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Valter Lubrano , Laura Sabatino , Angela Papa , Silvana Balzan *

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Review

Interleukin-6, C-Reactive Protein and Fibrinogen : Novel Insights as Inflammatory Risk Factors in Atherosclerosis and Diabetes

Valter Lubrano [1,†], Laura Sabatino [2], Angela Papa [1] and Silvana Balzan [2,*]

[1] Fondazione Regione Toscana G. Monasterio, Via Moruzzi 1, Pisa 56124, Italy; angela.papa@ftgm.it

[2] Institute of Clinical Physiology, CNR, Via Moruzzi 1, Pisa 56124, Italy; laura.sabatino@cnr.it

* Correspondence: silvana.balzan@gmail.com; Tel.: +39-0503153523; Fax +39-050-3153454

† Deceased.

Abstract: Background/Objectives: Atherosclerosis and diabetes are largely recognized as inflammatory disorders and several inflammatory markers are used in clinical settings. Here we investigate the link of interleukin-6 (IL-6), C-Reactive Protein (CRP) and fibrinogen (FIB) with predisposing factors for atherosclerosis and diabetes; NT-pro-BNP, glycemia, insulin resistance, HDL and LDL respectively. **Methods**: the literature was collected using PubMed database. **Results**: CRP provides complementary information to NT-pro-BNP for high risk for major adverse cardiac events (MACE) in post-MI patients. CRP predicts cardiovascular and mortality in type 2 diabetic subjects. CRP binds to LDL triggering structural changes in HDL. CRP is also found in atheromatous plaque. IL-6 is a predictor of incident heart failure (HF) and IL-6 inhibition reduces HF hospitalization. IL-6 is related to a greater body mass index, NT–pro-BNP levels and insulin resistance. By blocking IL-6 may be a strategy for insulin resistance treatment. IL-6 levels correlate with endothelial dysfunction and carotid intima-media thickness, activating LDL-Receptor transcription. The FIB-to-albumin ratio in HF is positively correlated with NT-pro-BNP. Diabetic patients and insulin resistance condition could be related to hyperfibrinogenemia. The glycation level in the fibrinogen molecule is 2–3-fold higher in type 2 diabetic than in non-diabetic individuals, forming fibrin clots with enhanced resistance to fibrinolysis. Finally, because FIB is independently associated with the expression of a more atherogenic lipoprotein subfraction profile, it should be included in the assessment of coronary risk factors. **Conclusions**: CRP, IL-6 and FIB could be active players and potential targets for antiatherosclerotic and anti-diabetic therapies.

Keywords: IL-6; CRP; fibrinogen; cardiovascular disease

1. Introduction

All evidence indicates that atherosclerosis and diabetes prevalence is increasing worldwide. Atherosclerosis is largely recognized as a chronic inflammatory disorder caused by vascular and extravascular inflammatory factors [1], many of which have been identified as consolidated predictive markers in the progression of atherosclerosis and in plaque rupture [2,3]. Diabetes, in particular Type 2 (T2D), is a chronic metabolic disorder whose pathophysiology includes cytokine dysregulation and inflammation [4].

C-reactive protein (CRP), interleukin-6 (IL-6), and fibrinogen (FIB) are the most consolidated inflammatory factors used in clinical laboratories for the diagnosis, prognosis and follow-up of individuals affected by atherosclerosis and/or diabetes.

In this review we focus on findings from recent literature regarding CRP, IL-6, and FIB in relation to NT-pro-BNP, glycemia, insulin resistance, HDL and LDL, that are considered markers of heart failure, diabetes and atherosclerosis, respectively.

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NT-pro-BNP is the N-terminal fragment of the B-type natriuretic propeptide. It derives from the peptide secreted predominantly by myocytes in the cardiac ventricles in response to volume expansion or pressure loading, then dissociating into the physiologically active BNP and NT-pro-BNP. Elevated NT-pro-BNP values indicate ventricular wall stress and volume overload as occurs in heart failure (consistent with severity based on NYHA classification) and left ventricular dysfunction [5].

Insulin deficiency, hyperglycemia and dyslipidemia determine the common features of T2D that are associated with long-term macrovascular (atherosclerosis, coronary heart disease, cardiomyopathy, cerebrovascular disease) and microvascular complications (retinopathy, nephropathy, and neuropathy) [4].

Atherosclerosis has been considered as chronic inflammation in the vascular system [6–8] and the accumulation of low-density lipoprotein (LDL) in the arterial intima and its subsequent oxidization (ox-LDL) are the initial steps of atherosclerosis process [9].

Unlike LDL, the high density lipoprotein cholesterol (HDL-C), which has anti-inflammatory properties, is reduced in atherosclerosis [10]. HDL best recognized ability is to promote the efflux of cholesterol from the cells and to be an effective antioxidant, inhibiting the oxidative modification of LDL. Moreover, HDL inhibits the expression of adhesion molecules in endothelial cells and reduce the recruitment of blood monocytes into the artery wall, protecting against the development of atherosclerosis [11,12]).

Here we intend to highlight if CRP, IL-6 and FIB are merely hallmarkers of atherosclerosis and inflammation in diabete, or whether they are instead active players in the pathogenesis of cardiovascular disease and potential targets for anti-atherosclerotic and anti-diabetic therapies.

2. CRP

CRP is a sensitive marker of inflammation [13]), that is synthesized by the liver under the stimulation by IL-6 [14]. It circulates at low concentrations in healthy individuals and increases dramatically in response to infections, tissue injury and inflammation [15]. CRP is also widely used for risk stratification of cardiovascular events [13]. CRP was thought to be a single, non glycosylated, multi subunit protein, arranged non covalently in a ring (MW ~120 kDa) [16]. Successively, CRP has been showed to exhist in three distinct isoforms: a pentamer of five identical globular subunits p(CRP), a monomer m(CRP) resulting from a conformational change when the subunits are dissociated from the pentamer, and a transitional isoform where the pentamer remains intact but is partially changed to express mCRP structural characteristics (pCRP*). Some studies have shown that the pro-inflammatory pCRP* and mCRP isoforms facilitate complement binding, immune cell activation, activate platelets, monocytes and endothelial cells [17], directly mediating the inflammatory reactions and the innate immune response in the context of localized tissue injury [18,19]. Moreover, the development of mCRP assays tested in recent years has suggested that mCRP is potentially a more accurate marker of atherosclerotic disease than CRP [20].

The role of CRP in host defense has been thought to be largely due to its ability to bind phosphocholine (PC) activating the classical complement cascade, enhancing phagocytosis and promoting the removal of damaged or apoptotic cells [21]. Furthermore, CRP can dissociate on the membranes of activates platelets [22], monocytes [19], endothelial cells [23] and microparticles [18], all of which are abundant in phosphocholin, thus providing the requisite binding site for CRP [24]. Interestingly, the dissociation of pCRP to mCRP appears to be dependent upon phospholipase A2 (PLA2) that, generating LPC, facilitates CRP binding [23].

2.1. CRP and Vascular Injury

Since CRP has been shown to be stable in the frozen sample, numerous studies have permitted to establish its vascular risk [25]. According to them, CRP stimulates the release of pro-inflammatory cytokines, VCAM-1, ICAM-1, and E-selectin from endothelial cells and monocytes, inducing endothelial dysfunction and monocyte adhesion to the endothelium [26,27]. In addition CRP

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decreases endothelial NO synthase (eNOS) mRNA and enzyme activity i.e., conversion of l-arginine to l-citrulline in cultured human endothelial cells [28,29] and reduces angiogenesis promoting NO-dependent apoptosis in the endothelial cells. These results support clinical observations of an inverse correlation between CRP levels and endothelial vasoreactivity in patients with coronary artery disease (CAD) [30], suggesting its implication in the destabilization of atherosclerotic plaque [31,32].

Other authors observed that CRP behaves as pro-coagulant downregulating Prostacyclin2, NO metabolism and altering the fibrinolytic system [33,34]. In fact, CRP infusion in healthy volunteers results in a significant increase in serum levels of prothrombin fragment 1 and 2, D-dimer, and plasminogen activator inhibitor-1 [35].

2.2. CRP and Cardiovascular Diseases

Several clinical studies reported the role of CRP with acute and chronic inflammation in cardiovascular disease [36–39]. Interestingly, an important study on 22.962 subjects showed that patients with CRP ranging from normal (⩽3 mg/l) to elevated (>3 mg/l) had the minimum hazard ratio (HR) for all-cause mortality increased of 6.7-fold ($p<0.001$) relative to cases whose CRP remained normal [40].

Furthermore a meta-analysis on 160.309 patients without a previous history of cardiovascular disease showed that increased high sensitive (hs) CRP levels were associated with increased risk of CAD, ischaemic stroke and cardiovascular death, of 37%, 27% and 55%, respectively, and that the magnitude of such risk was comparable with other traditional cardiovascular risk factors, including total cholesterol (16%), non-HDL cholesterol (28%) and arterial systolic blood pressure (35%) [41].

2.3. CRP and NT-pro-BNP

As concern NT-pro-BNP, previous studies have revealed that combined assays of NT-pro-BNP and hs-CRP improve the risk stratification in patients with CAD [42,43]. In fact, the activation of inflammation plays an important role not only in the pathogenesis of atherosclerosis, but also in the initiation of acute coronary syndrome [44]. Elevated levels of NT-pro-BNP, on the other hand, is released as a result of both ischemia and necrosis of myocardial cells and could predict subsequent coronary events [45–47]. A recent study found a strong association between NT-pro-BNP and hs-CRP, indicating a close relationship between myocardial stretch and inflammatory pathways in the setting of MI [48]. Moreover, it suggests that the enhanced vascular inflammation and activation of neurohumoral axis may play synergistic roles in the process of atherosclerosis. Therefore, combined use of NT-pro-BNP and hs-CRP provides complementary information that increases the prediction of high risk of MACE development in post-MI patients.

2.4. CRP, Glycemia and Insulin Resistance

Increased CRP levels have been linked to excess body weight since adipocytes produce tumor necrosis factor α (TNF-α) and IL-6, which are pivotal factors for CRP stimulation. Furthermore, it is known that hepatocytes of T2D patients produce elevated levels of CRP compared to health subjects. It has been documented the presence of high CRP levels in individuals with insulin resistance [49–51]. Insulin resistence is a reduced physiological response of peripheral tissues to the action of insulin that represents one of the major causes of TD2.

In a Japanese cohort, an association between insulin levels and inflammation was observed in populations with T2D and hyperglycemia [52–54]. Furthermore, a meta analysis including six prospective cohort studies involving 22.322 T2D patients confirmed that CRP predicts cardiovascular and all-cause mortality in T2D patients [55].

Recently, it was observed that the genetic ablation of CRP gene confers resistance to obesity and insulin resistance in rats. Glucose clamp studies revealed enhanced hepatic insulin signalling and actions, while deficiency of CRP gene enhanced the weight-reducing effect of central injected leptin [56]. Elevated CRP level is thought to induce IR through possible mechanisms that include promotion

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of thrombogenic agent production, activation of complement cascade, enhancement of endothelial adhesion molecule expression, and reduction of eNOS [28,57,58]. Strategies to support a relative reduction in serum insulin levels may reduce inflammation and its health consequences, including prediabetes and T2DM [59].

2.5. CRP, LDL and HDL

CRP binds to LDL and it is also found in atheromatous plaque so that its causal role in CAD has been proposed [60–62]. Furthermore, CRP was showed to be a better cardiovascular marker than LDL [63]. Above all, the recent EXAMINE trial, that enrolled T2D patients with recent acute coronary syndrome to assess the risk of MACE (major adverse cardiovascular events) by utilizing hsCRP and LDL-C, observed that hsCRP levels were associated with recurrent cardiovascular events. Furthermore, this association appears to be independent to the achieved LDL-C levels [64].

By in vitro study, Bian et al. found that CRP directly increased the transcytosis of LDL across endothelial cells and increased LDL retention in vascular walls. These actions were associated with generation of reactive oxygen species, activation of protein PKC and Src kinase, and translocation of caveolar or soluble forms of the N-ethylmaleimide-sensitive factor attachment protein [65].

In addition, CRP promotes the expression of LOX-1, which plays an important role in the damaging effects of ox-LDL on endothelial function [66].

In light of these data we can consider CRP a valid inflammatory marker for risk detection and in cardiovascular prognosis and it can be considered an interesting new target for intervention.

As concern HDL, a recent population-based cohort study including 6.554 participants from the China Health and Retirement Longitudinal Study (CHARLS) have showed a correlation between the hs-CRP/HDL-C ratio and the likelihood of developing CVD. Inflammation leads to structural changes in HDL and in a decrease in HDL-related proteins, enzymes, and transfer proteins that are involved in HDL metabolism and function undergoing to significant alterations [67]. Reverse cholesterol transport, antioxidant, anti-inflammatory, endothelial/vasodilatory, antithrombotic, and cytoprotective actions are the primary biological attributes of HDL-C [68].

Recently, a study enrolling 8581 adults from the National Health and Nutrition Examination Survey 2015–2018 reported that the hs-CRP/HDL-C ratio was a significant risk factor for CVD among US adults, in which hypertension, diabetes, hypercholesterolemia, and obesity played important mediating roles [69].

3. IL-6

IL-6 is a small glycoprotein first isolated by Hirano and colleagues [70]: this protein consists of 212 amino acids with a mass of 21–26 kDa. IL-6 is a member of the family of similar cytokines, that comprises IL-6, IL-11, IL-30, IL-31 and non-IL molecules including oncostatin M, leukemia inhibitor factor(LIF), ciliary neutrophic factor, cardiotrophin 1 and cardiotrophin like cytochine. They are characterized by sharing the common receptor subunit glycoprotein 130 (gp/130) and by the structure of four helices with an up-up down-down topology [71].

IL-6 is normally expressed in low amount in healthy individuals, while it is produced by many cell types under numerous stimuli [72], such as infections, trauma or cardiovascular diseases [73–76]. IL-6 increases in serum with age [77], which in turn can be positively correlated with insulin resistance [78]. Furthermore, IL-11 and IL-30 have also been implicated in cardiovascular disease, particularly cardiac fibrosis and coronary artery disease [79].

However, IL6 is the most widely used cytokine in clinical practice of Cardiovascular Disease Centers [80].

IL-6 exhibits a high degree of pleiotropic activities ranging from participation in the innate immune response [81], to the induction of acute phase proteins, CRP, several complement system proteins, and the coagulation cascade [50,81].

At cellular level IL-6 activates signaling through the Jak-STAT pathway, whereby the IL-6r–gp130 heterodimer activates members of the Janus-activated protein kinases (Jak), Jak1, Jak2 and

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Tyk2. These proteins then phosphorylate and activate the signal transducer and activator of transcription (STAT) in a multitude of cell types [82,83]. As a result of STAT- signalling, IL6 induce transcription of a family of proteins called the suppressors of cytokine signaling (SOCS) [84].

3.1. IL-6 and Vascular Injury

Among the high degree of IL-6 pleiotropic activities, IL-6 is related to tissue fibrosis and vascular endothelial injury, promoting angiogenesis and increasing vascular permeability by stimulating the proliferation and migration of circulating endothelial progenitor cells [85]. It also participates in the proliferation and migration of smooth muscle cells [86] that lead to extracellular matrix remodeling and consequently, to the development of CAD, stroke and peripheral arterial disease [87].

Furthermore IL-6 induces FIB production in hepatocytes, which increases blood clotting and promotes thrombosis [88].

3.2. IL-6 and Cardiovascular Disease

According to some authors, IL-6 seems to be a marker more sensitive and specific than CRP in vascular inflammation, thus showing a stronger association with cardiovascular disease [80,89]. Takeda et al. found that IL-6 administration exacerbated atherosclerosis in ApoE-/- mice fed with normal or high-fat diet, while the administration of IL-6 inhibitor (Am80) prevent atherosclerosis suppressing scavenger receptor expression and foam cell formation [90].

Other authors observed that IL-6 is responsible for the development and rupture of atherosclerotic plaques [91] determining the intensity of plaque inflammation and its vulnerability [92]. Therefore IL-6 seems to be an effective independent index of increased mortality in unstable CAD and could characterize subjects who benefit from an initial invasive strategy. In fact, increased preoperative IL-6 levels are predictors of both early graft occlusion and late cardiovascular events after coronary artery bypass grafting [93].

In the myocardial infarction process IL-6 induces cardiomyocyte apoptosis by reducing myocardial contractility and promoting the collection of inflammatory cells in the injured myocardium [94], that play an important role in the onset of ventricular remodeling [95,96] and myocardial infarction death [96]. In ischemia and hypoxia, IL-6 binds to its receptor-coupled protein gp130 by transducing signals into cells through JAK/STAT3, thus leading to cardiomyocyte hypertrophy and abnormal endothelium-dependent vasodilation [97], muscle atrophy [98] and left ventricular dysfunction [99].

3.3. IL-6 and NT-pro-BNP

Elevated NT-pro-BNP and IL-6 levels were observed in a large population of patients with HF [100]. Recently Alogna et al. measured IL-6 in 374 patients with HF and preserved ejection fraction (pEF), even in association with the severity of symptomatology. They found that patients with the highest IL-6 levels had greater body mass index, higher NT–pro-BNP, CRP, TNFα levels, worse renal function, lower hemoglobin levels and were more likely to suffer from diabetes. Although cardiac structure and function measured at rest were similar, patients with pEF and highest IL-6 concentrations had more severely impaired peak oxygen consumption. These findings support the hypothesis that therapies that inhibit IL-6 in patients with HF and pEF may improve clinical status [101].

Also in CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcome Study) study, IL-6 levels not only predicted incident HF, but inflammation inhibition in the IL-1β to IL-6 pathway reduced rates of HF hospitalization, an effect most pronounced among those with the greatest reductions in IL-6 and CRP [102]. In particular, a specific targeting of IL-1β (interleukin-1β) with the monoclonal antibody canakinumab results in a significant reduction of IL-6 and CRP. By contrast, the Cardiovascular Inflammation Reduction Trial [103] showed that the use of a nonspecific approach, such as a low-dose methotrexate, an agent that had no impact on circulating levels of IL-

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1β, IL-6 and hsCRP, had no benefit in terms of cardiovascular event reduction. Therefore focused cytokine inhibition and not broad spectrum anti-inflammatory therapy are likely to be crucial for atheroprotection.

3.4. IL-6, Glycemia and Insulin Resistance

IR is one of the major hallmarks for pathogenesis and etiology of T2D and it is directly interlinked with various inflammatory responses [104]. A low-grade of chronic inflammation in obesity is characterized by an increased systemic level of cytokines including IL-6, that represents a risk factor of the subsequent development of insulin resistance and T2D [105,106]. In T2D, hyperglycaemia is due to the failure of pancreatic beta-cells to compensate for peripheral insulin resistance [107].

The mechanism by which IL-6 induces insulin resistance is various and complex [78]. Among its actions, IL-6 prevents the metabolism of non-oxidative glucose and suppresses the lipoprotein lipase that consecutively increases the plasma levels of triglycerides [108]. In particular, IL-6 activates the SOCS proteins [109,110] which may block the cytokine-mediated transcriptional factor related to insulin receptor, such as transducer and activator of transcription STAT3, STAT5B belonging to the STAT family of transcription factors [111]. SOCS proteins have negative effects on insulin action while IL-6 can activate these SOCS proteins [112].

If IL-6 is implicated in causing insulin resistance and hyperglicemia in T2D patients, remains yet equivocal [113]. When glucose infusion rate was used to correlate IL-6 to insulin sensitivity during a clamp in T2D patients (and in matched healthy controls), no relationship was found, however a strong relationship was found between IL-6 and and BMI, suggesting that the increased IL-6 in T2D patients is strongly related to fat mass and not insulin response [113]. In support of this findings, Vozarova et al. demonstrated that, studing an ethnic population susceptible to insulin resistance, IL-6 was negatively correlated to insulin action and positively correlated to adiposity [114]. Obesity and/or insulin resistance is associated with the release of IL-6 from adipose tissue [115].

Another study investigated the effects of IL-6 on insulin-stimulated glucose metabolism in T2D patients by 1 h intravenous infusion with recombinant human IL-6, followed by 3 h of hyperinsulinemic-isoglycemic clamp. IL-6 infusion did not change glucose infusion rate during the clamp, however it enhanced phosphorylation of STAT3 in skeletal muscle without changing SOCS3 expression [116]. At the same time, other works report that IL-6 activates the suppressor of cytokine signaling (SOCS) proteins, as SOCS 1, SOCS 3 proteins which suppresses the activity of tyrosine kinase by significantly competing with STAT [109,110,117] which may block the cytokine-mediated transcriptional factor activation of insulin receptor [111].

In conclusion IL-6 could be considered as an important biomarker for the development of insulin resistance [112]. Therefore, by blocking IL-6 may be an effective strategy for the treatment of insulin resistance and type 2 diabetes.

3.5. IL-6, LDL and HDL

Several trials suggest that anti-inflammatory approaches targeting IL-6 signaling can reduce cardiovascular risk. However, it remains unknown whether targeting IL-6 signaling could reduce risk additively to LDL-C lowering. Recently, Georgakis et al divided 408. 225 White British individuals in UK Biobank into groups characterized by lifelong exposure to downregulated IL-6 signaling, lower LDL-C, or both and assessed the genetic scores for IL-6 signaling downregulation and LDL-C lowering. They found that, individuals with both genetic scores both for IL-6 signaling and LDL-C lower than the median, were at lower odds of cardiovascular disease (OR, 0.92; 95% CI, 0.90–0.95) compared with individuals with all or one genetic score above the median, suggesting that genetically downregulated IL-6 signaling and genetically lowered LDL-C are associated with additively lower lifetime risk of cardiovascular disease [118].

IL-6 levels predict future cardiovascular risk and correlate with endothelial dysfunction and carotid intima-media thickness [119,120]. In this regard, an vitro study in endothelial cells by Lubrano

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et al showed that modified LDL up-regulate IL-6 [121], that in turn induces the expression of macrophage scavenger receptors involved in the uptake of modified LDL, thus promoting the formation of foam cells [122] and establishing an inflammatory cycle in the plaque. Moreover another study in HepG2 cells has demonstrated that IL-6 activates LDL-R transcription by enhancing the binding of SREBP-1a and SREBP-2 as well as the binding of Sp1 and Sp3 to their cognate DNA sequence in repeat 2 and repeat 3 of the LDL-receptor (LD-R) promoter. Consequently, the LDL-R activity on the surface of liver cells is enhanced, leading to an increased uptake of LDL from the circulation. These data are consistent with the hypothesis that hypocholesterolemia after myocardial injury, surgery, or infection is partly due to an enhanced catabolism of LDL in the liver by IL-6. [123]. Large epidemiological studies have shown that low plasma levels of HDL-C are associated with increased incidence of coronary heart disease (CHD). In a population of 1044 community dwelling older Italian subjects from the InChianti study, Zuliani et al. provided the first epidemiological evidence that IL-6 is one of the factors that contribute to low HDL-C levels independently from the effects of a large number of possible confounders (triglycerides, fasting insulin, diabetes, hypertension, BMI, waist circumference), and life style habits (smoking, alcohol intake, physical activity) [124]. Successively, another Italian study of 429 patients with stable chest pain who underwent coronary computer tomography showed that low HDL cholesterol and high IL-6 are independent predictors of high risk of coronary diseases [125].

4. FIB

FIB is a large glycoprotein (340 kDa) made up of two identical units, each consisting of three polypeptides: Aα (610 aa, 67 kDa), Bβ (461 kDa, 56 kDa) and γ (411 aa, 48 kDa). The protein formation steps are quite complex: from RNA transcription, six chains are formed, which will assemble into a hexameric complex linked by disulfide bridges [126,127].

FIB is constitutively expressed mainly in hepatocytes and is regulated by acute-phase proteins, mainly by IL-6 produced by monocytes, macrophages, and endothelial cells, while IL-1β and TNF-α suppress its synthesis [127,128]. The production of fibrinogen is also increased by glucocorticosteroids. It is considered an acute phase protein, and its biosynthesis increases during inflammation until it exceeds 7 g/L [128].

4.1. FIB and Vascular Injury

The main role of fibrinogen is its involvement in the blood coagulation cascade, where plasma fibrinogen is converted into an insoluble fibrin clot in the presence of thrombin. The cleavage sites for thrombin are located in the E-region, the central part of molecule [129]. Within the fibrinogen sequence, lysine residues are located in close proximity to thrombin cleavage sites and polymerization motifs; fibrin cross-linking is accomplished by the formation of covalent bonds between glutamine and lysine residues within the α- and γ-chains in the presence of factor XIII (FXIII) [130].

Post-translational modifications of fibrinogen including limited proteolysis, alterations of N-glycosaminoglycans, amino acid phosphorylation, tyrosine sulfation, glycation, nitration and acetylation may play an important role in the pathophysiology of blood coagulation [131,132]. An in vitro study of isolated fibrinogen and plasma from patients with diabetes mellitus shows that fibrinogen glycation and the presence of glucose impair fibrin polymerization [133]. Moreover, fibrinogen nucleotide polymorphism(s) such as γ' fibrinogen polymorphism led to the formation of blood clots that are very resistant to fibrinolysis, which increased the risk of CVD [134–136].

4.2. FIB and Cardiovascular Disease

The increased fibrinogen plasma concentration directly activates many mechanisms, which, consequently, may intensify the progression of atherosclerosis [137]. This seems to affect CVD risk more than increased levels of serum cholesterol. In addition, fibrinogen is associated with an

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increased risk of future myocardial infarction, independently from other CVD risk factors, [138]; a 1 g/L increase in fibrinogen corresponds to a 142% increase of the risk of CAD, 146% increase in the risk of stroke, 176% increase of the risk of death from other vascular events, and 103% increase of the risk of death from nonvascular events, regardless of sex and age [139]. Furthermore, especially when combined with assessment of D'dimer or albumin concentration, plasma fibrinogen concentration is a valuable biomarker of primary and secondary CVD risk [140,141]. According to some authors, increased fibrinogen was independently associated with all-cause mortality and long-term cardiac mortality among patients with CAD undergoing percutaneous coronary intervention, especially those with diabetes mellitus and pre-diabetes [142] and independently predicted mortality in critically ill patients with acute exacerbation of chronic heart failure [143].

4.3. FIB and NT-pro-BNP

Elevated levels of fibrinogen and decreased levels of albumin are risk factors of thrombosis events. [144–146] and are common in patients with HF. The fibrinogen-to-albumin ratio (FAR) was developed to improve diagnostic sensitivity and specificity for predicting poor long-term outcomes of acute HF. According to a recent study, in patients with heart failure FAR was positively correlated with NT-pro-BNP, and this association was stronger than with fibrinogen, albumin, PAR, and PLR [147].

4.4. FIB, Glycemia and Insulin Resistance

A cohort study of 5237 patient investigate the impact of high FIB on cardiovascular outcomes in patients with stable CAD and pre-diabetes mellitus (pre-DM) or diabetes mellitus.

When patients were stratified by both glucose metabolism status and Fib levels, high Fib was associated with a higher risk of MACEs in pre-DM (HR 1.66, 95% CI 1.02–2.71, $P < 0.05$) and in DM (HR 2.28, 95% CI 1.42–3.66, all $P < 0.05$). After adding the combination of Fib and glucose status to the Cox model, the C-statistic was increased by 0.015 (0.001–0.026). This study suggests that Fib may provide incremental value in the cardiovascular risk stratification of pre-DM and DM patients [148]. Furthermore a relationship between plasma fibrinogen and elevated insulin levels, as well as the different parameters of the insulin resistance syndrome has been described. Raynaud et al studying 62 nondiabetic, nonhypertensive patients, found that only insulin sensitivity appeared to account for the ability to predict fibrinogen values. Thus, they hypothesized that the state of insulin resistance rather than hyperinsulinemia per se was related to hyperfibrinogenemia, in connection with some factors like free fatty acids or tumor necrosis factor-α, which have been implicated in the pathogenesis of insulin resistance [149].

Another study investigated if altered response to insulin contributes to hyperfibrinogenemia in T2D; they measured fibrinogen fractional (FSR) and absolute synthesis rates (ASR) using a leucine isotopic model in type 2 diabetic men (n = 7; age = 51 ± 3 years; BMI = 26.7 ± 1 kg/m2) compared with matched nondiabetic subjects under basal conditions and following a 4-h euglycemic-, euaminoacidemic-hyperinsulinemic clamp. Basal fibrinogen concentration (+35%, $P < 0.05$) and ASR (+35%, $P < 0.05$) were greater in the diabetic subjects. Following clamp, fibrinogen FSR and ASR were acutely increased by insulin when euglycemia and euaminoacidemia are maintained in T2D, instead they were unchanged in the control subjects. This study suggests that enhanced fibrinogen production by insulin is likely to be a key alteration contributing to cardiovascular risk in T2D. Unchanged fibrinogen production in nondiabetic individuals suggests a role of plasma amino acids in regulating fibrinogen production in humans [150].

Additionally, increased glucose concentration induces oxidative stress and the generation of highly reactive products, which is known to induce structural modifications and functional impairments of various proteins, including fibrinogen [151]. It has been observed that the glycation level in the fibrinogen molecule was 2–3-fold higher in T2D than in non-diabetic individuals [152–155].

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4.5. FIB, LDL and HDL

In 1996 Halle M showed that, clinically healthy nonsmoking men with serum FIB concentrations >2.90 g/L, have a significantly unfavorable LDL subfraction profile that was independent from other coronary risk factors, such as BMI, age, IR, total cholesterol, serum triglycerides, uric acid, and BP [156] (Halle M, 1996).

Therefore, in addition to its effect on coagulation, FIB could influence atherogenesis by worsening the LDL subfraction profile. Because FIB is independently associated with the expression of a more atherogenic lipoprotein subfraction profile, it should be included in the assessment of coronary risk factors, particularly in patients with dyslipoproteinemia.

The mortality risk predictive capacity of fibrinogen to HDL-cholesterol ratio (FHR) in AMI patients has been not yet well investigated. Recently Jai et al. explored this aspect in a retrospective study involving 13,221 patients with acute myocardial infarct (AMI) from the Cardiorenal Improvement II cohort (NCT05050877) [157] AMI patients with increased baseline FHR values had higher all-cause and cardiovascular mortality, regardless of established CVD risk factors suggesting FHR as a valuable tool for evaluating mortality risk in AMI patients.

Instead, as concern HDL, plasma fibrinogen concentration is inversely related to serum HDL cholesterol concentration [158].

5. Conclusions

This review provides an update on the relation between the role of consolidated inflammatory markers in atherosclerosis and diabetes. CRP, IL-6 and FIB are not merely hallmarkers of these common diseases, but play synergistic roles being active players in the pathogenesis of them. CRP provides complementary information to NT-pro-BNP for high risk of MACE in post-MI patients and predicts cardiovascular events and mortality in type T2D. CRP binds to LDL and leads to structural changes in HDL. CRP is also found in atheromatous plaque.

IL-6 predicts HF incidence, and inflammatory IL6 inhibition by the monoclonal antibody canakinumab reduces HF hospitalization. IL-6 is related to greater BMI, NT–pro-BNP and insulin resistance. IL-6 blockade may be a strategy for insulin resistance treatment. IL-6 levels predict future cardiovascular risk and correlate with endothelial dysfunction and carotid intima-media thickness, activating LDL-R transcription.

The fibrinogen-to-albumin ratio in HF is positively correlated with NT-pro-BNP. Diabetic patients and insulin resistance condition could be related to hyperfibrinogenemia. The glycation level in the FIB molecule is 2–3-fold higher in T2D than in non-diabetic individuals, forming fibrin clots with enhanced resistance to fibrinolysis. Finally, because FIB is independently associated with the expression of a more atherogenic lipoprotein subfraction profile, it should be included in the assessment of coronary risk factors.

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