Components of the insulin resistance syndrome are associated with progression of atherosclerosis in non-grafted arteries 5 years after coronary artery bypass surgery

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Aims Risk factors for progression of atherosclerosis in non-grafted coronary arteries were examined in a prospective 5-year follow-up study of 228 consecutive coronary artery bypass surgery patients, with the main emphasis on insulin resistance syndrome.

Methods and Results Serum lipids and lipoproteins were measured pre-operatively and 1, 2, 3 and 5 years after surgery; and a baseline oral glucose tolerance test with plasma insulin determinations was performed pre-operatively. Progression of atherosclerosis was assessed by means of computer-based quantitative coronary angiography. Compared to subjects without progression, the patients with progression of atherosclerotic lesions had a higher body mass index both at baseline (P = 0.022) and at 5 years (P = 0.007), were more often treated for hypertension at baseline (P = 0.008) and at 5 years (P = 0.012), used diuretics more often during the follow-up period (P = 0.002), had a larger blood glucose area under the curve (P = 0.015) and a lower insulin sensitivity index (P = 0.006) in the baseline oral glucose tolerance test, had a higher serum total cholesterol concentration at baseline (P = 0.044), and a higher serum triglyceride concentration (P = 0.005) during the whole follow-up period. Clustering of the components of insulin resistance syndrome at baseline was more frequently found in patients with progression of atherosclerotic lesions than in patients without progression (P = 0.025). For example, for patients with ≤ 1 component, the risk of progression was 17%, while for patients with ≥ 5 components the risk was 67%. As compared to the other patients, those with new atherosclerotic lesions had a lower insulin sensitivity index at baseline (P = 0.033), and a lower serum high density lipoprotein cholesterol concentration during the follow-up period (P = 0.033).

Conclusion In addition to high serum cholesterol, the components of the insulin resistance syndrome are associated with progression of atherosclerosis in non-grafted coronary arteries 5 years after coronary artery bypass surgery (Eur Heart J 1998; 19: 711-719)

Key Words: Atherosclerosis, coronary bypass surgery, triglycerides, insulin resistance.

Introduction

Progression of atherosclerosis in coronary arteries and grafts is common after coronary artery bypass graft surgery. However, angiographic studies after bypass surgery have focused on the progression of atherosclerosis in the grafts. Studies on the progression of atherosclerosis in the coronary arteries after surgery are few[1-3], or have focused mainly on pharmacological or surgical intervention (ileal bypass) on serum cholesterol and low density lipoprotein (LDL) cholesterol[4-10].

The long-term prognosis of bypassed patients in terms of angina pectoris symptoms and risk of acute myocardial infarction probably depends both on the patency of the grafts and on the progression of atherosclerosis in the coronary arteries after coronary artery bypass graft surgery[11,12]. We studied the risk factors in angiographically assessed progression of coronary artery disease in non-grafted coronary arteries 5 years after the
operation. The main emphasis was on the effect of the insulin resistance syndrome\textsuperscript{13} on the progression of atherosclerosis, since some recent studies have suggested its role as a risk factor for coronary artery disease\textsuperscript{14,15}. The variables related to insulin resistance in the present study were impaired glucose tolerance, reduced insulin sensitivity index\textsuperscript{16}, increased level of serum triglycerides, decreased level of serum high density lipoprotein (HDL) cholesterol, hypertension and obesity.

Methods

Subjects

The cohort consisted of 228 consecutive patients (201 males, 27 females) under the age of 65 years with stable ischaemic heart disease who underwent elective coronary artery bypass graft surgery in Turku University Hospital between February 1986 and December 1987. They represent 82% of all patients who have undergone bypass surgery in this hospital during that period. Initially, the subjects were randomized to conventional treatment and a comprehensive rehabilitation group. The results of the rehabilitation study have been reported elsewhere\textsuperscript{17,18}. Since the groups were similar as regards risk factors and angiographic findings, the subjects from the two groups were pooled for this study. The mean (SD) age of the patients was 54 (6) years at the time of the operation. The main (SD) effect of the operation was received by 25% of the patients at baseline, and 5% had diabetes mellitus. Complete revascularization was achieved in 62% of the patients, the average (SD) number of grafts per subject was 2.7 (0.9). All subjects gave verbal informed consent. The study protocol was approved by the Ethics Committee of Turku University Hospital.

Coronary angiography

Coronary angiography was performed on an average (SD) 61 (2) months after the operation. The range was 59–68 months, except for one subject who underwent angiography 39 months after the operation because of severe angina pectoris; the results of this examination were used in the analysis. All other subjects underwent angiography according to the study protocol. Catheterization was performed using the percutaneous femoral approach. Simultaneous biplane angiograms of the left ventricle, the coronary arteries and the bypass grafts were obtained. A Philips Optimus M 200 biplane cardiovascular system with Philips 9 inch/6.5 inch intensifiers or a Siemens Pandoros 1200 A biplane cardiovascular system with Sirecon 27/17 HN image intensifiers were used. Natrium ioxaglate-meglumine ioxaglate (Hexabrix, 320 mg iodine/ml, Querbet, Aulnay-Sous-Bois, France) was used as contrast medium. A dose of 0.5 mg sublingual nitroglycerin and 1.25 mg lingual isosorbide dinitrate by aerosol was administered to all subjects immediately before coronary angiography. Coronary arteries were catheterized selectively using Judkins left and right coronary catheters (M allinckrodt M edical, St. Louis, U.S.A.) and visualized in multiple views, including cranio-caudal angulations following a manual injection of 5–8 ml contrast medium. Care was taken in the 5-year control angiographies to use the same projections as in the pre-operative examinations.

Analysis of the angiograms

Coronary artery angiograms were analysed using validated quantitative coronary arteriography software, the Cardiovascular Measurements System (M edis, N uenen, T he N ederlands)\textsuperscript{20}, as described elsewhere in detail\textsuperscript{21}. Progression of atherosclerosis was evaluated in non-grafted coronary arteries by comparing the 5-year follow-up angiogram with the pre-operative angiogram. Objective anatomical landmarks, usually branch points, were used to define the coronary segments. All

adequately visible segments with an average reference (i.e. non stenosed) diameter of at least 1 mm were analysed. The proportion of diffusely diseased segments was less than 2% of all segments. Where no reliable reference diameter could be obtained these diffusely diseased segments were excluded from the analyses. If two approximately perpendicular views were available, the data from both were averaged.

Two different principles were applied to classify the progression of atherosclerotic changes. Both are modifications of methods evaluated in the Cholesterol Lowering Atherosclerosis Study[22]. The first classification was based on the follow-up of stenoses observed in the baseline angiograms. A stenosis was considered to be present when a diameter narrowing of at least 25% was detected in the follow-up angiogram, if a stenosis had been observed in the same location in the baseline angiogram. An increase or decrease of 20 percentage points in the diameter narrowing between the two angiograms was considered as a significant change. All stenoses in each segment of the coronary arteries were analysed, and if a segment showed more of progressed than regressed stenoses, it was classified as progressive. Correspondingly, if a segment showed more of regressed than progressed stenoses, it was classified as regressive. Other segments were classified unchanged. When the total number of progressed segments in a patient exceeded that of regressed segments by at least one, the patient was classified as a subject with progression, and the other patients were classified as subjects without progression.

The other classification was based on the occurrence of new lesions in the follow-up angiograms. A diameter narrowing of at least 25% in the follow-up angiogram was classified as a new lesion, if the region had been normal in the pre-operative angiogram. A stenosis observed in the pre-operative angiogram was considered to have disappeared, if it was not seen in the follow-up angiogram. A segment was classified as one with new lesions if the development of new stenoses exceeded those which had receded, and as one without new lesions if the opposite was the case. If a patient had at least two more segments with the new lesions, than segments without new lesions, they were classified as a subject with new lesions; the rest were classified as subjects without progression.

The reproducibility of the quantitative coronary arteriograms was assessed by analysing the angiograms of 10 subjects twice with a 1 month interval. The mean (SD) difference of percentual diameter stenosis between the two measurements was 5-17 (3-98) percentage points, which is in agreement with other studies[23].

Biochemical and other methods

Fasting serum cholesterol, high density lipoprotein (HDL), cholesterol, triglycerides and apolipoprotein A-I levels were measured pre-operatively and at 6 months, and 1, 2, 3 and 5 years after the operation. The apolipoprotein E phenotype was determined pre-operatively, and lipoprotein (a) and carboxyhaemoglobin levels at the 5-year follow-up. An oral glucose (75 g) tolerance test with blood glucose and plasma insulin determinations at 0, 60 and 120 min was performed pre-operatively. The area under the curve was measured for blood glucose and plasma insulin concentrations. All blood samples were drawn after an overnight fast. The samples for serum lipid determinations were frozen at −20 °C and analysed within a few days.

Serum cholesterol was determined by using a fully enzymatic CHOD-PAP method[24] (Boehringer-Mannheim, Germany). Average intra- and inter-assay coefficients of variation were 1·6% and 2·1%.

Serum triglycerides were determined using either a fully enzymatic method[25] (Boehringer-Mannheim, Germany) or a colorimetric GPO-PAP method (Merck, Darmstadt, Germany). Average intra- and inter-assay coefficients of variation were 2·5% and 3·9%.

Serum HDL cholesterol was assessed from the supernatant after precipitation of LDL and very low density lipoproteins with dextran sulphate 500 000 (Pharmacia, Uppsala, Sweden)[26]. Averge intra- and inter-assay coefficients of variation for HDL cholesterol were 1·5% and 2·8%. LDL cholesterol was calculated by using the formula presented by Friedewald et al.[27]. The HDL/total cholesterol and HDL/LDL cholesterol ratios were calculated.

Lipoprotein (a) concentration was determined by using a solid phase two-site immunoradiometric assay (Pharmacia, Uppsala, Sweden)[28]. Intra- and inter-assay coefficients of variation were 1·9% and 4·4% at the level of 180 mg . l−1, and 2·3% and 4·9% at the level of 45 mg . l−1. Serum apolipoprotein A-I was determined immunoturbidimetrically by using a commercially apolipoprotein A-I kit (Orion Diagnostica, Helsinki, Finland)[29].

Apolipoprotein E phenotyping was performed after sample delipidation with ethanol diethyl ether 3:1 (vol/vol) and cysteamine treatment. A nalytical isoelectric focusing on 5% polyacrylamide gels (LK B, Sweden) with a Bio-Rad Protein cell vertical electrophoresis unit was performed, followed by immunoblotting using an LKB 2117-2500 electroblotting unit[30].

Whole blood glucose was determined using the glucose oxidase method, and plasma insulin using radioimmunoassay (Novo Biolabs, Denmark). The insulin sensitivity index was calculated on the basis of the glucose and insulin values during the oral glucose tolerance test, using the formula presented by Cederholm and Wibell[16]. This index is not directly comparable with insulin sensitivity assessed by the euglycemic clamp technique, i.e. the ‘gold standard’ for measuring glucose disposal in response to insulin. However, the insulin sensitivity index of Cederholm and Wibell works like the euglycemic clamp technique or insulin suppression test in that it ranks groups of subjects with increasing degrees of glucose intolerance[16]. Subjects with previously diagnosed diabetes mellitus or who met...
the WHO criteria for diabetes in the oral glucose tolerance test were excluded.

Blood carboxyhaemoglobin was determined by using absorption photometry (OSM 3 Heximeter, Copenhagen, Denmark). Values of 1·5% or more were assumed to be caused by regular smoking[31]. Body height and weight were measured, and body mass index was calculated by dividing the weight by the square of the height (kg . m$^{-2}$).

Statistical analyses

SAS computer software was used for data analysis. Comparisons of continuous variables were performed using the Student’s t-test. Within-group changes were analysed using the paired t-test. Categorical variables were tested using the chi-square test or Fisher’s exact test. Yates’ correction for continuity was used in four-fold tables. Because of the skewed distribution, lipoprotein (a), triglycerides and insulin were analysed after logarithmic transformation. Weighted mean values, up to 60 months, of the lipids and lipoproteins were calculated, excluding the 6-month value and including the pre-operative, and the 1-, 2- and 3-year values once and the 5-year value twice. The body mass index and use of diuretics were included as covariates in the linear model comparing progression groups. P-values below 0·05 were taken as evidence for statistical significance.

Results

Altogether 176 subjects (87% of the survivors) had coronary angiography 5 years after the operation, and 128 (73%) of them had non-grafted coronary arteries that were analysed with quantitative coronary angiography. Lipid and lipoprotein values at the 5-year follow-up were similar in the subjects who underwent angiography and in those who did not. Of the angiography subjects, 126 (98% of the analysed) had stenoses in the baseline angiogram, and 32 (25%) of them were classified as having progression in the follow-up angiogram. Twenty-six (20% of the analysed) patients were classified as subjects with new lesions. The mean (SD) percent diameter stenosis in the baseline angiography was 32·4 (7·9), range 12·1–85·0 and at 60 months 36·8 (7·9), range 20·1–100. The mean (SD) percent diameter stenosis of the new lesions was 33·5 (6·3), range 25·0–51·3.

Progressive improvement was seen in all lipid values during the follow-up. The pre-operative and 5-year lipid and lipoprotein values were the following: total cholesterol 6·95 ± 1·29 mmol . l$^{-1}$ and 5·99 ± 0·99 mmol . l$^{-1}$ (P =0·0002), H D L cholesterol 1·02 ± 0·24 mmol . l$^{-1}$ and 1·05 ± 0·27 mmol . l$^{-1}$ (P =0·21), LDL cholesterol 5·02 ± 1·18 mmol . l$^{-1}$ and 4·21 ± 0·86 mmol . l$^{-1}$ (P =0·0001), H D L/ L D L cholesterol ratio 0·22 ± 0·07 and 0·26 ± 0·09 (P =0·0001), apolipoprotein A-I 1·10 ± 0·17 g . l$^{-1}$ and 1·19 ± 0·18 g . l$^{-1}$ (P =0·0001), triglycerides 2·25 ± 1·39 mmol . l$^{-1}$ and 1·80 ± 1·22 mmol . l$^{-1}$ (P =0·0001).

Progression of pre-operative stenoses

Compared to the subjects without progression, the subjects with progression of atherosclerotic lesions had a higher body mass index pre-operatively and at the 5-year follow-up, a larger area under the curve of blood glucose in the glucose tolerance test, and a lower insulin sensitivity index. They were also more often treated for hypertension at the baseline and at the 5-year follow-up, and were more often on treatment with diuretics during the follow-up period (Table 1).

The subjects in whom the baseline stenoses progressed had higher plasma triglyceride levels during the whole follow-up period and a higher concentration of serum total cholesterol at the baseline, as compared with those without progression (Table 2). H D L cholesterol at 60 months was lower in subjects with progression than in the others, but the difference was not statistically significant (P =0·080). No significant differences were seen in other lipids and lipoproteins.

Since the use of diuretics at any time during the follow-up period was associated with progression of the baseline stenoses, additional analyses were performed to study the association between progression and risk factors by adjusting for treatment with diuretics at each point of the follow-up. In these analyses, the insulin sensitivity index was lower (P =0·017), total cholesterol at the baseline higher (P =0·048), and the mean of the triglycerides during the follow-up higher (P =0·021) in patients with progression than in those without progression.

Since obesity has an influence on lipid and lipoprotein concentrations, insulin sensitivity, and hypertension, an adjustment for the body mass index was performed at each point of follow-up. In these analyses, the mean of the triglycerides during the follow-up was higher (P =0·046) and treatment for hypertension more common (P =0·049) in patients with progression than in those without progression.

Development of new lesions

Subjects with new lesions had a lower insulin sensitivity index at baseline, compared to the other subjects (Table 3), a lower serum H D L cholesterol concentration at 60 months and a corresponding weighted mean concentration during the follow-up period (Table 4). The groups were similar as regards the other lipid and lipoprotein values. After adjustment for treatment with diuretics, the insulin sensitivity index (P =0·040) was still lower in subjects with new lesions than in the others. After adjustment for the body mass index, the insulin sensitivity index (P =0·021) was lower in patients with new lesions than in those without progression.
sensitivity index (P = 0.041) was lower in subjects with new lesions than in the others.

Components of the insulin resistance syndrome

Subjects showing many insulin resistance syndrome risk factors more often had progression of the baseline stenosis than the patients with fewer risk factors (Fig. 1). No association was observed between the number of risk factors and formation of new lesions.

Other risk factors

Subjects with progression of atherosclerosis did not differ from those without progression in respect of age, ...
Apolipoprotein E phenotype was assessed in 109 subjects. Phenotypes 2/2, 3/2 and 3/3 were combined for the analysis to form the apoE4+ group (n=70). Phenotype 4/2 (n=3) was excluded from the analysis. Phenotypes 4/3 and 4/4 were combined for the analysis to form the apoE4+ group (n=36). There was no association between phenotype apoE4 and the formation of new lesions or progression of angiographically assessed coronary artery disease.

**Discussion**

The results of this prospective 5-year follow-up study, using computer-based quantitative analysis of coronary angiograms and serial measurements of lipid and
Insulin resistance and atherosclerosis

There is increasing evidence that serum triglycerides and triglyceride-rich lipoproteins are risk factors in the progression of atherosclerosis assessed by angiography and in acute myocardial infarction. In our study, triglycerides were strongly associated with the progression of atherosclerotic lesions and this association persisted, although weakened, after the adjustment for obesity or use of diuretics. Two possible mechanisms by which hypertriglyceridaemia is related to coronary artery disease have been proposed: a direct atherogenic effect of triglyceride-rich lipoproteins, particularly very low density lipoproteins and their remnants, or the metabolic consequences of hypertriglyceridaemia. The metabolic consequences of hypertriglyceridaemia that can be associated with coronary artery disease are many, including small dense LDL particles, low levels of HDL cholesterol, and a procoagulant state resulting from changes in blood coagulation factors or impaired fibrinolysis. Unfortunately, small dense LDL particles, blood coagulation or fibrinolysis were not assessed in our patients.

The baseline but not the 5-year concentration of serum total cholesterol was associated with progression of coronary artery disease in our patients. This is in line with the published results of the CASS study. The weak association of serum cholesterol with coronary artery disease in our study may be due to the fact that the inter-individual variation in the levels of serum cholesterol during the follow-up was relatively small. A larger variation in serum cholesterol and LDL cholesterol, as in intervention studies to decrease the LDL cholesterol concentration, could have revealed a more evident association between serum cholesterol and coronary artery disease.

Low HDL cholesterol concentration was associated with the occurrence of new lesions and its importance was accentuated over time. This is in agreement with previous studies, and emphasizes the role of low HDL cholesterol concentration on the genesis of early soft, cholesterol-rich atheromas.

As regards the other components of the insulin resistance syndrome, hypertension, high body mass index at baseline and at 5-year follow-up, and insulin resistance determined as the insulin sensitivity index, were all associated with the progression of pre-operative atherosclerotic lesions. A low insulin sensitivity index was also associated with the development of new lesions. These results are in accordance with some recent studies showing that a high fasting plasma insulin level is associated with the progression of atherosclerotic manifestations, and that subjects with angiographically diagnosed coronary artery disease are characterized by moderate or severe insulin resistance. However, the mechanisms of action of insulin resistance on the progression of atherosclerosis are not clear. An association between insulin resistance and lipid abnormalities, as observed in this study, as well as the impact of triglyceride-rich lipoproteins on changes in blood coagulation and fibrinolysis, have been suggested.

Our study focused on the association between risk factors and the progression of atherosclerosis in non-grafted coronary arteries. Previous studies have shown that 5 to 7 years after bypass surgery, progression of coronary artery disease is as common in non-grafted arteries as in segments distal to graft anastomosis of the bypassed vessels. However, in segments proximal to the graft anastomosis the rate of progression is faster than that in non-grafted arteries. Consequently, in addition to non-grafted arteries, our results may also be applicable to segments distal to graft anastomosis, but possibly not to segments proximal to graft anastomosis. However, further studies are needed to evaluate the role of...
the components of the insulin resistance syndrome in the progression of coronary artery disease in segments of bypassed arteries proximal or distal to the anastomosis.

In conclusion, the results of this study indicate that components related to the insulin resistance syndrome are associated with the progression of coronary artery atherosclerosis 5 years after coronary artery bypass graft surgery. As a practical consequence, we suggest that, in addition to lowering of LDL cholesterol, the treatment of the insulin resistance syndrome and its components is important in order to slow down the progression of the atherosclerosis in non-grafted coronary arteries after coronary artery bypass grafting.

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