridemia	- Statins
Estrogen/Progesteron hormone use	- Fibrates
	- Niacin
Chronic infections (gingivitis, bronchitis, arthritis)	- Aspirin

Increased CRP serum levels can be found in different conditions such as acute and chronic infections, tissue damage, metabolic syndrome, smo-king, estrogen/progesterone therapy. Decreased serum levels were detected during moderate alcohol consumption, weight reduction, after statins, fibrates and aspirin therapy (Table 5).

CRP and Atherosclerosis

It was found that CRP directly participates in atherosclerotic plaque formation. CRP induces the adhesion molecule expression in endothelial cells, stimulates monocyte chemoatractant protein-1 production, induces complement activation. Binding to oxidized LDL-particles CRP stimulates macrophage digestion (26, 27).

CRP and Cardiovascular Risk

A new generation of high specific and sensitive methods for CRP determination were introduced in mid 90's to laboratory practice – hsCRP(high sensitivity CRP). It was pointed out that increased CRP levels (even in values considered before as normal) could predict the risk for cardiovascular disease (28). This high correlation between hsCRP and cardiovascular disease was established in large epidemiological studies in healthy people (Physician' Health Study, Women's health Study) and in patients with coronary heart disease after adjusting for other risk factors. (FRISC Study, TIMI – 11A Study, CARE Study) (22).

The investigators recommend CRP as a useful additional marker for evaluation of absolute risk for cardiovascular disease. In patients with CRP over 3 mg/l the intensification of treatment for risk reduction is recommended. The patients have to be motivated for changing their life style. In patients with stable coronary heart disease hsCPR is an independent predictor of myocardial infarction and sudden death. In elderly population CRP is not recommended as a screening marker for cardiovascular risk estimation, as well as for serial monitoring of treatment effects (24).

The AHA recommendations for CRP determination include two assays in 14 days interval. When CRP values are over 10 mg/l a locus of infection is searched – lungs, uro-genital system, digestive system. If such a locus could not be found a level of risk is determined (15).

Low level of cardio-vascular risk – CRP under 1 mg/l

Average level of cardio-vascular risk – CRP 1-3 mg/l

High level of cardio-vascular risk – CRP over 3 mg/l

Conclusion

The investigations concerning application of inflammatory markers and especially hsCRP in clinical practice raise many questions. The reference ranges for hsCRP have to be specified for man, women, children, elderly, and for different ethnic groups. hsCRP has to be defined as a main or additional risk factor. Target groups of patients to be evaluated – healthy persons, patients in risk, or patients with angina pectoris or previous myocardial infarction – have to be determined. Objective, noninvasive methods for evaluating the stage of atherosclerosis in different parts of the vasculature have to be found. Cost–effective evaluation for the use of inflammatory markers for cardiovascular risk estimation has to be made. Future population, clinical and basic investigations are needed to estimate the efficiency of inflammatory marker detection in the prophylaxis and treatment of cardiovascular diseases.

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