Association between LDL-cholesterol, statin therapy, physical activity and inflammatory markers in patients with stable coronary heart disease

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Abstract

Evidence suggests that inflammatory parameters such as high sensitive C-reactive protein (hs-CRP), interleukin-6 (IL-6), serum amyloid-A (SAA) and fibrinogen (Fib) are associated with cardiovascular morbidity and mortality. In this study we investigated the association between LDL-cholesterol (LDL-C), lipid lowering drug therapy (LLD) and inflammatory markers in 436 subjects (age 64,2 ± 4.1 yr, BMI 27,6 ± 3,9 kg/m2) with coronary heart disease, participating in outpatient exercise groups for cardiac rehabilitation. In a subgroup analysis (n=229), we looked at the respective effects of physical activity (PA) alone and in combination with LLD.

For the whole group the levels of inflammatory markers were: hs-CRP 0,31±0,4 mg/dl; IL-6 2,04 ± 1,6 pg/ml; SAA 6,26 ± 14 mg/l; Fib 381 ± 97 mg/dl. Compared to patients without LLD, those with LLD showed modestly lower concentrations for CRP (–7%) and IL-6 (–12%), ($p<0.05$, respectively). In patients with an LDL-C < 100 mg/dl, CRP (–12 %) and Fib (–8%) were significantly lower ($p<0.05$, respectively) than in patients with LDL-C > 100 mg/dl. Patients with a high level of PA (PA ≥ 3 times/week) exhibited significantly lower values for CRP (–18%), Fib (–11%) and SAA (–37 %) ($p<0.01$, respectively) than patients with a low level of PA (≤ 1 time/week). The combination of a high level of PA, and intake of LLD further reduced CRP (–37 %) and SAA (–45 %), with no additional decrease in Fib (–10 %) ($p<0.01$, respectively) compared to patients with a low level of PA and taking LLD. The data from this cross-sectional study suggest that factors such as LLD, LDL-C (< 100 mg/dl), and a high level of physical activity are associated with lower levels of inflammatory markers in patients with coronary heart disease. Particularly with respect to CRP and SAA values, a high level of PA in combination with LLD, showed the most pronounced effects. The proof of causality of these findings should further be investigated in randomized controlled trials.

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Introduction

Recent data indicates that markers of systemic inflammation, such as high sensitive C-reactive protein (hs-CRP), interleukin-6 (IL-6), serum amyloid-A (SAA) and fibrinogen (Fib) are useful for identifying persons at high risk of coronary heart disease (CHD) [5,7,9-11,16,20,26,28]. It has been suggested that systemically inflammation reflects local inflammatory processes within the vessel wall at the site of plaque formation [5,29,34,43]. Various risk factors, including hypertension, diabetes, obesity, increased LDL-C, LDL-C peroxidation, physical inactivity and smoking initiate a chronic inflammatory reaction in the vessel wall. There is accumulating evidence that inflammatory processes play an integral role in the formation of atherosclerotic plaques [22,49,53]. Therefore, it is possible that an improvement of cardiovascular risk factors by lipid lowering drugs, increased physical activity or weight reduction would also reduce inflammatory processes, and hence, atherogenesis in the vessel wall [24, 31, 40, 48, 51].

The role of LDL cholesterol (LDL-C) in the pathogenesis of atherothrombotic diseases is well established [2, 13, 14, 47]. Accumulating evidence indicates that lowering LDL-C reduces the risk for fatal and non-fatal myocardial infarction in both primary and secondary prevention of coronary heart disease (CHD) [3,23,46]. Recommendations for optimal LDL-C concentrations were published by the Joint European Societies in 1994 and 1998 or the Adult Treatment Panel III of the United States National Cholesterol Education Program [1,54]. There is general agreement that LDL-C in secondary prevention of CHD should be lower than 100 mg/dl, and that in high risk patients, the target level for LDL-C should be < 70 mg/dl. In many cases, this goal can only be achieved by lipid-lowering drugs (LLD), which are well known to reduce morbidity and mortality associated with CHD [3, 21].

LLD is effective in reducing markers of inflammation [24,48,52]. However, it is currently unknown whether patients with CHD and LDL < 100 mg/dl exhibit lower plasma levels of inflammatory parameters than patients with

Table 1. Age, BMI and lipoprotein levels of patients investigated. LPA = low physical activity status, HPA = high physical activity status; LLD = lipid lowering drugs. Values are mean ± SD.
§ = p<0.01 within groups

	Whole group	Lipid lowering drugs		LDL < 100 mg/dl		Physical activity status		Physical activity status/ lipid lowering drugs	
	n=436	No n=160	Yes n=260	No n=294	Yes n= 142	Low n=159	High n=70	LPA+LLD n=150	HPA+LLD n=52
Age (yr)	64,2 ± 4,1	64,9 ± 3,2	63.8 ± 2.9	64,4 ±3,3	63.3 ± 3.8	64,5 ± 3,6	65,0 ± 2,9	64,5 ± 3,2	64,2 ± 3,4
BMI (kg/m2)	27,6 ± 3,9	27,4 ± 4,6	27,5 ± 3,41	27,8 ± 4,1	27,1 ± 3,4	27,4 ± 3,8	26,9 ± 4,0	27,3 ± 3,7	26,5 ± 3,9
TChol (mg/dl)	224 ± 42	242 ± 42	214 ± 40§	242 ± 35	186 ± 27§	233 ± 47	214 ± 37	218 ± 42	209 ± 34
TG (mg/dl)	242 ± 153	231 ± 123	250 ± 170	232 ± 123	264 ± 202	257 ± 19	213 ± 107	256 ± 198	229 ± 109
LDL-C (mg/dl)	120 ± 32	134 ± 32	112,3 ± 29§	136 ± 24	86,0 ± 10§	126 ± 34	113 ± 31	114 ± 30	109 ± 28
HDL-C (mg/dl)	49,8 ± 16	53,8 ±18	47,2 ± 14	51,2 ± 16	47,2 ± 16	51,0 ± 17	50,1 ± 6,3	46,9 ± 14	48,1 ± 15

LDL > 100 mg/dl. Furthermore, few data are available concerning whether subjects taking LLD present a more favourable inflammatory state than patients without LLD in a cross sectional design. In addition, few studies have investigated the effect of physical activity on inflammatory markers in patients with CHD [31,45], and the results are not consistent [51].

Therefore, in the present study we looked at the association between hs-CRP, IL-6, SAA, Fib and the LDL-level, the intake of LLD and the level of physical activity in a large sample of patients participating in outpatient exercise groups for cardiac rehabilitation.

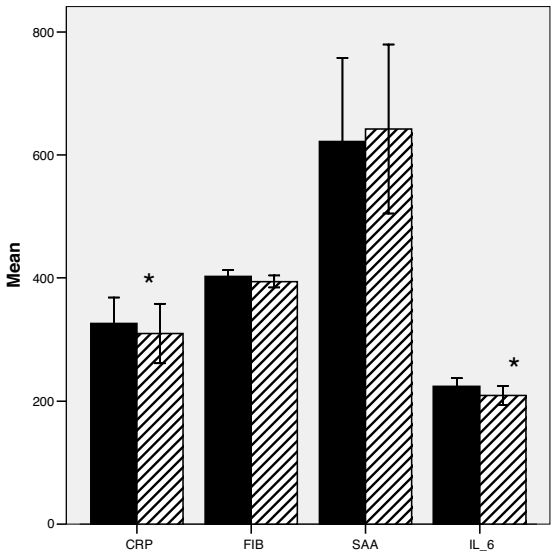

Fig. 1. Mean values for hs-C-reactive protein (CRP), fibrinogen (fib), serum-amyloid-A (SAA) and interleukin-6 (IL-6) in dependence on the intake of lipid lowering drugs (Mean±S.E.M). Non-users = black bars, Users = hatched bars; * = $p < 0.05$. For better visualisation, the concentrations of inflammatory markers were multiplied as followed (CRP*1000, SAA *100 and IL-6*100).

Material and Methods

Patients (n=436) with diagnosed stable coronary heart disease and state after myocardial infarction were enrolled in the investigation. All subjects participated regularly in prescribed outpatient exercise groups for cardiac rehabilitation. Subjects were asked whether they took lipid lowering drugs (LLD) and what kind of LLD. In a subset (n=299) information was obtained about their physical activity (≤ 1time/week, 2 times/week or ≥ 3 times/week). Leisure time physical activity (> 45 min. duration) of ≤ 1 time/week was labelled as a low physical activity status and ≥ 3 times/week as a high physical activity status.

Blood samples were collected before the exercise sessions and plasma concentrations of hs-CRP, Fib, IL-6, SAA, total cholesterol (TCho), triglycerides (TG), LDL-cholesterol (LDL-C) and HDL-cholesterol (HDL-C) were determined. Hs-CRP, SAA and Fib were quantified nephelometrically using reagents from Dade Behring (Dade Behring, Schwalbach, Germany). IL-6 was measured using ELISA kits (R&D-Systems, Wiesbaden, Germany). Lipoprotein levels were determined by lipid electrophoresis (REP, Greiner, Limburg, Germany). Most of the exercise sessions were in the afternoon; therefore, the lipoprotein concentrations do not represent fasting levels. Groups were tested for significant differ-

ences using the Mann-Whitney U-Test for unpaired samples. P-values < 0.05 were considered significant.

Results

Subject characteristics regarding age, body mass index (BMI) and lipoprotein levels are shown in Table 1. There were no significant differences within and between groups for age, BMI, HDL-C and TG levels. Due to the selection criteria, significant differences were observed for TChol and LDL-C. More than half (58%) of patients took LLD (98% statins), but only 48 % achieved the desired level of LDL-C < 100mg/dl (59% with LLD and 79% without LLD, data not shown).

Compared to patients without LLD, those with LLD showed lower concentrations for CRP (–7%) and IL-6 (–12%), ($p<0.05$, respectively) (Fig. 1). In patients with an LDL-C < 100 mg/dl, CRP (–2 %) and Fib (–8%) were significantly lower ($p<0.05$, respectively) than in patients with LDL-C > 100 mg/dl (Fig. 2).

Slightly more than half (53%) of patients showed a low level of PA, and 23% a high level (data for the group with PA = 2 times/week not shown). Patients with a high level of PA showed significantly lower values for CRP (–18%), Fib (–11%) and SAA (–37%) ($p<0.01$, respectively) compared to those with a low level of PA (Fig. 3).

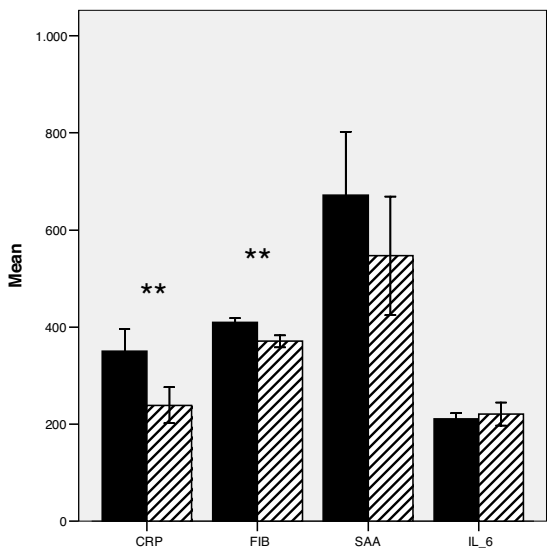

Fig. 2. Mean values for hs-C-reactive protein (CRP), fibrinogen (fib), serum-amyloid-A (SAA) and interleukin-6 (IL-6) in dependence on LDL-C lower than 100 mg/dl (Mean±S.E.M). LDL-C > 100 mg/dl = black bars, LDL-C < 100 mg/dl = hatched bars; ** = $p< 0.01$. For better visualisation, the concentrations of inflammatory markers were multiplied as followed (CRP*1000, SAA *100 and IL-6*100).

The combination of a high level of PA and intake of LLD (17% of patients) further reduced CRP (–37%) and SAA (–45%), with no additional decrease in Fib (–10%) ($p<0.01$, respectively) compared to those patients with a low level of PA and taking LLD (32% of patients) (Fig.4).

Discussion

The results of the present study demonstrate that factors such as the intake of LLD, attainment of LDL-C levels below 100 mg/dl or a high level of PA _ particularly in combination with LLD _ were associated with a reduction in inflammatory parameters. Therefore, our findings are in keeping with most previous studies that an improvement of cardiovascular risk factors reduces systemic inflammation in patients with CHD [39,40,45,48,52].

In the past years, the pathophysiological role of inflammatory mediators in atherogenesis has been well established [4,22,33,42,44]. Inflammatory processes play an important role in virtually all stages of atherogenesis, and involve both innate and adaptive immune responses [18,30]. Evidence suggests that the established coronary risk factors such as hypertension, dyslipoproteinemia, hyperglycemia or smoking greatly enhance pro-inflammatory potential. The so called inflammatory cascade, as described by Libby et al., starts with the pro-inflammatory risk factors mentioned above. These factors induce primary cytokines (e.g. IL-1, TNF-_), followed by increased production of IL-6, ICAM-1, selectins and heat shock proteins, and finally increased formation and liberation of acute phase proteins by the liver [32]. Elevated levels of IL-6, hs-CRP, SAA and fibrinogen in subjects with atherosclerosis or acute coronary syndromes are commonly observed, and are often associated with the severity of atherosclerosis and prognosis of coronary heart disease [20,24,28]. Many authors have designated inflammatory markers as an independent risk factor for atherosclerosis [9,20,42]. Therefore, measurement of hs-CRP _ the parameter that has been most consistently associated with atherosclerosis, has been recommended (level of evidence B) by the American Heart Association to identify high risk patients with coronary heart disease [42].

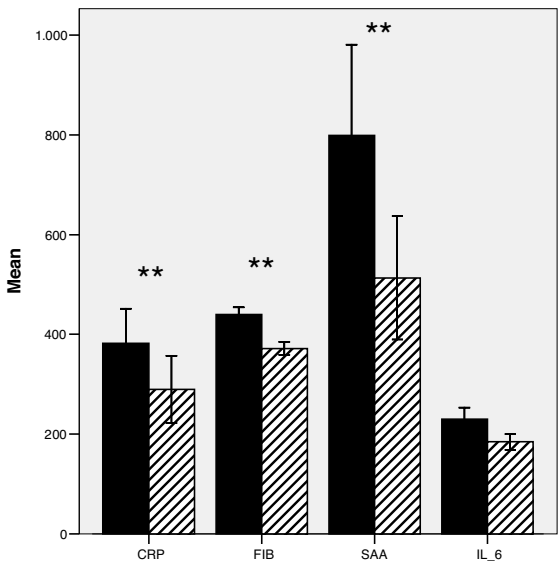

Fig. 3. Mean values for hs-C-reactive protein (CRP), fibrinogen (fib), serum-amyloid-A (SAA) and interleukin-6 (IL-6) in dependence on the level of physical activity (PA) (Mean±S.E.M). Low PA level = black bars, high PA level = hatched bars; ** = p< 0.01. For better visualisation, the concentrations of inflammatory markers were multiplied as followed (CRP*1000, SAA *100 and IL-6*100).

Also in our investigation, hs-CRP was the only inflammatory marker that was significantly lowered by LDL-C < 100 mg/dl, LDD and PA. For the whole group hs-CRP concentration were 0.31 mg/dl. Therefore, according to the American Heart Association scientific statement [42], the patients investigated were a high risk population. The lower hs-CRP values by intake of LLD, LDL-C levels below 100 mg/dl or a high level of PA, downgrades these patients into a population with an average risk. Similar to hs-CRP, SAA was also considerably lower in these groups; Fib was moderately lower, whereas IL-6 showed the least difference. The latter finding is not necessarily consistent with current literature, as IL-6 has shown to be elevated in subjects with CHD, and responds to therapeutic interventions such as statin therapy [35,43,55]. Nevertheless, other investigations have also found that the decrease in IL-6 was comparatively small following lipid lowering interventions [36,37].

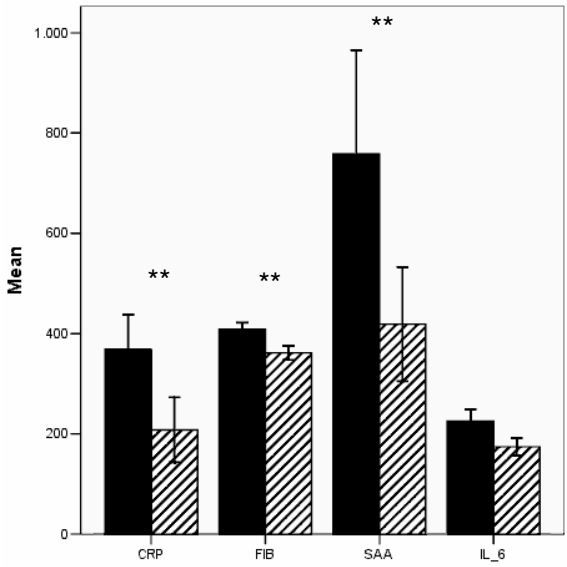

Fig. 4. Mean values for hs-C-reactive protein (CRP), fibrinogen (fib), serum-amyloid-A (SAA) and interleukin-6 (IL-6) in dependence on the level of physical activity (PA) and intake of lipid lowering drugs (LLD) (Mean±S.E.M). Low PA level + LLD = black bars, high PA level + LLD = hatched bars; ** = p< 0.01. For better visualisation, the concentrations of inflammatory markers were multiplied as followed (CRP*1000, SAA *100 and IL-6*100).

It was surprising that the effect of PA, particularly in combination with LLD was far more pronounced than the sole effect of LLD or LDL<100 mg/dl. The long-term anti-inflammatory effect of moderate exercise is well established [12,25,27]. Recent trials have shown that regular physical activity is associated with reduced concentrations of pro-inflammatory markers specifically related to atherosclerosis [25,31,51]. Milani et al. reported a 41% reduction in hs-CRP by exercise training in patients with CHD that was comparable to our results [40]. Nevertheless, epidemiologic and prospective trials have convincingly demonstrated that lipid-lowering interventions, particularly statin therapy, can effectively reduce inflammatory parameters in patients with CHD [24,48,50,52]. Statins have shown to inhibit the migration of macrophages to sites of inflammation, and also to reduce the levels of pro-inflammatory cytokines (IL-6, IL-8) and adhesion molecules (ICAM-1, VCAM-1) [38,41,50,53]. With regard to the patients in the

present study, it is possible that statins were not fully effective, given the relatively high number of patients who did not achieve the desired LDL-C < 100 mg/dl.

The selection of patients in the present study who were participating in outpatient exercise groups for cardiac rehabilitation should have resulted in a sample of relatively well-guided and informed patients. Hence, the fact that only 59% with LLD showed LDL-C levels below 100 mg/dl is alarming. Nevertheless, our results have clearly demonstrated that a high level of PA was associated with markedly lower levels of hs-CRP and SAA. Evidence is increasing that a physically active lifestyle and resulting increased physical fitness is associated with a reduction in cardiovascular risk factors and coronary events [17,19]. Recently, the Cochrane Library stated that inclusion of exercise programs in cardiac rehabilitation was associated with a significant benefit regarding total mortality and fatal cardiovascular events [23]. However, in this meta-analysis, LDL-C was not decisively lower in subjects participating in exercise programs compared to comprehensive cardiovascular rehabilitation without PA. Furthermore, studies not dealing specifically with patients in secondary prevention of CHD have reported that the direct effect of PA on LDL-C is relatively small [6,15]. Beyond doubt, the influence of LLD on LDL-C levels is decisively stronger than the effect of PA. Despite the limitations of our cross sectional design, the present the results suggest that reduced pro-inflammatory markers may contribute to the beneficial effect of PA on the reduced cardiovascular event rate [8].

In conclusion, the data from this investigation suggest that factors such as LLD, LDL-C < 100 mg/dl and a high level of physical activity are associated with reduced levels of inflammatory markers in patients with coronary heart disease. Particularly with respect to CRP and SAA values, a high level of PA in combination with LLD, showed the most pronounced effects. In the future, studies should investigate the amount and intensity of PA needed to induce favourable changes within the inflammatory profile in CHD patients.

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