Inflamm. res. 55 (2006) 221–227
1023-3830/06/060221-7
DOI 10.1007/s00011-006-0076-y



Inflammation Research

Review

# YKL-40, a new inflammatory marker with relation to insulin resistance and with a role in endothelial dysfunction and atherosclerosis

**C. N. Rathcke, H. Vestergaard**

Department of Endocrinology, Herlev Hospital, University of Copenhagen, Herlev, Denmark, e-mail: cnr@dadlnet.dk

Received 16 November 2005; returned for revision 25 January 2006; accepted by I. Ahnfelt-Rønne 8 February 2006

**Abstract.** Substantial evidence supports a role of chronic subclinical inflammation and activation of the innate immune system in the pathogenesis of insulin resistance and endothelial dysfunction and the development of type 2 diabetes (T2D) and atherosclerosis. Several proinflammatory cytokines, acute phase-reactants and cell adhesion molecules play a pivotal role in this chronic subclinical inflammation but a comprehensive understanding of the interrelations of these molecules is still needed.

YKL-40 is a new inflammatory marker with relation to acute and chronic inflammation as well as cancer. It is secreted *in vitro* from a variety of human cells, including vascular smooth muscle cells (VSMCs), activated macrophages and macrophages during late stages of differentiation and is found *in vivo* in subpopulations of macrophages in tissues with inflammation and extracellular tissue remodelling, such as macrophages in atherosclerotic plaques. YKL-40 promotes chemotaxis, cell attachment and migration of VSMCs and the formation of branching tubules suggesting that YKL-40 plays a role in angiogenesis. Latest studies reveal that YKL-40 is elevated in patients with T2D and is related to insulin resistance. This article reviews the studies of YKL-40 with focus on a possible role of YKL-40 in insulin resistance, endothelial dysfunction and atherosclerosis.

**Key words:** YKL-40 – Insulin resistance – Endothelial dysfunction – Atherosclerosis

*Correspondence to:* C. N. Rathcke

## Introduction

Through the last decade there has been an increasing focus on chronic subclinical inflammation and activation of the innate immune system as common pathogenesis to both insulin resistance and endothelial dysfunction and the development of type 2 diabetes (T2D) and atherosclerosis.

Subclinical inflammation is associated with insulin resistance and precedes the development of T2D [1–3]. Furthermore, it induces endothelial dysfunction, which appears to be the earliest event in atherogenesis, and plays a pivotal role in all phases of atherosclerosis from the initiation of the fatty streak to plaque rupture with culmination in acute coronary syndrome [4–6].

Several proinflammatory cytokines, acute phase-reactants and cell adhesion molecules have been shown to play a pivotal role in this chronic subclinical inflammation and today there is substantial evidence supporting the role of CRP, IL-6, TNFα, VCAM-1, ICAM-1 and E-Selectin among others in the pathogenesis of the abovementioned states [7–13].

Although it is well established that chronic subclinical inflammation is a unifying factor of both T2D and atherosclerosis, a comprehensive understanding of the interrelations of the participating proinflammatory cytokines, acute phase-reactants and cell adhesion molecules is still needed. In the search for such an understanding new inflammatory markers are being revealed and may present new possible explanations for the pathogenesis of insulin resistance or endothelial dysfunction.

YKL-40, an inflammatory marker with relation to both acute and chronic inflammation and with an established role in extracellular remodelling and angiogenesis, was recently shown to be correlated with insulin resistance and is elevated in patients with T2D [14]. This article reviews the studies of YKL-40 with focus on and an hypothesis on a possible role of this inflammation marker in insulin resistance, endothelial dysfunction and atherosclerosis.

## Biochemistry, biology and physiology

YKL-40, also known as human cartilage glycoprotein 39 (HC-gp39), chondrex or CHI3-L1, is a 40kDa lectin, a glycoprotein belonging to the family 18 of glycosyl hydrolases comprising chitinases from various species. The abbreviation YKL-40 is based on the one letter code for the first three N-terminal amino acids and its apparent molecular weight [15]. The gene for human YKL-40 is localized in chromosome 1q31-q32 and its crystal structure has been described [16–18].

In mammals, five proteins of this family have been described [19–23]. Two of the mammalian proteins have glycohydrolase activity whereas three proteins, including YKL-40, do not have enzymatic properties, but adhere strongly to chitin and heparin [24]. It is a single amino acid substitution of glutamate with leucin in the catalytic site of the enzymatic active protein, which results in the loss of glycohydrolase activity and instead creates the capacity to bind to chitin [19].

YKL-40 is secreted *in vitro* by a variety of human cells including neutrophils [25], activated macrophages and macrophages during late stages of differentiation [18, 26–29], differentiated vascular smooth muscle cells [30–32], arthritic chondrocytes [22, 33, 34] and fibroblast-like synovial cells [22, 35, 36].

*In vivo* YKL-40 protein expression is found in a subpopulation of macrophages in different tissues with inflammation and extracellular matrix remodelling such as macrophages in atherosclerotic plaques [37], in inflamed synovial membranes of patients with rheumatoid artheritis and osteoarthritis [26, 28, 34] and in CD68+ macrophages and giant cells located in tunica media of artheritic vessels of patients with giant cell artheritis [38]. YKL-40 protein expression is also found *in vivo* in human smooth muscle cells in adventitial vessels [39] and atherosclerotic plaques [32].

The physiological function or functions of YKL-40 are not fully elucidated. Chitin, which YKL-40 adheres to, is not found in vertebrates, and it is speculated that divergent evolution has altered the specificity of the vertebral enzyme so that YKL-40 cleaves a different glycosidic linkage [40]. Since it has not been possible to demonstrate any endo- or exoglycosidase activity of YKL-40 experimentally, it may instead utilize some of the structural elements of the chitinases to mediate its own function such as binding to specific carbohydrates. Since YKL-40 seems to play a major role in extracellular matrix remodelling, it has been speculated that YKL-40 interferes with the synthesis of hyaluronan, one of the most widespread and abundant glycosaminoglycanes in humans, but no degenerative activity of YKL-40 against hyaluronan has yet been demonstrated [22].

YKL-40 is a growth factor for fibroblasts, chondrocytes and human synovial cells [41, 42], and the promotion of growth and proliferation occurs in a dose-dependent manner in a concentration range similar to the effective dose of insulin-like growth factor (IGF-1). The regulation of YKL-40 is scantily evaluated, but the secretion of YKL-40 by human chondrocytes *in vitro* is not influenced by IGF-1, while transforming growth factor-β (TGF-β) reduces the release of YKL-40 to barely detectable levels [22]. YKL-40 and IGF-1 work in a synergistic fashion when present in suboptimal concentrations [42]. Neither IL-1, which is known to decrease the level of synthesis of many of the structural components of articular cartilage, nor TNF-α affects the secretion of YKL-40 by human synovial cells *in vitro* [35].

YKL-40 initiates mitogen-activated protein kinase (MAP) and phosphoinoside-3 kinase (PI-3K) by phosphorylation of the extracellular signal-regulated kinase-1 and 2 (ERK1/ERK2) and protein kinase B (AKT) respectively, and thereby mediate signalling cascades. Both pathways have well-established roles in the propagation of mitogenic signals and play a central role in cell mitogenesis. The activation of these cytoplasmatic signal-transduction pathways suggests, that YKL-40 interacts with one or several signalling components on the plasma membrane. Specific cell surface receptors or the nature of potential YKL-40 ligands are yet speculative and remains to be determined [42].

## YKL-40 in acute and chronic inflammation.

Serum levels of YKL-40 are elevated in patients with purulent meningitis [43] and pneumonia [44] as well as in patients with endotoxemia coursed by injection of E. coli endotoxin [45].

In both meningitis and pneumonia, YKL-40 is secreted by locally activated macrophages and neutrophils and is released by exocytosis from specific granules at the site of inflammation, when needed for bactericidal activity [43, 44]. Because of this local production, YKL-40 levels show a more rapid peak and a more rapid decline after initiation of antibiotic treatment, which is opposite CRP levels that decline slowly [44]. Opposite YKL-40, CRP is primarily a systemic inflammation marker secreted by hepatocytes in response to proinflammatory mediators such as IL-6. Therefore, YKL-40 may serve as a specific serologic marker of granulocyte function and macrophage activation at the site of tissue inflammation as a supplement to conventional acute-phase proteins.

The plasma level of YKL-40 is also increased in chronic inflammatory conditions and increased levels of YKL-40 have been demonstrated *in vivo* in macrophages in inflamed synovial membranes of patients with rheumatoid artheritis (RA) and osteoarthritis [26, 28, 34], in synovial fluids of patients with rheumatoid arthritis and osteoarthritis [22, 40, 46] and in CD68+ macrophages and giant cells located in tunica media of artheritic vessels of patients with giant cell artheritis, where it reflects the local activity of these cells in the inflamed artery [38].

In RA the concentration of YKL-40 in serum and synovial fluid reflects the degree of synovial inflammation and articular cartilage degradation [40, 47], and the serum level of YKL-40 is positively correlated to disease activity and disease progression [39, 48].

Plasma levels of YKL-40 are also increased in chronic inflammatory conditions without joint involvement such as SLE, inflammatory bowel disease and sarcoidosis [49–52].

Elevated levels of serum YKL-40 are also seen in patients with alcoholic cirrhosis and other liver diseases characterized by fibrosis where this may reflect active fibrogenesis and the remodelling of liver fibrosis [53, 54].

Since YKL-40 acts as a growth and survival factor for connective tissue cells of various kinds, is involved in degra-

dation of extracellular matrix and active fibrogenesis and is found in elevated serum levels in a variety of chronic inflammatory and fibrotic conditions, it is possible that YKL-40 plays a central role primarily in pathological conditions with relation to the homeostasis of connective tissue.

## YKL-40 and cancer

Substantial evidence supports a role for YKL-40 in relation to cancer. YKL-40 is secreted *in vitro* by osteosarcoma [55], glioblastoma cells [56] and myeloid leukaemia cell lines [26, 29] and is strongly expressed by tumor associated macrophages in small cell lung cancer biopsies [57]. Several studies of patients with solid tumours have demonstrated that serum YKL-40 is elevated in patients with primary or metastatic carcinoma of the breast [58–60], colon/rectum [61, 62], ovary [63–65], lung [66], prostate [67], kidney [68], glioblastoma [69] and melanoma [70, 71] and is related to tumor grade and burden. High serum YKL-40 in patients with these types of solid tumours is a prognostic marker of short recurrence-free interval and short overall survival and is independent of other prognostic markers.

The exact biological function of YKL-40 in cancer is unknown, but YKL-40 seems to play an important role in tumor invasion. The protein is strongly expressed by murine mammary tumours initiated by *neu/ras* oncogenes but is not expressed by mammary tumours initiated by c-*myc* or *int*-2 oncogenes [72]. The functional ligand for the chitin-binding site in YKL-40 in relation to cancer is not presently known. Other lectins are found in elevated concentrations in a variety of neoplastic cells and some of these lectins may function as adhesion molecules for tumour metastasis in vivo [73–75]. It has been suggested that YKL-40 plays a role in cancer cell proliferation and differentiation, protect cells from undergoing apoptosis and has an effect on extracellular tissue remodelling. The occurrence of high serum levels of YKL-40 in recurrent cancer states and what seem to be highly differentiated cancers may be explained by the role of YKL-40 in both angiogenesis and fibrogenesis. Highly differentiated tumours are characterized by high vascularization and a high turnover of extracellular matrix and one could hypothesize that it is a combination of these processes, which explains the higher serum levels of YKL-40. *In vivo* proof of this is yet to be obtained.

## YKL-40 and insulin resistance, endothelial dysfunction and atherosclerosis.

The participation of YKL-40 in inflammatory states and vascular processes implies that comparison can be made to the inflammatory markers associated with insulin resistance and T2D, as well as with endothelial dysfunction and atherosclerosis.

YKL-40 is isolated from explants of swine thoracic aorta, where it is synthesized *in vitro* by vascular smooth muscle cells (VSMCs) during the time of transition from monolayer culture to a non-proliferating differentiated multilayer culture [76, 77]. The secretion of YKL-40 continues as the cells reorganize and form multicellular nodules, in which cells re-express markers of differentiated VSMCs [30, 31, 76]. This *in vitro* nodule forming process mimics some of the characteristics of the *in vivo* changes that occur in VSMCs following injury, where media smooth muscle cells dedifferentiate, migrate and contribute to the process of restenosis and neointima formation [78].

*In vitro* studies have also shown that YKL-40 promotes chemotaxis, cell attachment, spreading and migration of vascular endothelial cells suggesting that YKL-40 has a role

| In vitro secretion by |
|---|
| Neutrophils |
| Activated macrophages |
| Macrophages in late stage of differentiation |
| Differentiated VSMCs |
| Arthritic chondrocytes |
| Fibroblast-like synovial cells |
| **Acute infectious conditions** |
| Purulent meningitis |
| Pneumonia |
| E.coli endotoxemia |
| **Chronic inflammatory conditions** |
| RA |
| Osteoarthritis |
| SLE |
| IBD |
| Sarcoidosis |
| **Conditions characterized by fibrosis** |
| Alcoholic cirrhosis |
| Liver disease characterized by fibrosis |

| In vivo secretion by |
|---|
| Macrophages and VSMCs in atherosclerotic plaques |
| Macrophages in inflamed synovial membranes |
| Macrophages in acute bacterial infections |
| VSMCs in adventitial vessels |
| CD68+ macrophages/Giant cells in Giant cell artheritis |
| **Cancers** |
| Osteosarcoma |
| Glioblastoma |
| Myeloid leukaemia cell lines |
| Breast |
| Colon/rectum |
| Ovary |
| Lung |
| Prostate |
| Kidney |
| Melanoma |
| **Conditions characterized by subclinical inflammation** |
| Atherosclerosis/atherosclerotic plaques |
| Insulin resistance/T2D |

**Table 1.** *In vitro* secretion and *in vivo* protein expression/secretion of YKL-40 as well as clinical conditions in which levels of YKL-40 are elevated. VSMCs = vascular smooth muscle cells; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; IBD = inflammatory bowel disease; T2D = type 2 diabetes.

in the process of atherosclerotic plaque formation, where smooth muscle cells are induced to migrate through the intima in response to exogenous signals [31]. YKL-40 also modulates vascular endothelial cell morphology by promoting the formation of branching tubules, indicating that YKL-40 has a role in angiogenesis by stimulating the migration and reorganization of VSMCs [31]. These *in vitro* studies are supported by immunohistochemical analysis which has shown *in vivo* protein expression of YKL-40 in human smooth muscle cells in atherosclerotic plaques [32].

Furthermore, the expression of YKL-40 mRNA is highly up-regulated in distinct subsets of macrophages in the atherosclerotic plaque, a plaque that is characterized by the infiltration of monocytes into the subendothelial space of the vessel wall and the subsequent lipid accumulation of the activated macrophages. Particularly macrophages that had infiltrated deeper in the lesion show high YKL-40 mRNA expression and highest expression are seen in macrophages in the early lesion of atherosclerosis [37]. An *in vitro* study with emphasis on biomarker discovery for atherosclerosis by proteomics, show elevated levels of YKL-40 in the supernatant of macrophages following treatment with oxidized low-density lipoprotein, a process that mimics the formation of "foam cells" [79]. This also suggests a role of YKL-40 in the differentiation of monocytes to lipid-laden macrophages during formation of the atherosclerotic plaque.

Studies show that the differentiation and maturation of CD14+ monocytes to CD14-, CD16+ macrophages is attended by an expression of YKL-40 from CD16+ macrophages [28]. CD14 is a key molecule in the innate immune response, where activation of membrane-receptors initiates the secretion of pro-inflammatory cytokines and leads to clustering with other receptors involved in atherogenesis, such as CD11b/CD18 and scavenger receptor CD36 [80]. It is well known that macrophages incorporate oxidized low-density lipoprotein (oxidized LDL) via the scavenger receptor pathway (CD36, scavenger receptor-A) thereby becoming foam cells, which are the hallmark of the early fatty streak lesion [4, 5]. Recent studies have shown other important roles of scavenger receptors in the development of endothelial dysfunction and atherosclerosis [81, 82]. *In vitro* studies show glucose-induced up-regulation of CD36 in microvascular smooth muscle cells which is followed by increased molecular markers of oxidative stress/damage and causes vascular endothelial dysfunction evident by increasing concentrations of stress response proteins [81].

Furthermore, *in vivo* studies show that monocytes from diabetic patients have significantly higher levels of CD36, CD14 and CD18 expression. Studies of YKL-40 in relation to these membrane-bound markers are not yet performed but a possible relation through the maturation and change of phenotype of CD14+-monocytes is not unlikely and may be one of several components of the atherosclerotic state.

The latest results around YKL-40 reveal elevated serum levels of YKL-40 in patients with T2D and a positive correlation between YKL-40 and insulin resistance and features of dyslipidaemia. Interestingly, no correlation is found with parameters of the glycaemic profile neither with BMI. Furthermore, no correlation is found between YKL-40 and CRP in patients with T2D, which may indicate a role of YKL-40 of inflammatory/atherosclerotic significance in diabetes independent from CRP [14].

Patients with T2D are often characterized by high BMI. Obesity is associated with increased macrophage infiltration of adipose tissue, and these macrophages may be an important component of the chronic inflammatory response playing a crucial role in the development of insulin resistance [83]. Although no correlation has been found between the level of YKL-40 and BMI in patients with T2D, it is possible that the correlation between YKL-40 and insulin resistance is based on the macrophage infiltration in the adipose tissue. Whether YKL-40 actually causes insulin resistance remains speculative.

In obesity there is also an increased expression of several chemokine genes in adipose tissue. One of these promotes the production of monocyte chemoattractant protein-1 (MCP-1), which is secreted into the extracellular space, where it primarily acts as a local factor. MCP-1 influences the function of adipocytes, promotes chemotaxis and entry of monocytes into the subendothelial space, and may be a crucial link among chemokines between adipose tissue inflammation and insulin resistance [84]. Studies of YKL-40 in relation to monocytes chemoattractant protein-1 (MCP-1) seem to be fundamental in understanding the role of YKL-40 in relation to monocytes/macrophages-differentiation, especially in insulin resistance as well as the atherosclerotic process.

There is only one study that examines the relation between YKL-40 and insulin resistance but based on these first results and the knowledge of YKL-40 in relation to angiogenesis and fibrogenesis, one could also speculate that the elevated levels of YKL-40 in patients with T2D play a greater role in the process of the well-known accelerated atherosclerosis in this group of patients rather than in the deregulated glucose metabolism. In the light of such speculation, further studies of patients with T2D as well as studies of YKL-40 in patients with Type 1 Diabetes (Juvenile Diabetes), who gradually develop micro- and macroangiopathy but rarely show insulin resistance, could be of interest.

Patients with T2D are known to have elevated levels of CRP, IL-6 and cell adhesion molecules ICAM-1, VCAM-1 and E-selectin [85]. Although a correlation has not been found between YKL-40 and CRP, a recent study shows that YKL-40 is regulated by IL-6 (unpublished data), which is known to stimulate the production and secretion of CRP. Further studies of YKL-40 in relation to proinflammatory cytokines, acute phase-reactants and cell adhesion molecules under different conditions are needed to clarify whether the elevated concentrations of YKL-40 in T2D is caused by the general inflammatory state or in some kind plays a central role in the accelerated atherosclerosis in patients with T2D.

In summary, substantial evidence supports a role for YKL-40 in acute and chronic infections and in cancer, where it is associated with a poor prognosis. YKL-40 plays a role in relation to cell migration, reorganization and tissue remodelling during atherogenesis and seems to play a pivotal role in the differentiation of monocytes to activated macrophages in tissues characterized by inflammation. Together these data imply a significant role of YKL-40 in endothelial dysfunction and in the process of atherosclerosis.

Studies of serum YKL-40 in patients with cardiovascular disease have not yet been performed, and only a single study has suggested a role of YKL-40 in relation to insulin resistance and T2D [14]. Further studies of YKL-40 in relation to other parameters of chronic subclinical inflammation, as well as to parameters involved in macrophage differentiation and activation are needed to clarify the role of YKL-40 in relation to insulin resistance and endothelial dysfunction and in the development of T2D and atherosclerosis.

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