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Nonesterified Fatty Acids, Albumin, and Platelet Aggregation

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It has been known for five decades that nonesterified fatty acids (NEFAs) have a role in the activation of platelets and thrombosis. Thus, the infusion of NEFAs leads to massive thrombosis and platelet activation (1–4). It has also been shown that their binding to albumin protects the platelets from activation (5). Thus, it follows that a fall in the concentrations of albumin, as in the nephrotic syndrome, would potentially lead to platelet activation. This has been demonstrated in several studies (6). Similarly, any condition that leads to an increase in NEFAs or a decrease in plasma albumin concentrations or a combination of the two would contribute to platelet hyperactivity. Insulin is a potent antilipolytic hormone and thus insulin-resistant states are characterized by accelerated lipolysis and increased NEFA concentrations. This promotes platelet aggregation. In addition, elevated NEFA concentrations interfere with insulin signal transduction and induce insulin resistance (7). NEFAs also induce oxidative and inflammatory stress (8) and thus activate monocytes, which express the prothrombotic tissue factor (TF) on their cell membranes (9). TF activates the extrinsic pathway of thrombin generation and hence may precipitate thrombosis. Activated platelets in patients with diabetes and peripheral vascular disease also release 5-hydroxytryptamine (5-HT), which leads to an increase in plasma 5-HT concentrations, which in turn promotes further vasoconstriction causing further platelet hyperaggregability (10).

It is also important to emphasize the fact that as increased NEFAs induce insulin resistance, the action of insulin at the cellular and molecular level would also be reduced. Insulin exerts a potent antiplatelet effect (11), and the presence of insulin resistance would potentially enhance platelet aggregation. The antiplatelet effect of insulin is mediated by nitric oxide (NO) generated by intraplatelet NO synthase (12). Reactive oxygen species generated by the action of NEFAs would oxidize NO to its metabolites, peroxynitrite, NO_2, and NO_3. These actions of NEFA have already been shown to impair flow-mediated vascular dilation within 2 h of their infusion (8). In addition, it has been shown that an increase in NEFA concentrations and a decrease in albumin concentrations reduce the stability of prostacyclin generated by the endothelium (13), which is a potent inhibitor of platelet aggregation and modulates platelet activity in the circulation. In addition, vascular ADPase activity, which inhibits ADP-induced platelet aggregation, is also inhibited by NEFAs (14). Thus, two potent antiplatelet modulators from vascular tissue are inhibited by NEFAs. NEFAs also inhibit prostacyclin production by aortic segments in vitro (15). In these three aspects, unsaturated fatty acids exert a significantly greater effect than saturated fatty acids.

Following the demonstration that NEFAs induce oxidative and inflammatory stress, it was also shown that an infusion of NEFA results in a hypertensive effect (16). Such an effect would promote atherogenesis. Thus, NEFAs induce several effects detrimental to platelet function and cardiovascular health.

It is in the context of these previous observations that Blache et al. (17) have now investigated the paradigm that the glycation or glycoxidation of albumin is relevant to NEFA-related pathophysiology as such modifications of albumin would potentially result in an impaired binding to NEFAs and an increase in unbound NEFAs and thus to platelet hyperactivity. The authors have shown that glycation of albumin induced in vitro with glucose or methylglyoxal, an advanced glycation end product, leads to

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COMMENTARY

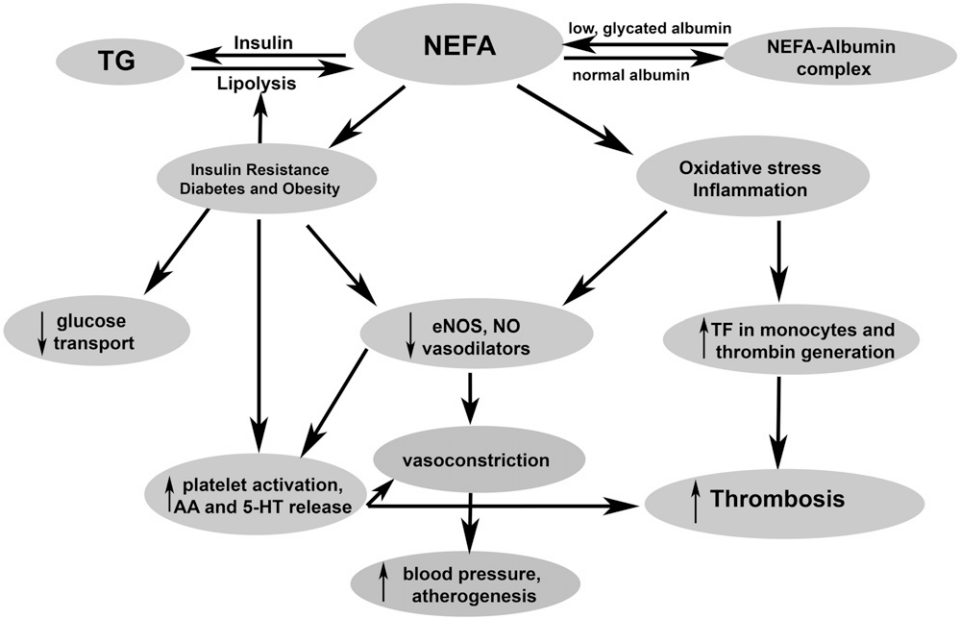

Figure 1—Role of NEFAs in prothrombotic state in insulin resistance and diabetes. eNOS, endothelial nitric oxide synthase.

a reduction in the binding of NEFA to albumin; these changes were similar to those observed in albumin prepared from patients with diabetes. The NEFA binding capacity of albumin isolated from patients with diabetes was lower by 32%. In addition, there were similarities in structural changes induced in vitro to those observed in albumin obtained from patients with diabetes, as analyzed with sophisticated fluorescence techniques.

An increase in NEFA concentrations promotes the oxidation of the Cys^{34} in the albumin molecule and consequent reduction of albumin's antioxidant capacity, which leads to a further decrease in NEFA binding sites and the activation of platelets. Such activated platelets lead to a greater release of arachidonic acid (AA) and its metabolites, cyclooxygenase and lipoxygenase products, after stimulation and thus result in a greater magnitude of aggregatory response to AA. Blache et al. studied the ability of albumin isolated from patients with type 2 diabetes or that of modified albumin (by glucose or methylglyoxal) to inhibit thrombin-induced platelet aggregation. In both the cases, the ability of albumin to block platelet aggregation was reduced by ~50% as compared with normal albumin. It is likely that the ability of modified albumin to sequester platelet-derived NEFAs, such as AA, is diminished, thus accounting for its decreased ability to inhibit platelet aggregation.

It is important to note that the mean HbA_{1c} of patients in the study by Blache et al. was 9.3 ± 1.4%. For the in vitro experiments, albumin was modified after incubation with very high glucose concentrations (25 mmol/L). It is not clear if the study results will be applicable to patients with diabetes with a lesser degree of hyperglycemia or in patients with prediabetes. Studies in those populations will be needed to ascertain if albumin is modified to a significant degree and has lower NEFA binding capacity.

Thus, there are multiple mechanisms that may predispose patients with diabetes to a prothrombotic state (Fig. 1). Clearly, an increase in NEFA concentrations promotes platelet aggregation and thus contributes to the prothrombotic state in diabetes. Albumin concentrations also play a cardinal role in the regulation of unbound NEFAs, including platelet-derived AA, and thus a concomitant fall in albumin concentrations enhances the proaggregatory and prothrombotic milieu characterizing diabetes. In addition, the effect of NEFAs on oxidative and inflammatory stress is also proatherogenic.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

References

1. Connor WE, Hoak JC, Warner ED. Massive thrombosis produced by fatty acid infusion. J Clin Invest 1963;42:860–866
2. Hoak JC, Warner ED, Connor WE. Platelets, fatty acids and thrombosis. Circ Res 1967;20:11–17
3. Hoak JC, Spector AA, Fry GL, Warner ED. Effect of free fatty acids on ADP-induced platelet aggregation. Nature 1970;228:1330–1332
4. Burstein Y, Berns L, Heldenberg D, Kahn Y, Werbin BZ, Tamir I. Increase in platelet aggregation following a rise in plasma free fatty acids. Am J Hematol 1978;4:17–22
5. Nordøy A. Albumin-bound fatty acids, platelets and endothelial cells in thrombogenesis. Haemostasis 1979;8:193–202
6. Barbano B, Gigante A, Amoroso A, Cianci R. Thrombosis in nephrotic syndrome. Semin Thromb Hemost 2013;39:469–476
7. Boden G, Lebed B, Schatz M, Homko C, Lemieux S. Effects of acute changes of plasma free fatty acids on intramyocellular fat content and insulin resistance in healthy subjects. Diabetes 2001;50:1612–1617

8. Tripathy D, Mohanty P, Dhindsa S, et al. Elevation of free fatty acids induces inflammation and impairs vascular reactivity in healthy subjects. Diabetes 2003; 52:2882–2887
9. Mach F, Schönbeck U, Bonnefoy JY, Pober JS, Libby P. Activation of monocyte/macrophage functions related to acute atheroma complication by ligation of CD40: induction of collagenase, stromelysin, and tissue factor. Circulation 1997;96:396–399
10. Barradas MA, Gill DS, Fonseca VA, Mikhailidis DP, Dandona P. Intraplatelet serotonin in patients with diabetes mellitus and peripheral vascular disease. Eur J Clin Invest 1988;18:399–404
11. Trovati M, Anfossi G, Cavalot F, Massucco P, Mularoni E, Emanuelli G. Insulin directly reduces platelet sensitivity to aggregating agents. Studies in vitro and in vivo. Diabetes 1988;37:780–786
12. Trovati M, Anfossi G, Massucco P, et al. Insulin stimulates nitric oxide synthesis in human platelets and, through nitric oxide, increases platelet concentrations of both guanosine-3′, 5′-cyclic monophosphate and adenosine-3′, 5′-cyclic monophosphate. Diabetes 1997;46:742–749
13. Mikhailidis DP, Mikhailidis AM, Barradas MA, Dandona P. Effect of nonesterified fatty acids on the stability of prostacyclin activity. Metabolism 1983;32:717–721
14. Barradas MA, Mikhailidis DP, Dandona P. The effect of non-esterified fatty acids on vascular ADP-degrading enzyme activity. Diabetes Res Clin Pract 1987;3:9–19
15. Jeremy JY, Mikhailidis DP, Dandona P. Simulating the diabetic environment modifies in vitro prostacyclin synthesis. Diabetes 1983;32:217–221
16. Umpierrez GE, Smiley D, Robalino G, et al. Intravenous intralipid-induced blood pressure elevation and endothelial dysfunction in obese African-Americans with type 2 diabetes. J Clin Endocrinol Metab 2009;94:609–614
17. Blache D, Bourdon E, Salloignon P, et al. Glycated albumin with loss of fatty acid binding capacity contributes to enhanced arachidonate oxygenation and platelet hyperactivity: relevance in patients with type 2 diabetes. Diabetes 2015; 64:960–972