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Research Article

Acute Lipoprotein (a) Reduction after PCI and the Incidence of Restenosis: a Clinical Study

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Abstract

Background: Lipoprotein (a) [Lp(a)] is a well-documented independent risk factor for Coronary Artery Disease (CAD) that also affects the lipid and coagulation systems. Nevertheless, the influence of Lp (a) on the manifestation of restenosis after Percutaneous Coronary Intervention (PCI) is not fully explored. We investigate Lp (a), fibrinogen, and plasminogen levels pre- and post-Percutaneous Coronary Intervention (PCI) to assess interaction of Lp (a) with the coagulation system.

Methods: Patients with CAD and PCI with bare metal stents were recruited between August 1998 and June 1999. Blood samples to measure Lp (a), plasminogen, and fibrinogen were taken pre-PCI, immediately after PCI, and on days one and three after PCI. Patients were followed up after six months by scheduled Coronary Angiogram (CAG).

Results: A total of 89 patients were recruited, 81 of which were examined by CAG, and 28 had restenosis after PCI (34.5%). Following PCI, patients with restenosis had a larger decrease in Lp (a) levels and fibrinogen neither of both had reached baseline by day three (Lp (a) p=0.008, fibrinogen p=0.0121).

Conclusions: From the fact that neither Lp (a), nor fibrinogen, or plasminogen had returned to baseline levels by day three after PCI, we hypothesise that there may exist a bridge between Lp (a) and the thrombosis and fibrinolysis pathways at the site of vascular injury after PCI which promotes restenosis after PCI.

Keywords: Restenosis; PCI; Lipoprotein (a); Fibrinogen; Plasminogen

Background

Lipoprotein (a) [Lp (a)] was first described by Berg et al. in 1963 and is a risk factor for Cardiovascular Disease (CVD) although its role in promoting restenosis after Percutaneous Coronary Intervention (PCI) is still unclear. Lp (a) is an LDL-like lipoprotein with an additional Apolipoprotein (a) [apo (a)] attached to the apolipoprotein B-100 by a disulphide bridge. Plasma Lp (a) concentration is genetically determined. Levels vary widely between individuals and are not influenced by diet or exercise. The apo (a) molecule has a similar structure to that of plasminogen, thus Lp (a) can potentially reduce fibrinolysis by inhibiting the plasmin that binds to fibrin. Examination of atherosclerotic plaques have shown ingestion of Lp (a) by macrophages resulting in lipid accumulation and the building of foam cells. Another atherogenic effect of Lp (a) is reduced activation of transforming growth factor-β which inhibits cellular migration and proliferation of smooth muscle cells [1-3].

Many studies have shown elevated Lp (a) plasma levels to be an independent risk factor for CVD. Elevated Lp (a) levels have also been associated with an increased risk of major cardiac events in patients with Coronary Artery Disease (CAD) after PCI. A correlation between elevated plasma levels and incidence of restenosis was reported in one meta-analysis; however, these data remain controversial [4-6].

In the era of Bare Metal Stents (BMS), a scheduled Coronary Angiogram (CAG) was standard to detect restenosis after PCI, which occurs in about 30% of patients. Restenosis typically occurs 3 to 6 months after PCI and is defined as neointimal growth that causes a loss of more than 50% in the luminal diameter in the stent. More recently, long-term outcome after CAG with PCI has been monitored to assess a correlation between Lp (a) and CAD [7-12].

Our study aimed to ascertain the existence of a possible correlation between Lp (a) and the coagulation and fibrinolytic system with the emergence of restenosis. Most other studies focused to the absolute levels of Lp (a) before coronary interventions but the dynamic of Lp (a) changes and its correlation to the coagulation and fibrinolytic system was not investigated already.

To assess the influence of Lp (a) on the incidence of restenosis, we chose to use historic data from the BMS era because of the high incidence of restenosis at that time. The data were obtained from a study originally created to detect stent thrombosis due to high Lp (a) levels.

Methods

To search for a possible correlation between Lp (a) and the emergence of restenosis in the fibrinolytic system, we recruited 89 patients with coronary disease and single-vessel PCI with BMS between August 1998 and June 1999. Eighty-one patients were followed up with a CAG (16 females, 65 males, mean age of 63 years +/- 10.1). Blood samples werken before PCI (time A), immediately

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after PCI (time B) and on days one (time C) and three (time D) following PCI and prior to discharge. Blood was tested for Lp (a), plasminogen activity, and fibrinogen. Patients were followed up after 6 months and examined by scheduled CAG. CAG, PCI, and restenosis were assessed according to the European Society of Cardiology (ESC) guidelines.

The data were placed into a Microsoft Access database and documented. The statistical analyses were performed using the SPSS statistical software. Data are either presented as the mean ± SD, the median, or as counts or proportions (percentages) as appropriate. Normally distributed, continuous variables are expressed as means (±SD), while the media is given for continuous data. Categorical variables were compared using the chi-squared statistics, while the Wilcoxon test was used for continuous and ordinal variables. Significance was defined as $p< 0.05$.

Written concern was given from all patients. The ethic committee of the university of Bochum declared no objections to the implementation of the research project.

Results

From the 81 patients that were followed up with CAG, 28 (34.5%) had restenosis after PCI defined as 50% stenosis in the PCI segment. Using a multivariate analysis we found no significant difference in the distribution of risk factors, such as hypertension, diabetes, hyperlipidaemia, or smoking, between patients with and without restenosis.

The median Lp (a) level before PCI (time A) was 42.74 mg/dl (±43.0). Following PCI, there was a sharp decrease in Lp (a) levels in both groups (time B) with an increase on day 1 (time C) and return to nearly normal levels on day three after PCI (time D).

To exclude the influence of heparin on LP (a) levels, we determined the Lp (a) concentration in a group of 50 patients with CAG outside the study collective after a dose of 5000IE heparin. The results yielded no change in Lp (a) levels after CAG. In the group with restenosis the Lp (a) levels were 40.4 mg/dl (±37.6) before PCI, 32.9 mg/dl (±33.1) after PCI, 33.4 mg/dl (±36.0) at day 1, and 37.9 mg/dl (±37.8) at day 3 ((Figure 1), Lp (a) levels in the restenosis group). In the group without restenosis the Lp (a) levels were 43.9 mg/dl (⁺45.9) before PCI, 36.0 mg/dl (±37.2) after PCI, 39.7 mg/dl (±41.1) at day 1, and 41.3 mg/dl (±43.7) at day 3 (Figure 2), Lp (a) levels in the group without restenosis).

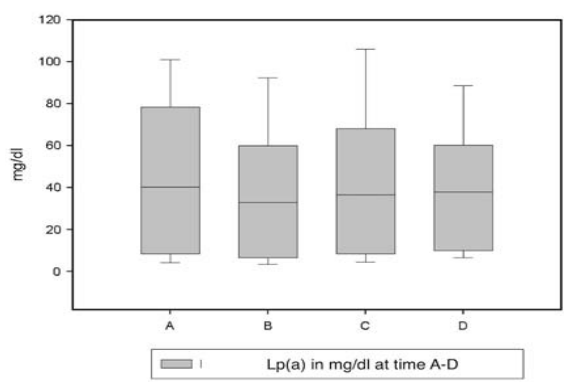

Figure 1: Lp (a) levels in cases of restenosis.

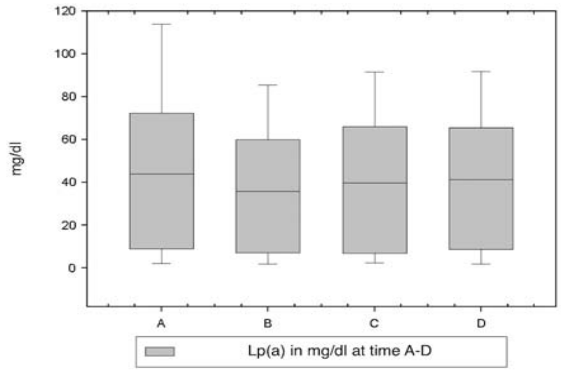

Figure 2: Lp (a) levels in cases without restenosis.

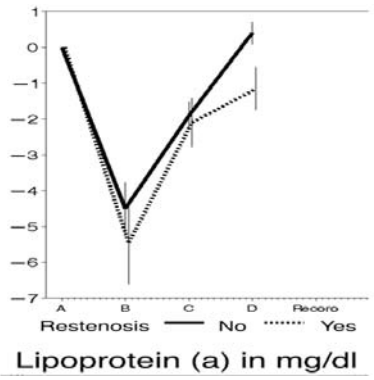

Figure 3: Lp (a) change from baseline at time A-D.

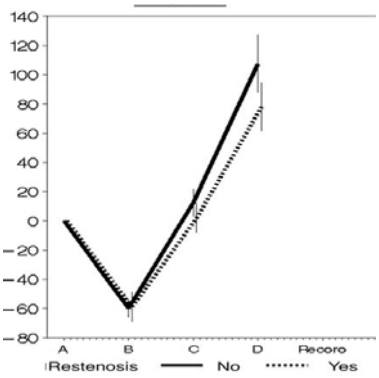

Figure 4: Fibrinogen change from baseline at time A-D.

While absolute levels of Lp (a) levels were higher in the group without restenosis than in the group with restenosis; however, this difference was not statistically significant. In contrast, a strong statistically significant correlation was observed between the median Lp (a) change relative to baseline on the third day. Patients with restenosis showed a larger decrease and remained below baseline Lp (a) levels ($p=0.008$) ((Figure 3), Lp (a) changes relative to baseline in groups with/without restenosis). Also the levels of fibrinogen showed a similar decrease after PCI with levels recovering over the following three days. This decrease in fibrinogen levels relative to baseline was slightly more pronounced in the restenosis group and visible on day

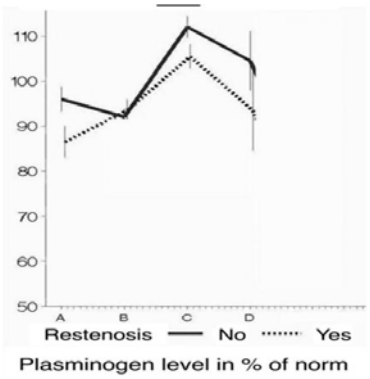

Figure 5: Plasminogen levels at time A-D.

one (time C, p=0.0068) and still on day three (time D, p= 0.0121) ((Figure 4), Fibrinogen changes relative to baseline in groups with/without restenosis).

Mean plasminogen levels were 351.8 mg/dl (⁺98.7) before and 283.1 mg/dl (⁺78.8) after PCI. By day one the mean level had risen to 363.3 (⁺90.6) and by day three it had reached 447.2 (⁺112.3). Plasminogen activity also decreased in both groups after PCI and reached normal levels on day one and were still normal by day three ((Figure 5), Mean plasminogen changes over time in groups with/without restenosis). This did not correlate to incidence of restenosis.

A multivariate analysis showed that classical risk factors for CAD (including hypertension, hypercholesterolemia, familial predisposition and smoking but excluding diabetes) did not have any influence on the incidence of restenosis after PCI with BMS in our study population. In patients with diabetes, restenosis after PCI occurred in 47.06% of cases (n=17) compared to 31.25 % of cases (n=64) without diabetes. However, due to the small sample size, this result did not reach statistical significance (p=0.258).

Discussion

Numerous studies have attempted to assess whether Lp (a) is a risk factor for restenosis after PCI with varying results. Most studies only measured baseline Lp (a) levels and did not consider a change in Lp (a) levels over time. In our study, we found that while absolute levels of Lp (a) were not associated with restenosis after PCI, they were higher in the group without restenosis although this result did not reach statistical significance. In agreement with Horie et al. who were first to demonstrate that patients with a more pronounced decrease in Lp (a) after PCI had significantly more restenosis [13], we also found a decrease in median Lp (a) levels to be the only risk factor in this study significantly associated with restenosis. In our study we also observed a larger decrease in median Lp (a) levels in the restenosis group compared to patients without restenosis. And Lp (a) levels in the restenosis group had not returned to baseline levels by day three.

Local thrombus formation at a vascular injury can be detected by examination of the PCI site of the coronary artery by Intravascular Ultrasound (IVUS) [14-16]. Numerous studies have shown that Lp (a) can bind to fibrin, enhance the effect of plasminogen and interact with the local fibrinolysis pathway. We measured fibrinogen levels in addition to the Lp(a) levels and found a significant decrease of fibrinogen after PCI with a return to baseline levels by day three. We interpreted this as a consumption of fibrinogen and of plasminogen by local thrombosis and fibrinolysis pathways due to the endothelial injury caused by PCI.

Lp (a) has the ability to bind to fibrinogen and to inhibit the fibrinolysis of a local thrombus formation. Because of the local thrombus, Lp (a) has the potential to be incorporated into the artery wall and to promote local neointimal growth [17,18]. The facts that Lp (a) had not reached baseline levels by day three and that even the fibrinogen levels were lower in the restenosis group could imply ongoing consumption at the site of vascular injury.

Conclusion

While Lp (a) is an established risk factor for CAD, it is unclear whether it also constitutes a risk factor for restenosis after PCI. Although several studies have shown Lp (a) to be a risk factor for Major Cardiac Adverse Events (MACE) after PCI, this result and its exact role remains controversial [4]. Until now, the mechanism for promoting neointimal growth by Lp (a) has not been fully explained. In our study, we demonstrate similar changes in Lp (a), plasminogen, and fibrinogen levels after PCI in all patients. Those with restenosis showed a larger decrease in median Lp (a) and fibrinogen levels and these levels did not reach baseline at day three postinterventional. We therefore hypothesise that there may exist a bridge between Lp (a) and the thrombosis and fibrinolysis pathways at the site of vascular injury after PCI to promote restenosis after PCI. In our study, the overall level of Lp (a) was not a risk factor for restenosis but the median change relative to baseline as well as the fact that median relevels had not reverted to baseline after three days were both significantly correlated to restenosis.

Declarations

Ethics approval and consent to participate

Prior to a patient's participation in the trial, the written informed consent was given from all patients. The ethic committee of the University of Bochum declared no objections to the implementation of the research project in 1998. (Statute of the Ethics Commissions of the Medical Faculty of the Ruhr-University Bochum of 27 May 1998).

Availability of Data and Material

The datasets used and/or analysed during the current study are available at the institutional bibliography of the University of Bochum. http://www-brs.ub.ruhr-uni-bochum.de/netahtml/HSS/Diss/SchulteMichael/diss.pdf

Authors' Contributions

MSH is the author of this manuscript. OKW, PS and MS assisted in writing the manuscript. All authors read and approved the final manuscript.

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