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C-reactive protein and coronary artery disease: influence of obesity, caloric restriction and weight loss

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Abstract

C reactive protein (CRP) values in blood are a good indicator of the likelihood of acute coronary and cerebral events in both healthy subjects and patients with coronary artery disease. This indicates that atherosclerotic lesions rich in inflammatory cells and cytokines are more likely to produce acute events either through vasospasm and/or thrombosis and also can be readily detected through elevations in CRP when measured using a high sensitivity assay (hsCRP). However the arterial wall is only one potential source of cytokines which induce CRP production. Fat cells also produce cytokines, in particular IL-6 which induces the synthesis of CRP by the liver. Obesity, especially abdominal obesity, is associated with elevations of hsCRP. This may be of pathogenic significance as CRP stimulates the uptake of LDL by macrophages, induces complement activation which may cause cellular damage in the artery, and enhances monocyte production of tissue factor, thus enhancing the risk of thrombosis. Caloric restriction and weight loss lowers IL-6 and CRP levels and may beneficially suppress an immune response. Whether particular dietary macronutrients or micronutrients alter IL-6 or CRP is unknown but this issue is clearly becoming more important.

Keywords: CRP; Adipose tissue; IL-6; Weight loss

1. Introduction

C-Reactive protein (CRP) is an acute phase reactant expressed principally by the liver. In healthy, lean individuals CRP circulates at low concentrations in plasma (<3 mg/L). These levels rise dramatically in response to injury, infection and inflammation [1], in response to bacterial lipopolysaccarides (LPS), interleukin-1 β (IL-1 β), interleukin-6 (IL-6), oncostatin M and leukemia inhibitory factor (LIF) [2]. Slightly increased CRP concentrations, detected with high sensitivity kits, but still within what has traditionally been regarded as the normal range (1–10 mg/L) may reflect chronic low-grade inflammation.

2. CRP and cardiac events

There is a growing body of evidence that local and perhaps systemic inflammation is involved in the initiation and progression of atherosclerosis [3]. Therefore, measuring inflammatory markers such as CRP may increase the ability to predict thrombotic events which tend to occur in unstable plaques rich in monocytes, T lymphocytes and lipids. In 1990, Berk et al. [4] first demonstrated markedly elevated CRP levels (22 mg/L) in patients with unstable angina (the pathology of which is a state of transient but recurrent thromboses and/or vasospasm) in comparison with patients with either non-ischemic heart disease or stable angina. Liuzzo et al. [5] showed that elevated CRP (>3 mg/L) would predict subsequent events in patients with severe unstable angina. CRP was associated with increased risk of a subsequent myocardial event (within 2 years) in a large multi-center trial conducted in patients with angina [6]. Since then, numerous studies have observed increased levels of CRP (but still in the normal range) and other inflammatory markers in apparently healthy subjects who then develop acute vascular events [7]. Ridker et al. [8] investigated the baseline CRP levels in 543 men who subsequently went on to develop venous thrombosis, stroke or myocardial infarction and 543 controls who did not in the Physicians Health Study. CRP was higher in the group who had a subsequent myocardial infarction (1.51 vs. 1.13 mg/L), or

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stroke (1.38 vs. 1.13 mg/L) independently of smoking. Onat et al. [9] observed a 4.2 fold increased risk of prevalent coronary heart disease (as assessed clinically and by ECG) in the highest quartile of CRP as compared to the lowest quartile after adjustment for waist circumference, total cholesterol, fibrinogen, physical activity (all of which were associated with CRP levels) and systolic blood pressure in a Turkish population with a low plasma cholesterol. This suggests that CRP serves as a marker for either an enhanced thrombotic risk or a stage of atherosclerosis more likely lead to acute thrombotic events as opposed to prevalent early atherosclerosis (as assessed by carotid intima-media thickness) [10] or calcified lesions [11]. IL-6, which promotes the synthesis of CRP, is abundantly expressed in advanced/complicated human atherosclerotic lesions [12]. Moreover both statin therapy and aspirin are more effective in subjects with high CRP levels, regardless of lipid levels [8,13,14]. Pravastatin [15,16] and lovastatin [14] lower CRP by about 15% and the CRP-lowering is unrelated to lipid lowering. Simvastatin inhibits atherosclerosis in mice without altering lipid levels and also has anti-inflammatory activity similar to indomethacin [17]. Statins have anti-inflammatory action in blood vessels in the rat when NO synthesis is chronically inhibited by L-NAME [18].

3. CRP—A proatherogenic, prothrombotic molecule?

While CRP reflects an ongoing inflammatory response in atherosclerotic vessels, it is unclear if CRP itself contributes to the progression of atherosclerosis, plaque vulnerability and thrombosis. CRP [19] and activated complement [20] are found in atherosclerotic plaques. Some support for the hypothesis that CRP is pro-atherogenic is evidence that CRP binds to LDL and promotes its uptake by macrophages via the CD32 receptor [21]. CRP may mediate tissue damage through activation of the complement system by binding to modified LDL with exposed phosphorylcholine [22]. Activated complement, enzymatically modified LDL and CRP can be found in close proximity to each other in the deep intima of early atherosclerotic coronary artery lesions. Uptake of enzymatically modified LDL by macrophages also releases IL-6 thus providing a potential forward feedback loop to increase liver production of CRP and enhance local complement activation. [23]. Endothelial cell adhesion molecule expression (ICAM-1, VCAM-1 and E- selectin) can be enhanced 10 fold by 10 mg/L CRP in the presence of serum [24]. CRP also stimulates peripheral monocytes to produce tissue factor, a potent stimulus for thrombosis [25]. CRP in the normal concentration range enhanced tissue factor production 4–6 fold and had interactive effects with gamma interferon and lipopolysaccharide. Increasing age and the menopausal state enhanced tissue factor production while hormone replacement therapy diminished it [26]. The production of CRP is non-specific and is elevated by smoking, bacterial and viral infections and tissue damage [1,27] and CRP may explain why patients with inflammatory conditions such as rheumatoid arthritis may have higher rates of acute coronary events [28] and why chlamydia and helicobacter infections and gingivitis have been associated with coronary artery disease [29].

4. CRP and obesity

CRP is also elevated in obesity. BMI and CRP have been correlated in young adults (n = 16,000) [30], middle aged men (n = 303) [31] and elderly men and women (n = 5201) from the Cardiovascular Health Study [32]. Cook et al. [33] investigated the association between obesity and CRP in children aged 10 and 11 years. In this study they observed that CRP was 270% higher in the top quintile for ponderal index (weight/height^3) as compared to subjects in the bottom quintile. CRP is associated with waist circumference in some studies [34–36] and this association often persists after adjustment for BMI [30]. Recently, the association between CRP and visceral fat as assessed by CT scan was investigated in 159 middle-aged men with a wide variation in adiposity [37]. In this study, a strong correlation was observed between CRP and total fat mass and visceral fat mass. However, subjects with an elevated fat mass but normal waist girth did not have significantly raised CRP concentrations. On the other hand, when both conditions were present CRP was significantly elevated above baseline. Forouhi et al. [38] investigated the associations between body fat distribution (as assessed by DEXA and CT scan) and CRP in 113 South Asian and European subjects. Visceral fat was the strongest correlate of CRP, while fasting and 2h insulin and HDL concentrations were correlated with CRP but not after adjustment for visceral fat.

5. CRP and IL-6

The reason for increased production of CRP in obesity is most likely due to IL-6. Il-6 is a cytokine that activates the production of CRP from the liver and CRP levels are a direct indicator of IL-6 levels in vivo [39]. Approximately 25–30% of serum IL-6 originates from adipose tissue and the secretion of IL-6 from subcutaneous fat is in proportion to fat mass [40]. Although obesity increases CRP levels and may increase coronary risk partly through CRP, CRP is associated with the risk of cardiac events independently of BMI. Omental fat cells secrete approximately 2–3 times more IL-6 as compared to subcutaneous adipocytes [41]. Therefore subjects with more abdominal fat may have increased IL-6 and CRP, which could partially account for increased mortality rates in abdominally obese subjects if IL-6 or CRP contributed to disease promotion. Recombinant IL-6 treatment increased lesion size in C57Bl/6 and ApoE-deficient mice 1.9- to 5.1-fold over lesions in saline-treated animals [42]. IL-6 is also abundantly expressed in

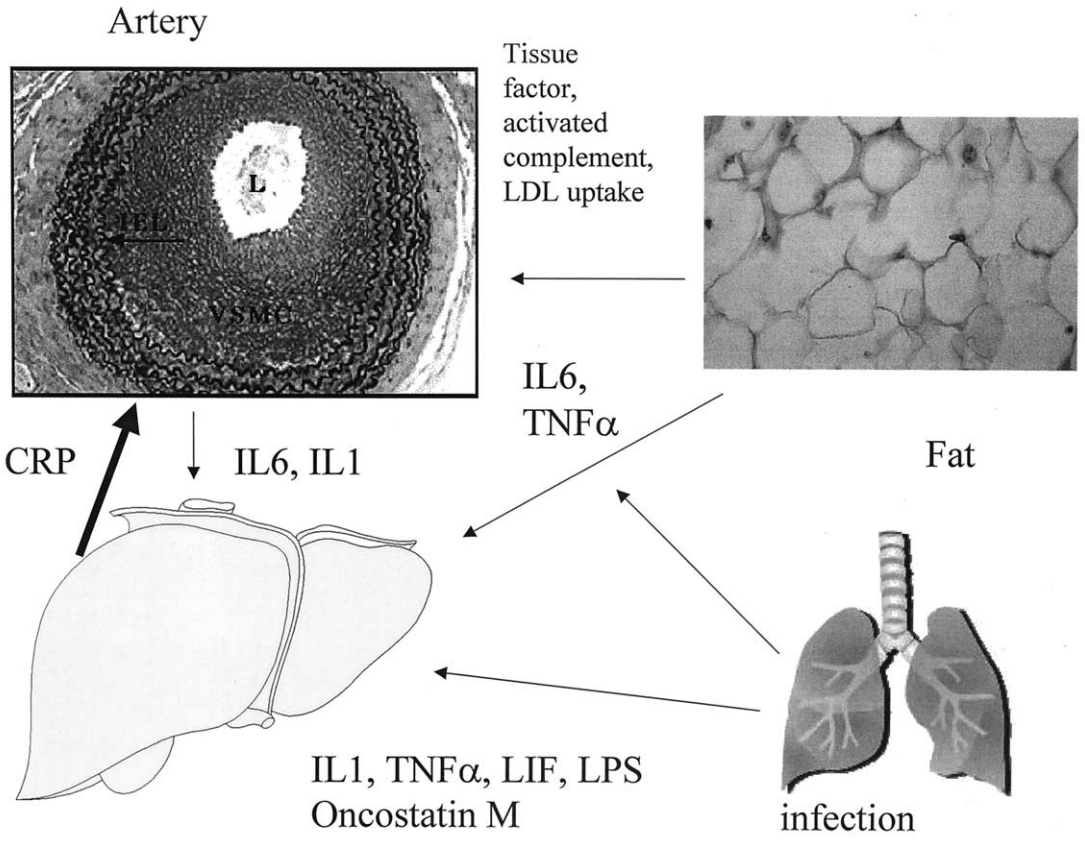

Fig. 1. Connections between cytokines, fat, liver and the artery wall.

advanced human atherosclerotic lesions [12] suggesting IL-6 directly or via CRP has a role in lesion development. IL-6 injections in mice enhance macrophage degradation of oxidized LDL [43] and increase macrophage CD36 mRNA (the receptor through which oxidized LDL is taken up) but do not cause a rise in CRP.

6. CRP gene regulation and IL-6

The CRP gene is also regulated independently of IL-6. Mice transgenic for human CRP with IL-6 knocked out do not respond to LPS whereas the IL-6 competent mouse does but injection of IL-6 in the knockout does not cause an increase in CRP, suggesting other factors are also required. IL-1β, oncostatin M and LIF cause an increase in CRP on both genetic backgrounds [2]. Complement activation products also act in concert with IL-6 and IL-1 to induce CRP [44]. Interestingly in mice testosterone is required for constitutive expression of CRP and for a response to IL-6 [45]. In humans treated with statins CRP is reduced without a change in IL-6 [46].

7. CRP and insulin resistance

Acute, severe inflammation such as sepsis and tissue necrosis can provoke marked insulin resistance [47] and this has been suggested to be an adaptive response [48]. Normal range levels of CRP have also been associated with features of the insulin resistance syndrome as assessed by waist girth, fasting glucose, hyperinsulinemia, insulin sensitivity, triglyceride and low HDL cholesterol [34,36]. Hak et al. [34] observed that after controlling for BMI these associations were lost while Yudkin et al. [36] observed that adjusting for all measures of obesity did not alter the relationships between CRP and insulin sensitivity (as assessed by HOMA). Festa et al. [35] also observed that CRP was independently related to insulin sensitivity as assessed by the frequently sampled intravenous glucose tolerance test in 1008 subjects (33% with IGT). These observations suggest that mild inflammation or elevated CRP itself contribute to insulin resistance although it is not clear how the latter would occur mechanistically.

Pradhan et al. [49] examined the association between CRP, IL-6 and type 2 diabetes prevalence. In this study, which was a part of the ongoing women's health study initiated in 1992, 188 apparently healthy women developed type 2 diabetes. These cases were matched by age to 362 disease-free controls. The case group had significantly higher CRP (and IL-6) as compared to the controls. These associations remained after adjustment for BMI, family history of diabetes, smoking, exercise, and HRT with a relative risk of 4.2 when comparing highest to lowest quartile. Similar results were obtained when analyses were lim-

ited to women with a baseline HbA1C of <6% and after adjusting for fasting insulin. The latter observation suggests that it is not just the insulin resistance of inflammation that contributes to the risk of developing diabetes. Concordant results were also observed in the Cardiovascular Health Study in adults >65 years [50], although in Pima Indians IL-6 levels do not appear to be related to insulin secretion although they are related to insulin action [51].

Women may also have higher concentrations of CRP than men [52], probably because of a greater amount of fat, although this has not been observed in all populations [9]. Girls at the age of 10 have higher CRP than boys [33]. The implications of high CRP in women are unclear as their risk of coronary artery disease is lower than men up to the age of 70 years. Women using hormone replacement therapy (HRT) have a higher concentration of CRP as compared to post-menopausal women not using HRT [53–54] after adjustment for BMI and strong correlations were observed between CRP and weight, BMI, visceral fat and subcutaneous fat in both HRT and non-HRT users. CRP enhances tissue factor production which in combination with an HRT induced fall in the concentrations of tissue factor pathway inhibitor would be expected to enhance thrombotic risk [55]. HRT has been shown to cause acute thrombotic events in women with pre-existing heart disease [56].

8. Weight loss, diet and CRP

Weight loss reduces many risk factors for CVD and retards lesion growth [57]. Insulin sensitivity is improved and triglyceride, total cholesterol and LDL cholesterol concentrations are reduced while HDL-C is elevated after the reestablishment of caloric balance. In a recent study performed by our laboratory in 83 healthy obese women, CRP concentrations were reduced by 26% following 12 weeks of energy restriction and loss of 7.9 kg and were related to changes in body weight [58]. It would be interesting to determine if this reduction was apparent following an energy balance phase and whether macronutrient composition of the weight loss diet influences CRP changes. Tchernof et al [59] demonstrated a 32% fall in CRP values in 25 obese postmenopausal women who lost 15.6% of their body weight. CRP changes were correlated with changes in body weight and fat mass.

Plasma TNF-α and IL-6 are produced by adipocytes and are elevated in obese subjects [60,61]. TNF-α also induces IL-6 production [62,63] which in turn regulates the production of CRP in the liver. Therefore, as TNF-α and IL-6 [61] production is reduced by weight loss, one would expect CRP to be reduced as well. There is also some evidence that caloric restriction alone damps down the inflammatory response in rat myocardium to ischemic and reperfusion damage by reducing the DNA binding affinity of NF-kappaB which modulates the production of the cytokines IL-1β and TNF-α [64]. Short term 3 week feed restriction of about 25% decreased serum TNF-α and TNF-α and IL-6 mRNA in pulmonary nodes 2 weeks after pulmonary antigen presentation in rats [65]. The reduced inflammatory response may account for some of the enhanced longevity in calorically restricted rats [66]. Subtotal fasting for 7 days in patients with active rheumatoid arthritis reduced serum IL-6 by 37% and lowers CRP, and the fall in IL-6 was related to clinical improvement. A ketogenic diet (<40 g/day of carbohydrate) did not reduce inflammatory markers or improve symptoms [67].

9. Does IL-6 have a local role in adipocytes?

IL-6 (like TNF-α, IL-1 and LIF) inhibits the differentiation of 3T3-L1 into mature adipocytes suggesting that it may function locally as an adipostat. These effects are overcome by troglitazone [68] which clinically induces fat gain. Further evidence of a potential role as an adipostat comes from its inhibition of heparin releasable lipoprotein lipase although it is much weaker than TNF-α or LIF [69]. Dexamethasone reduces [41] and β agonists [70] increase the production of IL-6 from adipocytes. Thus some drugs which might have a beneficial effect on inflammation or insulin resistance by reducing or opposing the actions of IL-6 and CRP may induce fat gain as a side effect.

10. Conclusion

CRP is a moderately good predictor of acute vascular events probably because atherosclerotic arteries with an inflammatory infiltrate are more likely to induce acute events and express abundant IL-6 which stimulates CRP production in the liver.

It is possible but not proven that IL-6 and CRP may enhance atherosclerosis by stimulating uptake of LDL by macrophages, and inducing complement activation and CRP may enhance thrombosis by stimulating tissue factor production. Obesity and insulin resistance are associated with elevated IL-6 and CRP, and caloric restriction and weight loss lowers IL-6 and CRP and possibly may damp down inflammation and reduce acute events.

References

[1] D.M. Steel, A.S. Whitehead, The major acute phase reactants: C-reactive protein, serum amyloid P component and serum amyloid A protein, Immunol Today 15 (2) (1994) 81–88.
[2] B. Weinhold, U. Ruther, Interleukin-6-dependent and -independent regulation of the human C-reactive protein gene, Biochem J 327 (1997) 425–429.
[3] R. Ross, Atherosclerosis—an inflammatory disease, N Engl J Med 340 (1999) 115–26.
[4] B.C. Berk, W.S. Weintraub, R.W. Alexander, Elevation of C-reactive protein in "active" coronary artery disease, Am J Cardiol 65 (1990) 168–172.

[5] G. Liuzzo, L.M. Biasucci, J.R.Gallimore, et al. The prognostic value of C-reactive protein and serum amyloid A protein in severe unstable angina, N Engl J Med 331 (1994) 417–424.
[6] S.G. Thompson, J. Kienast, S.D. Pyke, F. Haverkate, J.C. van de Loo, Hemostatic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris, European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group, N Engl J Med 332 (1995) 635–641.
[7] J. Danesh, R. Collins, P. Appleby, R. Peto, Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies, JAMA 279 (1998) 1477–1482.
[8] P.M. Ridker, M. Cushman, M.J. Stampfer, R.P. Tracy, C.H. Hennekens, Inflammation, Aspirin, and the risk of cardiovascular disease in apparently healthy men, N Engl J Med 336 (1997) 973–979.
[9] A. Onat, V. Sansoy, B. Yildirim, I. Keles, O. Uysal, G. Hergenc, C-reactive protein and coronary heart disease in western Turkey, Am J Cardiol 88 (2001) 601–607.
[10] A.R. Folsom, J.S. Pankow, R.P. Tracy, D.K. Arnett, J.M. Peacock, Y. Hong, L. Djousse, J.H. Eckfeldt, Association of C-reactive protein with markers of prevalent atherosclerotic disease, Am J Cardiol 88 (2001) 112–117.
[11] M.E. Hunt, P.G. O'Malley, M.N. Vernalis, I.M. Feuerstein, A.J. Taylor, C-reactive protein is not associated with the presence or extent of calcified subclinical atherosclerosis, Am Heart J 141 (2001) 206–210.
[12] Y. Seino, U. Ikeda, M. Ikeda, K. Yamamoto, Y. Misawa, T. Hasegawa, S. Kano, K. Shimada, Interleukin 6 gene transcripts are expressed in human atherosclerotic lesions, Cytokine 6 (1994) 87–91.
[13] P.M. Ridker, N. Rifai, M.A. Pfeffer, F.M. Sacks, L.A. Moye, S. Goldman, G.C. Flaker, E. Braunwald, Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels, Cholesterol and Recurrent Events (CARE) Investigators, Circulation 98 (1998) 839–844.
[14] P.M. Ridker, N. Rifai, M. Clearfield, J.R. Downs, S.E. Weis, J.S. Miles, A.M. Gotto Jr, Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events, N Engl J Med 344 (2001) 1959–6.
[15] P.M. Ridker, N. Rifai, M.A. Pfeffer, F. Sacks, E. Braunwald, Long-term effects of pravastatin on plasma concentration of C-reactive protein. The Cholesterol and Recurrent Events (CARE) Investigators, Circulation 100 (1999) 230–235.
[16] M.A. Albert, E. Danielson, N. Rifai, P.M. Ridker, Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study, JAMA 286 (2001) 64–70.
[17] C.P. Sparrow, C.A. Burton, M. Hernandez, S. Mundt, H. Hassing, S. Patel, R. Rosa, A. Hermanowski-Vosatka, P.R. Wang, D. Zhang, L. Peterson, P.A. Detmers, Y.S. Chao, S.D. Wright, Simvastatin has anti-inflammatory and antiatherosclerotic activities independent of plasma cholesterol lowering, Arterioscler Thromb Vasc Biol 21 (2001) 115–121.
[18] W. Ni, K. Egashira, C. Kataoka, S. Kitamoto, M. Koyanagi, S. Inoue, A. Takeshita, Antiinflammatory and antiarteriosclerotic actions of HMG-CoA reductase inhibitors in a rat model of chronic inhibition of nitric oxide synthesis, Circ Res 89 (2001) 415–421.
[19] G.D. Reynolds, R.P. Vance, C-reactive protein immunohistochemical localization in normal and atherosclerotic human aortas, Arch Pathol Lab Med 111 (1987) 265–269.
[20] R. Vlaicu, F. Niculescu, H.G. Rus, A. Cristea, Immunohistochemical localization of the terminal C5b-9 complement complex in human aortic fibrous plaque, Atherosclerosis 57 (1985) 163–177.
[21] T.P. Zwaka, V. Hombach, J. Torzewski, C-reactive protein-mediated low density lipoprotein uptake by macrophages: implications for atherosclerosis, Circulation 103 (2001) 1194–1197.
[22] S. Bhakdi, M. Torzewski, M. Klouche, M. Hemmes, Complement and atherogenesis: binding of CRP to degraded, nonoxidized LDL enhances complement activation, Arterioscler Thromb Vasc Biol 19 (1999) 2348–2354.
[23] M. Klouche, S. Gottschling, V. Gerl, W. Hell, M. Husmann, B. Dorweiler, M. Messner, S. Bhakdi, Atherogenic properties of enzymatically degraded LDL: selective induction of MCP-1 and cytotoxic effects on human macrophages, Arterioscler Thromb Vasc Biol 18 (1998) 1376–1385.
[24] V. Pasceri, J.T. Willerson, E.T. Yeh, Direct proinflammatory effect of C-reactive protein on human endothelial cells, Circulation 102 (2000) 2165–2168.
[25] J. Cermak, N.S. Key, R.R. Bach, J. Balla, H.S. Jacob, G.M. Vercellotti, C-reactive protein induces human peripheral blood monocytes to synthesize tissue factor, Blood 82 (1993) 513–520.
[26] A. Nakagomi, S.B. Freedman, C.L. Geczy, Interferon-gamma and lipopolysaccharide potentiate monocyte tissue factor induction by C-reactive protein: relationship with age, sex, and hormone replacement treatment, Circulation 101 (2000) 1785–1791.
[27] T. Palosuo, T. Husman, J. Koistinen, K. Aho, C-reactive protein in population samples, Acta Med Scand 220 (1986) 175–179.
[28] S. Wallberg-Jonsson, H. Johansson, M.L. Ohman, S. Rantapaa-Dahlqvist, Extent of inflammation predicts cardiovascular disease and overall mortality in seropositive rheumatoid arthritis. A retrospective cohort study from disease onset, J Rheumatol 26 (1999) 2562–2571.
[29] J. Danesh, R. Collins, R. Peto, Chronic infections and coronary heart disease: is there a link? Lancet 350 (1997) 430–436 (Review).
[30] M. Visser, L.M. Bouter, G.M. McQuillan, M.H. Wener, T.B. Harris, Elevated C-reactive protein in overweight and obese adults, JAMA 282 (1999) 2131–2135.
[31] M.A. Mendall, P. Patel, L. Ballam, D. Strachan, T.C. Northfield, C Reactive protein and its relation to cardiovascular risk factors: a population based cross sectional study, BMJ 312 (1996) 1061–1065.
[32] R.P. Tracy, R.N. Lemaitre, B.M. Psaty, D.G. Ives, R.W. Evans, M. Cushman, E.N. Meilahn, L.H. Kuller, Relationship of C-reactive protein to risk of cardiovascular disease in the elderly. Results from the Cardiovascular Health Study and Rural Health Promotion Project, Arterioscler Thromb Vasc Biol 17 (1997) 1121–1127.
[33] D.G. Cook, M.A. Mendall, P.H. Whincup, I.M. Cary, L. Ballam, J.E. Morris, J.E. Miller, G.J. Miller, D.P. Strachan, C-reactive protein concentration in children: relationship to adiposity and other cardiovascular risk factors, Atherosclerosis 149 (2000) 139–150.
[34] A.E. Hak, C.D.A. Stehouwer, M.L. Bots, K.H. Polderman, C.G. Schalkwijk, I.C.D. Westendorp, A. Hofman, J.C.M. Witteman, Associations of C-reactive protein with measures of obesity, insulin resistance and subclinical atherosclerosis in healthy, middle-aged women, Arterioscler Thromb Vasc Biol 19 (1999) 1986–1991.
[35] A. Festa, R. D'Agostino, G. Howard, L. Mykkanen, R.P. Tracy, S.M. Haffner, Chronic subclinical inflammation as part of the insulin resistance syndrome. The insulin resistance atherosclerosis study (IRAS), Circulation 102 (2000) 42–47.
[36] J.S. Yudkin, C.D.A. Stehouwer, J.J. Emeis, S.W. Coppack, C-Reactive protein in healthy subjects, Associations with obesity, insulin resistance, and endothelial dysfunction. A potential role for cytokines originating from adipose tissue? Arterioscler Thromb Vasc Biol 19 (1999) 972–978.
[37] I. Lemieux, A. Pascot, D. Prud'homme, N. Almeras, P. Bogaty, A. Nadeau, J. Bergeron, J.P. Despres, Elevated C-reactive protein: another component of the atherothrombotic profile of abdominal obesity, Arterioscler Thromb Vasc Biol 21 (2001) 961–967.
[38] N.G. Forouhi, N. Sattar, P.M. McKeigue, Relation of C-reactive protein to body fat distribution and features of the metabolic syndrome in Europeans and South Asians, Int J Obes 25 (2001) 1327–1331.
[39] R. Bataille, B. Klein, C-reactive protein levels as a direct indicator of interleukin-6 levels in humans in vivo, Arthritis Rheum 35 (1992) 982–4.
[40] V. Mohamed-Ali, S. Goodrick, A. Rawesh, J.M. Mile, D.R. Katz, J.S. Yudkin, S.W. Coppack, Human subcutaneous adipose tissue releases

IL-6 but not TNF-α in vivo, J Clin Endocrinol Metab 82 (1997) 4196–4200.
[41] S.K. Fried, D.A. Bunkin, A.S. Greenberg, Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid, J Clin Endocrinol Metab 83 (1998) 847–850.
[42] S.A. Huber, P. Sakkinen, D. Conze, N. Hardin, R. Tracy, Interleukin-6 exacerbates early atherosclerosis in mice, Arterioscler Thromb Vasc Biol 19 (1999) 2364–2367.
[43] S. Keidar, R. Heinrich, M. Kaplan, T. Hayek, M. Aviram, Angiotensin II administration to atherosclerotic mice increases macrophage uptake of oxidized LDL: a possible role for interleukin-6, Arterioscler Thromb Vasc Biol 21 (2001) 1464–9.
[44] A.J. Szalai, F.W. van Ginkel, Y. Wang, J.R. McGhee, J.E. Volanakis, Complement-dependent acute-phase expression of C-reactive protein and serum amyloid P-component, J Immunol 165 (2000) 1030–1035.
[45] A.J. Szalai, F.W. van Ginkel, S.A. Dalrymple, R. Murray, J.R. McGhee, J.E. Volanakis, Testosterone and IL-6 requirements for human C-reactive protein gene expression in transgenic mice, J Immunol 160 (1998) 5294–5299.
[46] I. Jialal, D. Stein, D. Balis, S.M. Grundy, B. Adams-Huet, S. Devaraj, Effect of hydroxymethyl glutaryl coenzyme a reductase inhibitor therapy on high sensitive C-reactive protein levels, Circulation 103 (2001) 1933–1935.
[47] C.H. Lang, C. Dobrescu, Sepsis-induced changes in in vivo insulin action in diabetic rats, Am J Physiol 257 (1989) E301–E308.
[48] J.M. Fernandez-Real, W. Ricart, Insulin resistance and inflammation in an evolutionary perspective: the contribution of cytokine genotype/phenotype to thriftiness, Diabetologia 42 (1999) 1367–1374.
[49] A.D. Pradhan, J.E. Manson, N. Rifai, J.E. Buring, P.M. Ridker, C-Reactive protein, interleukin-6 and risk of developing type 2 diabetes, JAMA 286 (2001) 327–334.
[50] J.I. Barzilay, L. Abraham, S.R. Heckbert, M. Cushman, L.H. Kuller, H.E. Resnick, R.P. Tracy, The relation of markers of inflammation to the development of glucose disorders in the elderly: the Cardiovascular Health Study, Diabetes 50 (2001) 2384–2389.
[51] B. Vozarova, C. Weyer, K. Hanson, P.A. Tataranni, C. Bogardus, R.E. Pratley, Circulating interleukin-6 in relation to adiposity, insulin action, and insulin secretion, Obes Res 9 (2001) 414–417.
[52] E.S. Ford, Body mass index, diabetes, and C-reactive protein among U.S. adults, Diabetes Care 22 (1999) 1971–1983.
[53] P.M. Ridker, C.H. Hennekens, N. Rifai, J.E. Buring, J.E. Manson, Hormone replacement therapy and increased plasma concentration of C-reactive protein, Circulation 100 (1999) 713–716.
[54] E. Barinas-Mitchell, M. Cushman, E.N. Meilahn, R.P. Tracy, L.H. Kuller, Serum levels of C-reactive protein are associated with obesity, weight gain, and hormone replacement therapy in healthy postmenopausal women, Am J Epidemiol 153 (2001) 1094–1101.
[55] M.D. Luyer, S. Khosla, W.G. Owen, V.M. Miller, Prospective randomized study of effects of unopposed estrogen replacement therapy on markers of coagulation and inflammation in postmenopausal women, J Clin Endocrinol Metab 86 (2001) 629–634.
[56] S. Hulley, D. Grady, T. Bush, C. Furberg, D. Herrington, B. Riggs, E. Vittinghoff, Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women, Heart and Estrogen/progestin Replacement Study (HERS) Research Group, JAMA 280 (1998) 605–613.
[57] K. Karason, J. Wikstrand, L. Sjostrom, I. Wendelhag, Weight loss and progression of early atherosclerosis in the carotid artery: a four-year controlled study of obese subjects, Int J Obes Relat Metab Disord 9 (1999) 948–956.
[58] L.K. Heilbronn, M. Noakes, P.M. Clifton, Energy restriction and weight loss on very-low-fat diets reduce C-reactive protein concentrations in obese, healthy women, Arterioscler Thromb Vasc Biol 21 (2001) 968–970.
[59] A. Tchernof, A. Nolan, C.K. Sites, P.A. Ades, E.T. Poehlman, Weight loss reduces C-reactive protein levels in obese postmenopausal women, Circulation 105 (2002) 564–569.
[60] G.S. Hotamisligil, P. Arner, J.F. Caro, R.L. Atkinson, B.M. Spiegelman, Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance, J Clin Invest 95 (1995) 2409–2415.
[61] J.P. Bastard, C. Jardel, E. Bruckert, P. Blondy, J. Capeau, M. Laville, H. Vidal, B. Hainque, Elevated levels of interleukin-6 are reduced in serum and subcutaneous adipose tissue of obese women after weight loss, J Clin Endocrinol Metab 85 (2000) 3338–3342.
[62] Y. Amrani, A.J. Ammit, R.A. Panettieri Jr, Tumor necrosis factor receptor (TNFR) 1, but not TNFR2, mediates tumor necrosis factor-alpha-induced interleukin-6 and RANTES in human airway smooth muscle cells: role of p38 and p42/44 mitogen-activated protein kinases, Mol Pharmacol 60 (2001) 646–655.
[63] P. De Cesaris, D. Starace, A. Riccioli, F. Padula, A. Filippini, E. Ziparo Tumor necrosis factor-alpha induces interleukin-6 production and integrin ligand expression by distinct transduction pathways, J Biol Chem 273 (1998) 7566–7571.
[64] B. Chandrasekar, J.F. Nelson, J.T. Colston, G.L. Freeman, Calorie restriction attenuates inflammatory responses to myocardial ischemia-reperfusion injury, Am J Physiol Heart Circ Physiol 280 (2001) H2094–H2102.
[65] W. Dong, F.W. Kari, M.K. Selgrade, M.I. Gilmour, Attenuated allergic responses to house dust mite antigen in feed-restricted rats, Environ Health Perspect 108 (2000) 1125–1131.
[66] L.T. Frame, R.W. Hart, J.E. Leakey, Caloric restriction as a mechanism mediating resistance to environmental disease, Environ Health Perspect 106 (Suppl 1) (1998) 313–324.
[67] D.A. Fraser, J. Thoen, O. Djoseland, O. Forre, J. Kjeldsen-Kragh, Serum levels of interleukin-6 and dehydroepiandrosterone sulphate in response to either fasting or a ketogenic diet in rheumatoid arthritis patients, Clin Exp Rheumatol 18 (2000) 357–62.
[68] J. Ohsumi, S. Sakakibara, J. Yamaguchi, K. Miyadai, S. Yoshioka, T. Fujiwara, H. Horikoshi, N. Serizawa, Troglitazone prevents the inhibitory effects of inflammatory cytokines on insulin-induced adipocyte differentiation in 3T3–L1 cells, Endocrinology 135 (1994) 2279–2282.
[69] M. Berg, D.L. Fraker, H.R. Alexander, Characterization of differentiation factor/leukaemia inhibitory factor effect on lipoprotein lipase activity and mRNA in 3T3–L1 adipocytes, Cytokine 6 (1994) 425–432.
[70] G. Path, S.R. Bornstein, M. Gurniak, G.P. Chrousos, W.A. Scherbaum, H. Hauner, Human breast adipocytes express interleukin-6 (IL-6) and its receptor system: increased IL-6 production by beta-adrenergic activation and effects of IL-6 on adipocyte function, J Clin Endocrinol Metab 86 (2001) 2281–2288.