



# LUND UNIVERSITY

## **Resialylation of sialic acid deficit vascular endothelium, circulating cells and macromolecules may counteract the development of atherosclerosis: A hypothesis.**

Lindberg, Gunnar

*Published in:*  
Atherosclerosis

*DOI:*  
[10.1016/j.atherosclerosis.2007.03.011](https://doi.org/10.1016/j.atherosclerosis.2007.03.011)

2007

[Link to publication](#)

*Citation for published version (APA):*

Lindberg, G. (2007). Resialylation of sialic acid deficit vascular endothelium, circulating cells and macromolecules may counteract the development of atherosclerosis: A hypothesis. *Atherosclerosis*, 192(2), 243-245. <https://doi.org/10.1016/j.atherosclerosis.2007.03.011>

*Total number of authors:*  
1

### **General rights**

Unless other specific re-use rights are stated the following general rights apply:

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

Read more about Creative commons licenses: <https://creativecommons.org/licenses/>

### **Take down policy**

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

LUND UNIVERSITY

PO Box 117  
221 00 Lund  
+46 46-222 00 00



LUND UNIVERSITY  
Faculty of Medicine

---

# LU:*research*

*Institutional Repository of Lund University*

---

This is an author produced version of a paper published in Atherosclerosis. This paper has been peer-reviewed but does not include the final publisher proof-corrections or journal pagination.

Citation for the published paper:  
Lindberg, Gunnar.

"Resialylation of sialic acid deficit vascular endothelium, circulating cells and macromolecules may counteract the development of atherosclerosis: A hypothesis."

Atherosclerosis, 2007, Vol: 192, Issue: 2, pp. 243-5.

<http://dx.doi.org/10.1016/j.atherosclerosis.2007.03.011>

Access to the published version may  
require journal subscription.  
Published with permission from: Elsevier

Resialylation of sialic acid deficit vascular endothelium, circulating cells and macromolecules may counteract the development of atherosclerosis: A hypothesis.

Gunnar Lindberg, M.D., Ph.D.

The NEPI Foundation (the Swedish Network for Pharmacoepidemiology)

Correspondence to: The NEPI Foundation, Clinical Research Centre, Malmö University Hospital, 205 02 Malmö, Sweden.

## **Abstract**

Deficit sialylation of vascular endothelium, circulating cells and macromolecules has been associated with the development of atherosclerosis. On the other hand, an elevated serum level of sialic acid is a long-lasting marker of atherosclerosis and complications from atherosclerosis. One may speculate that the inverse associations with atherosclerosis risk are due to some common underlying cause. One mission for the elevated serum sialic acid level might be to act as a substrate for resialylation of sialic acid deficit structures and thereby counteract the atherosclerotic process.

## **Introduction**

Human sialic acids (SA) are N-acetylated derivates of neuraminic acid that are abundant terminal monosaccharides of glycoconjugates. A significant quantity of serum SA constitutes parts of glycoproteins, e.g., orosomucoid, alpha 1-antitrypsin and haptoglobin and of lipoproteins and complement proteins [1].

SA are attributed a number of biological functions; they impart a net negative charge to cell surfaces and are important in cell-to-cell or cell-to-matrix interactions; they have ability to mask specific cellular recognition sites; they play an important role in the transfer of biological information, they are often parts of antigenic determinants of glycoproteins or glycolipids and they can affect the macromolecular structure of glycoconjugates [2].

Vascular endothelium most likely depends on sufficient sialylation to protect from atherosclerosis, i.e., atherosclerotic lesions are most frequent at low-sialylated areas of aortic endothelium and removal of SA from the intima of rabbit aorta by the action of neuroaminidase increases the adhesion of circulating platelets as well as the uptake of low

density lipoprotein (LDL) and fibrinogen [3-5]. Also, insufficient sialylation of circulating macromolecules may contribute to their atherosclerotic prosperities. In vitro desialylated LDL, as well as SA deficit LDL from atherogenic patients, are more rapidly accumulated in human aortic intimal smooth muscle cells as compared to non-desialylated LDL and LDL from healthy donors respectively [6]. According to Bastida and colleagues, asialo von Willebrand factor enhances platelet adhesion to vessel subendothelium [7]. Hadengue and colleagues found an inverse association between serum SA level and erythrocyte membrane SA content [8]. They concluded that decreased erythrocyte membrane SA content might participate in the development of atherotrombotic complications.

However, high serum level of SA is a determinant of atherosclerosis and complications from atherosclerosis. My colleges and I have reported positive associations, lasting for twenty years, between elevated serum SA level and of deaths from myocardial infarction and stroke [9,10]. We also have reported a significant positive association between asymptomatic carotid atherosclerosis measured by B-mode ultrasound and serum SA level [11].

Other investigators have attained similar results. During 17 years of follow-up of western Australians free from cardiovascular disease at baseline, the risk of coronary artery disease was positively associated with serum SA level [12]. Further, Watts and colleagues reported an association for serum SA level with change in coronary artery disease [13].

Thus, SA-deficit vascular endothelium, circulating cells and macromolecules as well as excess level of serum SA is associated with atherosclerosis risk. One may speculate that the inverse associations with atherosclerosis risk are due to some common underlying cause. One task for the elevated serum SA level might be to act as a substrate for resialylation of SA-deficit structures and thereby counteract the atherosclerotic process.

One major step in resialylation is the activity of sialyltransferase. Recently, Gracheva and co-workers reported that sialyltransferase activity of human plasma and aortic intima is enhanced in atherosclerosis [14]. Although they assumed that the increase in sialyltransferase activity might be related to the pathological processes in atherosclerosis, this does not leave out the possibility that the enzyme activity participate in resialylation.

Resnitzky and co-workers provides one more example of possibly resialylation. The SA content of erythrocyte membranes is essential for the electrophoretic mobility of erythrocytes. In the seventies, Resnitzky and colleagues reported low electrophoretic mobility of erythrocytes from patients with atherosclerotic complications. When incubated in plasma

from healthy donors, the electrophoretic mobility returned to normal [15]. Their results indicate the existence of a plasma factor affecting the electric charge of erythrocytes. It is possible that this plasma factor transfers SA from a plasma substrate to erythrocyte membranes and thereby restores the negative charge of the membrane. Later, Kelm and co-workers reported in vitro resialylation of erythrocytes [16].

The impact from pharmacological drugs on serum levels of SA and possibly resialylation is not investigated. However, many common drugs are anti-inflammatory and thereby may possess the ability to lower the serum concentration of SA-containing acute phase glycoproteins.

Thus, anti-inflammatory drugs have been associated with an elevated cardiovascular risk. A recent observational study reported a significantly increased risk of first myocardial infarction in users of most non-steroid anti-inflammatory drugs (NSAID) [17]. Further, in the APPROVE trial, the relative risk of myocardial infarction in users of rofecoxib was 2.8 compared with placebo [18]. An increased risk of serious cardiovascular events has also been reported for celecoxib when used in a clinical trial [19].

Influence on blood pressure and increased thrombotic risk by altering the COX-1 / COX-2 balance has been suggested as causes of the cardiovascular risk associate with NSAID [20]. The present hypothesis adds the possibility that NSAID, due to their anti-inflammatory property, reduce the availability of SA and possibly also other compounds necessary for resialylation.

However, low-dose aspirin (acetylsalicylic acid) is widely used to prevent thrombosis and myocardial infarction. The mechanism mediated by aspirin is believed to be via irreversible inhibition of COX-1-mediated platelet aggregation [21]. Apparently, the low dose of aspirin used to prevent cardiovascular events does not interrupt resialylation. Also, the anti-inflammatory effect of statins, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may be too weak or not specific enough to seriously affect resialylation.

One may object that atherosclerosis is a process of advanced age and therefore counteracting atherosclerosis has low evolutionary priority. However, lipid accumulation in the vascular wall starts in early life and the development of advanced atherosclerotic lesions may be successfully inhibited by resialylation [22].

## **The hypothesis**

Based on the observations given above, it may be hypothesised that a fraction of the elevated serum level of sialic acid observed in subjects with elevated risk of atherosclerosis and complications from atherosclerosis originate from a SA providing substrate for resialylation of SA deficit structures. The postulated substrate provider may be a glycoside or glycoprotein. Indeed, the serum levels of several glycoproteins are elevated in sera from atherosclerotic subjects. My colleagues and I have previously reported elevated levels of serum orosomucoid, haptoglobin and alpha-1-antitrypsin in asymptomatic carotid artery atherosclerosis [11].

The following mechanism for development and prevention of atherosclerosis and complications from atherosclerosis involving desialylation and resialylation is suggested:

i) Desialylation of vascular endothelium, circulating cells and macromolecules enhance the formation and rupture of atherosclerotic plaques due to disturbed endothelial function and enhanced migration, adherence and endothelial uptake of monocytes. Further, intima macrophage uptake of desialylated LDL as well as adherence of platelets and fibrinogen to dysfunctional endothelium may promote subendothelium lipid accumulation and formation of thrombus respectively. ii) Macrophage cytokines from the atherosclerotic lesions trigger liver synthesis and release of sialylated glycoproteins. iii) Liver released sialylated glycoproteins or glycolipids provide substrate for resialylation of desialylated vascular endothelium, circulating cells and macromolecules and thereby counteracting the atherosclerotic and thrombotic processes.

## **Hypothesis testing**

The effect by desialylation on endothelial function and on the development of atherosclerosis may be tested in animal models. The possibly resialylation of sialic acid deficit compounds may be confirmed in vitro (in the presence of plasma) and in vivo by use of free radioactivity labelled SA and also by use of SA donors such as glycoproteins and glycolipids with radioactivity labelled SA.

The impact on atherosclerosis may be indirectly tested in animal models by blocking one or more steps in the purposed pathway of resialylation. Most straightforward would be to block the transfer of SA from circulating glycoproteins or glycolipids. Transfer of SA probably involves acting of a specific sialyltransferase. Blocking the transferase activity may result in a more rapid development of atherosclerotic lesions and thrombus formation. Another step to

block may be the action of macrophage cytokines on the liver synthesis of SA rich glycoproteins and thereby lower the output of SA compounds from the liver. Also, more unspecific actions to lower the concentration of sialylated glycoproteins and glycolipids may be utilised. The hypothesis of resialylation is supported if these interventions accelerate the development of atherosclerotic lesions. However, until the mechanism of possibly resialylation is further understood, it may be too early to identify interventions appropriate for enhancing the resialylation of SA deficit structures.

## References

- 1 Lindberg G, Råstam L, Gullberg B, Lundblad A, Nilsson-Ehle P, Hanson BS. Serum concentrations of total sialic acid and sialoglycoproteins in relation to coronary heart disease risk markers. *Atherosclerosis* 1993;103:123–9.
- 2 Schauer R. Chemistry, metabolism, and biological functions of sialic acids. *Adv Carbohydr Chem Biochem* 1982;40:131–234.
- 3 Görög P, Born GV. Uneven distribution of sialic acids on the luminal surface of aortic endothelium. *Br J Exp Pathol* 1983;64:418–24.
- 4 Görög P, Schraufstatter I, Born GVR. Effect of removing sialic acids from endothelium on the adherence of circulating platelets on arteries in vivo. *Proc R Soc Lond B Biol Sci* 1982;214:471–80.
- 5 Görög P, Born GVR. Increase uptake of circulating LDL and fibrinogen by arterial walls after removal of sialic acids from their endothelial surface. *Br J Exp Pathol* 1982;63:447–51.
- 6 Orekhov AN, Tertov VV, Mukhin DN, Mikhailenko IA. Modification of low density lipoprotein by desialylation causes lipid accumulation in cultured cells: Discover of desialylated lipoprotein with altered cellular metabolism in the blood of atherosclerotic patients. *Biochem Biophys Res Commun* 1989;162:206–11.
- 7 Bastida E, Monteagudo J, Ordinas A, De Marco L, Castillo R. Asialo von Willebrand factor enhances platelet adhesion to vessel subendothelium. *Thromb Haemost* 1988;60:30–4.
- 8 Hadengue A, Razavian SM, Del-Pino M, Simon A, Levenson J. Influence of sialic acid on erythrocyte aggregation in hypercholesterolemia. *Thromb Haemostas (Stuttgart)* 1996;76:944–9.

- 9 Lindberg G, Eklund GA, Gullberg B, Råstam L. Serum sialic acid concentration and cardiovascular mortality. *BMJ* 1991;302:143–6.
- 10 Lindberg G, Råstam L, Gullberg B, Eklund GA. Serum sialic acid concentration predicts both coronary heart disease and stroke mortality: multivariate analysis including 54, 385 men and women during 20.5 years follow-up. *Int J Epidemiol* 1992; 21: 253–7.
- 11 Råstam L, Lindberg G, Folsom AR, Burke GL, Nilsson-Ehle P, Lundblad A. Association between serum sialic acid concentration and carotid atherosclerosis measured by B-mode ultrasound. *Int J Epidemiol* 1996;22:953–8.
- 12 Knuiman MW, Watts GF, Divitini ML. Is sialic acid an independent risk factor for cardiovascular disease? A 17-year follow-up study in Busselton, Western Australia. *Ann Epidemiol* 2004 ;14:627–32.
- 13 Watts GF, Crook MA, Haq S, Mandalia S. Serum sialic acid as an indicator of change in coronary artery disease. *Metabolism* 1995;44:147–8.
- 14 Gracheva EV, Samovilova NN, Golovanova NK, Il'inskaya OP, Tararak EM, Malyshev PP, Kukharchuk VV, Prokazova NV. Sialyltransferase activity of human plasma and aortic intima is enhanced in atherosclerosis. *Biochim Biophys Acta* 2002;1586:123–8.
- 15 Resnitzky P, Yaari A, Danon. Biophysical characteristics of erythrocytes during acute myocardial infarction and venous thrombosis. *Thromb Diath Haemorrh* 1972;28:524–32.
- 16 Kelm S, Shukla AK, Paulson JC, Schauer R. Reconstitution of the masking effect of sialic acid groups on sialidase-treated erythrocytes by the action of sialyltransferases. *Carbohydr Res* 1986;149:59–64.
- 17 Helin-Salmivaara A, Virtanen A, Vesalainen R, Gronroos JM, Klaukka T, Idanpaan-Heikkila JE, Huupponen R. NSAID use and the risk of hospitalization for first myocardial infarction in the general population: a nationwide case-control study from Finland. *Eur Heart J*. 2006;27:1635-6.
- 18 Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, Lines C, Riddell R, Morton D, Lanis A, Konstam MA, Baron JA; Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial Investigators. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med*. 2005;352:1092-102.
- 19 Solomon SD, McMurray JJ, Pfeffer MA, Wittes J, Fowler R, Finn P, Anderson WF, Zauber A, Hawk E, Bertagnolli M; Adenoma Prevention with Celecoxib (APC) Study



Investigators. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med*. 2005;352:1071-80.

20 Antman EM, DeMets D, Loscalzo J. Cyclooxygenase inhibition and cardiovascular risk. *Circulation*. 2005;112:759-70.

21 FitzGerald GA, Sherry S. Pharmacology and pharmacokinetics of platelet-active drugs under current clinical investigation. *Adv Prostaglandin Thromboxane Leukot Res*. 1982;10:107-72.

22. Strong JP, Malcom GT, McMahan CA, Tracy RE, Newman WP 3rd, Herderick EE, Cornhill JF. Prevalence and extent of atherosclerosis in adolescents and young adults: implications for prevention from the Pathobiological Determinants of Atherosclerosis in Youth Study. *JAMA* 1999;281:727–35.