Acarbose improves fibrinolytic activity in patients with impaired glucose tolerance

Yuichi Shinoda¹, Ikuo Inoue²*, Takanari Nakano¹, Makoto Seo¹, Masatoshi Sassa², Sei-ichi Goto², Takuya Awata², Tsugikazu Komoda¹, Shigehiro Katayama²

¹Department of Biochemistry, Saitama Medical School, Saitama 350-0495, Japan
²Department of Diabetes and Endocrinology, Saitama Medical School, Saitama 350-0495, Japan

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Abstract

Acarbose has been shown to ameliorate insulinemia, suggesting that it may exert favorable effects on the impaired fibrinolytic state in prediabetic patients. We therefore conducted a randomized controlled study to examine the effects of acarbose on fibrinolysis in patients with impaired glucose tolerance (IGT). The participants were randomized to receive (n = 20) or not (control, n = 20) 100 mg of acarbose before each meal (300 mg/d) for 3 months. A marked decrease in the plasma levels of plasminogen activator inhibitor 1 (by 42%) and fibrinogen (by 27%) was observed in the acarbose group at the end of the study, whereas no significant changes in the levels of these parameters were observed in the control group. We also conducted postprandial evaluation of insulin-related clinical markers and found ameliorated hyperinsulinemia in the subjects treated with acarbose. These results indicate that acarbose could improve fibrinolysis in patients with IGT, mainly by ameliorating insulinemia. Other favorable effects of acarbose, such as reduction in the plasma levels of oxidized low-density lipoprotein, glucose toxicity, and hyperglycemia, might also contribute, at least in part, to the beneficial effects of the drug on the fibrinolytic state in patients with IGT.

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1. Introduction

Atherosclerosis is accelerated in diabetic patients and the resultant cardiovascular (CV) events are a major threat, especially in patients with type 2 diabetes mellitus, as they account for 40% to 50% of all deaths in this population [1]. Thus, appropriate control of dyslipidemia, hypertension, and hyperglycemia in diabetic patients is crucial [2,3], although macrovascular diseases remain an unresolved challenge in these patients. On the other hand, it has also been acknowledged that the pathogenesis of macrovascular diseases begins before the onset of overt diabetes [4]. This contention is supported by the findings that the glycemic severity and disease duration are not associated with the incidence of macrovascular complications [5] and that early intervention in the early course of the disease can decrease the risk of the above adverse consequences [6]. Accumulating evidence has shown that hyperinsulinemia plays a key role in the pathogenesis of macrovascular diseases in the prediabetic state [4]. A long period, sometimes several decades, of hyperinsulinemia precedes clinical type 2 diabetes mellitus, and consequently increased plasma levels of insulin may contribute to the hyperlipidemia and hypertension. There is also direct evidence that hyperinsulinemia predicts the development of coronary heart disease in nondiabetic populations.

Acarbose, an α-glucosidase inhibitor, retards glucose absorption and thereby reduces postprandial hyperglycemia [7,8]. The Study To Prevent Non-Insulin Dependent Diabetes Mellitus (STOP-NIDDM) [6,9] showed that treatment with acarbose prevented or delayed the conversion of impaired glucose tolerance (IGT), a prediabetic state characterized by moderate postprandial hyperglycemia, to overt type 2 diabetes mellitus [10]. A subanalysis in the same trial revealed that acarbose may also reduce the risk of CV disease in these patients [6]. It is noteworthy that a statistically significant reduction in the risk of CV disease was noted after acarbose treatment, even after adjustment for...
several factors, such as body weight, blood pressure, and lipid status, suggesting that these favorable effects of acarbose may be mediated by as yet unclarified mechanisms.

Acarbose has been shown to improve insulin sensitivity in patients with IGT [11], suggesting that it may reduce the risk of CV disease by ameliorating hyperinsulinemia. One of the other factors involved in the increased risk of CV disease in diabetic patients is the hypercoagulate state, characterized by increased plasma levels of the plasminogen activator inhibitor 1 (PAI-1), a fast-acting inhibitor of fibrinolysis, and fibrinogen. Based on the data above, it was considered that acarbose may improve fibrinolysis in patients with IGT because the serum levels of the above 2 molecules are considered to be correlated with the degree of insulinemia. However, data to prove this contention are still lacking. Therefore, we conducted a randomized controlled study to examine the effects of acarbose on the coagulable state of blood and CV risk reduction in patients with IGT by measuring the serum levels of various coagulation-related molecules in these patients.

2. Research design and methods

2.1. Subjects

The subjects of the study were recruited from among outpatients who visited our hospital between June 2000 and December 2002. Impaired glucose tolerance was diagnosed in the subjects according to the World Health Organization criteria after a 75-g oral glucose challenge [10]. Patients with clinically overt diabetes mellitus or under any medication were excluded from the study, and finally, 40 eligible patients with IGT were chosen for the study. All the participants were enrolled in an intensive dietary education program and encouraged to exercise regularly. The program included a 2-hour session with a dietitian who provided personalized recipes and written suggestions for eating out and instructions on food choices. The dietitian inspected the dietary record of each patient and reinforced these instructions once every month during the study period. All the subjects gave written informed consent before their participation in the study, which was conducted with the approval of the Ethics Committee of Saitama Medical School.

2.2. Study design

The participants were randomized to receive (n = 20) or not (control without placebo, n = 20) 100 mg of acarbose 30 minutes before each meal (300 mg/d) for 3 months. They were started on the drug at 100 mg once a day for a week, which was then gradually increased to 100 mg 3 times a day (300 mg/d) if no side effects were observed. Some of the patients showed gastrointestinal symptoms, such as flatulence during the first few weeks, but these symptoms were within tolerable limits in all the cases. None of the patients developed hypoglycemia or liver dysfunction during the study.

All the patients also underwent a standardized mixed meal test at 0, 1, and 3 months of the study. The meal was a standardized breakfast, the size of which was calculated individually to provide 30% of a subject’s total daily energy requirements with a macronutrient composition according to the nutritional recommendations of the American Diabetes Association (55%/15%/30% of energy from carbohydrate/protein/fat, respectively). The meal was consumed over a period of 15 minutes, and blood samples were drawn before (0 hour, at 9:00 AM) and 1 and 2 hours after the meal and assayed for plasma glucose, immunoreactive insulin, C-peptide, triglyceride, and free fatty acid using the following commercial kits: glucose CII Test Wako (Wako Pure Chemicals, Osaka, Japan); immunoreactive insulin, Ab Beads Insulin (Eiken, Tokyo, Japan); C-peptide kit (Daiichi Radioisotope, Tokyo, Japan); Triglyceride E Test Wako (Wako Pure Chemicals); and NEFA-C Test Wako (Wako Pure Chemicals), respectively. The plasma levels of proinsulin were determined by an in-house radioimmunoassay method [12].

Blood samples collected at 9:00 PM in the fasting state were also assayed for insulin-related and coagulation markers using commercially available kits, as follows: PAI-1 (PAI-1 ELISA kit, Monozyme, Hoersholm, Denmark); tissue plasminogen activator inhibitor (Imulyze t-PA, Biopool, Umea, Sweden); coagulation factor VIII–von Willebrand factor (vWF) complex (Asserachrom vWF, Boehringer Mannheim, Germany); fibrinogen (fibrinogen, BMY:1, Boehringer Mannheim); the plasma activity of coagulation factor VII (Chromoquick, Behringwerke, Marburg, Germany); and vWF (von Willebrand Reagent, Behringwerke).

2.3. Statistical analysis

Data were expressed as means ± SD. Differences between the mean measured values before and after the trial were assessed using the paired t test. We considered P values of less than .05 to be significant. All the analyses were performed using StatFlex, a statistical software package (Artech, Osaka, Japan).

3. Results and discussion

The demographic and blood biochemistry data of the subjects at baseline and at the end of the study are reported elsewhere [13]. Briefly, there were no significant differences in the data between the 2 groups. As has been shown for other populations, the patients with IGT had higher body mass index (27.5 ± 4.0 in the control group and 27.5 ± 3.8 in the acarbose group; mean ± SD), blood pressure (systolic and diastolic blood pressure: 157.3 ± 9.0 and 70.5 ± 7.0 mm Hg, respectively, in the control group and 158.5 ± 8.0 and 71.5 ± 7.2 mm Hg, respectively, in the acarbose group). Acarbose treatment reduced the body weight by 3.2%, body mass index by 3.3%, systolic blood pressure by 6.4%, diastolic blood pressure by 1.4%, total cholesterol by 6.1%, hemoglobin A1c by 3.5%, and plasma triglyceride...
by 28.5%. No differences in these parameters were, however, observed between before and after the study in the control group.

A marked decrease in the plasma levels of PAI-1 (by 42%) and fibrinogen (by 27%) was observed in the acarbose group at the end of the study, whereas no significant changes of these parameters were observed in the control group (Fig. 1A). In contrast, no significant differences in the plasma levels of tissue plasminogen activator, factor VII activity, factor VII–vWF antigen complex, or vWF activity were observed in either group (data not shown). Consistent with previous reports, there were significant decreases in the fasting plasma glucose by 25%, fasting plasma insulin by 56%, proinsulin by 40%, and C-peptide by 45% in the subjects of the acarbose group (Fig. 1B). These results suggest that acarbose might improve not only the insulin sensitivity, but also the fibrinolytic state in patients with IGT.

It has been suggested that acarbose improves insulin sensitivity by reducing glucose toxicity [14,15] and hyperinsulinemia [16]. Moreover, Qualmann et al [17] reported that acarbose could prolong the secretion of glucagon-like peptide 1, an incretin hormone that mediates parts of the enteroinsular axis to reduce the insulin and C-peptide levels. Considering that increased plasma PAI-1 levels have been linked to not only thrombosis and fibrosis, but also insulin resistance [18], these effects of acarbose may be mainly responsible for the decrease in the plasma PAI-1. However, improved insulin sensitivity by itself may not entirely explain the decrease in the plasma PAI-1 levels. In fact, metformin and troglitazone, both of which improve insulin sensitivity, failed to decrease both the plasma PAI-1 level and the fibrinogen level [19]. Thus, the effects of acarbose may be mediated by some other mechanisms.

As well as the improvement of insulin sensitivity, the decrease of body weight after acarbose administration is likely to be a key factor in the reduction of the plasma PAI-1 because adipose tissue is one of the major sites of PAI-1 production [20]. Hämäläinen et al [21] have shown that intensive lifestyle intervention for 1 year in patients with IGT decreased the body weight by 4.7 kg and the plasma...
PAI-1 level by 31%. In the present study, the subjects treated with acarbose lost 2.2 kg of body weight on the average during the 3 months of treatment that appears to account in part for the reduction. On the other hand, in the study by Hämäläinen et al. [21], the intensive lifestyle intervention resulted in no significant change in the plasma fibrinogen levels. Moreover, in another study, a weight loss of 13.6 kg resulted in only a 6% decrease of the plasma level of fibrinogen [22]. Thus, it does not appear that weight loss may have much influence on the decrease of the plasma fibrinogen levels.

One of the possible mechanisms for the improved fibrinolytic state is reduction of the low-density lipoprotein (LDL) toxicity by acarbose. In the same subjects, we also found that acarbose treatment ameliorated the oxidative susceptibility of LDL and enlarged the size of LDL molecules by enriching them with triglyceride [13]. Considering that oxidized LDL is a strong inducer of PAI-1 [23], it is possible that the inhibition of LDL oxidation by acarbose may be responsible for the decrease of the PAI-1 level. Moreover, analysis of the fatty acid composition of LDL showed that acarbose treatment significantly decreased the composition of n-6 fatty acids in LDL particles that cause endothelial cell dysfunction and injury [24], whereas those of n-3 fatty acids, which prevent CV disease, increased. It is possible that acarbose alters carbohydrate digestion products, including fatty acids from the colon, resulting in favorable changes of the fatty acid compositions [14]. In the present study, both plasma PAI-1 and fibrinogen levels substantially decreased, whereas other clinical studies with lifestyle intervention [21] and metformin and troglitazone therapy in type 2 diabetic population [19] did not obtain such improvements. Under physiologic conditions, PAI-1 is produced by only a few cells, liver cells, smooth muscle cells, adipocytes, and platelets, whereas fibrinogen is released from the hepatocytes. One of the common factors that the production of the 2 molecules are associated with is inflammatory conditions. In fact, both PAI-1 and fibrinogen are up-regulated by inflammatory cytokines. Thus, these decreases could be mediated by the ameliorated inflammatory status by acarbose treatment [25]. In fact, PAI-1 and fibrinogen are inflammatory markers and independent risk markers of CV disease. Moreover, we observed that plasma levels of glucose, triglyceride, and free fatty acid, which induce the production of reactive oxygen species [26,27], decreased during the postprandial period (Fig. 1B) in the acarbose-treated group that might suppress oxidative stress and improve the inflammatory state.

In conclusion, we found that acarbose markedly reduces the plasma PAI-1 and fibrinogen levels in subjects with IGT, suggesting that this drug may be a useful agent to improve fibrinolytic state and inflammatory states. These favorable effects may explain the reduced risk of CV disease in patients with IGT treated with acarbose.

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