Characteristics of Adiponectin and Coronary Plaque – An Intravascular Ultrasound Study

a report by

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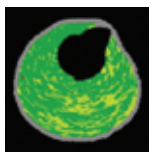
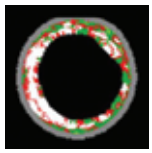
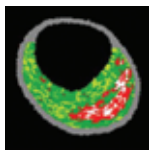
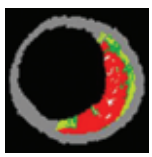
Adiponectin (also known as APM1, Acrp 30, AdipoQ or GBP28) is a 30kD circulating plasma protein and is the most abundant adipokine secreted by adipose tissue. In humans, adiponectin accounts for approximately 0.01% of circulating plasma proteins.[1] It is thought to have a unique spectrum of properties for an adipokine, many of which are anti-atherosclerotic, and is downregulated in the presence of increasing central adiposity. Low levels have been shown to be associated with inflammation, risk of metabolic syndrome, decreased low-density lipoprotein (LDL) cholesterol particle size and small dense high-density lipoprotein (HDL) cholesterol, as well as insulin resistance,[2] type 2 diabetes,[3] lipid oxidation[4] and risk of myocardial infarction. Increased levels have also been associated with reduced risk of myocardial infarction even following adjustment for traditional cardiovascular risk factors.[5]

Adiponectin is thought to be involved in foam cell transformation. Although extensively studied, lipid accumulation in the vessel wall is incompletely understood. It is believed that transport of lipoproteins across the endothelial cell monolayer is an initial step in atherogenesis and is also likely enhanced in the presence of oxidised LDL cholesterol. A biological association between adiponectin and atherosclerosis seems plausible. Adiponectin suppresses macrophage to foam cell maturation and induces the production of anti-inflammatory mediators, including interleukin-10 and interleukin-1 receptor antagonist.[6]

Figure 1: Plaque Phenotype Classification Using Intravascular Ultrasound–Virtual Histology (IVUS-VH) and Representative IVUS-VH Image of Each Phenotype

Lesion Type	Brief Description	Sample Frame
ID-AIT	<600μm thick on any IVUS frame. Histopathologically, this type of lesion is termed 'intimal xanthoma'.	
ID-PIT	>600μm thick and predominantly fibrous tissue with or without >15% fibrofatty tissue and without either confluent necrotic core or confluent dense calcium.	
ID-FC	>600μm thick and confluent dense calcium without confluent necrotic core.	
ID-FA	>600μm thick and confluent necrotic core not at the lumen or, if at the lumen surface, ≤14 pixels along lumen circumference on three consecutive frames with or without confluent dense calcium.	
ID-TCFA	>600μm thick, >50% plaque burden and confluent necrotic core extending >14 pixels along the circumference of the lumen on three consecutive frames with or without confluent dense calcium.	

Intravascular ultrasound (IVUS) provides transmural imaging of the coronary artery wall and assists with early detection of atherosclerosis. Virtual Histology™ (VH) is an emerging adjunct to IVUS that categorises atherosclerotic plaque into four distinct colour-coded components (green = fibrous; light green = fibrofatty; white = dense calcium; and red = necrotic core) using autoregressive modelling of radiofrequency data. To understand the association between adiponectin and human plaque composition, we studied a cohort of patients enrolled in the Diabetes Genome Project undergoing IVUS-VH.

Methods

In a recent analysis from the Diabetes Genome Project (clinicaltrials.gov identifier: NCT00428961), 185 patients underwent IVUS-VH and provided informed consent for the provision of biomarker data. The methods have been previously described.[6] Briefly, all IVUS frames within the pullback area comprised the region of interest for this analysis. IVUS frames were classified by plaque composition and phenotype (see *Figure 1*).

Results

Of the total study group, 66 patients had diabetes and 119 did not. Adiponectin levels correlated with age (r= 0.3; p<0.0001), body mass index (r=-0.17; p=0.02) and markers of insulin resistance, including homeostasis model assessment (r=-0.17; p=0.02) and fasting insulin (r=-0.20; p=0.008). There were no associations between adiponectin and diabetes, glycated haemoglobin (HbA_{1c}), fasting glucose or albuminuria.

There were significant associations between adiponectin and several lipoproteins, specifically triglycerides (r=-0.27; p=0.0002), HDL cholesterol (r=0.4; p<0.001), small, dense LDL_3 (r=-0.27; p=0.003) and LDL_4 (r=-0.25; p=0.0005) subfractions and the larger, more buoyant LDL_2 (r=0.18; p=0.015). The relationship between adiponectin and IVUS measures of atherosclerosis is shown in *Figure 2* and *Table 1*. In the total study group, plaque consisting of fibrofatty tissue declined with increasing adiponectin level (see *Figure 2*), mostly driven by the non-diabetic cohort (see *Table 1*). The association between fibrofatty volume and adiponectin was significant in non-diabetic (r=-0.23; p=0.009) but not diabetic patients. When classified by phenotype, the proportion of plaque identified as pathological intimal thickening also declined as adiponectin levels increased in the non-diabetic but not in the diabetic cohort (see *Figure 3*).

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Table 1: Plaque Composition by Adiponectin Quartile

Plaque Characteristic (mm^3)	Adiponectin Level (µg/ml)				
	0.91–3.53	3.54–6.0	6.1–9.3	9.31–50.1	p-value
No diabetes (n=119)					
Fibrous	122.2 (86.7, 220.2)	105.0 (66.2, 148.6)	86.6 (39.9, 119.3)	91.7 (58.8, 110.1)	0.02
Fibrofatty	44.2 (26.2, 68.1)	28.2 (15.7, 59.6)	24.7 (9.8, 44.3)	23.4 (15.0, 37.4)	0.01
Dense calcium	7.9 (2.7, 15.1)	14.0 (7.5, 24.6)	9.3 (2.7, 18.0)	10.0 (7.1, 25.3)	0.22
Necrotic core	16.6 (10.5, 31.1)	25.5 (10.8, 34.5)	12.1 (8.2, 23.5)	17.7 (12.0, 26.7)	0.21
Diabetes (n=66)					
Fibrous	81.9 (36.3, 124.0)	145.8 (61.0, 187.8)	94.6 (65.8, 146.1)	70.2 (56.1, 147.8)	0.36
Fibrofatty	23.0 (15.7, 54.6)	37.4 (16.6, 98.8)	32.1 (24.2, 46.9)	18.4 (11.3, 37.4)	0.13
Dense calcium	9.6 (2.4, 20.1)	17.3 (10.4, 30.8)	12.4 (7.7, 23.1)	18.2 (11.9, 38.0)	0.10
Necrotic core	16.6 (5.1, 29.3)	25.9 (18.6, 50.3)	17.5 (12.8, 40.7)	28.4 (14.7, 56.5)	0.11

Data are median (interquartile range).

Figure 2: Associations Between Adiponectin and Fibrofatty Volume Expressed as Continuous Values (A) and Stratified by Quartile Values of Adiponectin (B)

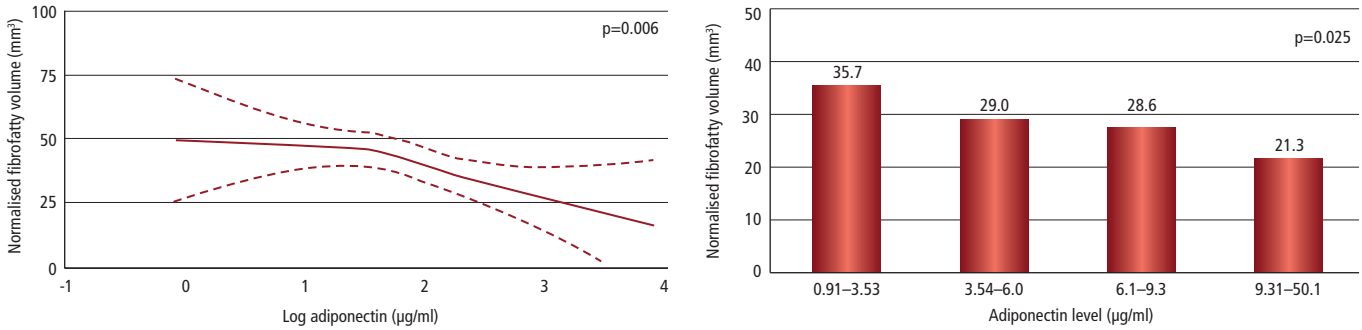
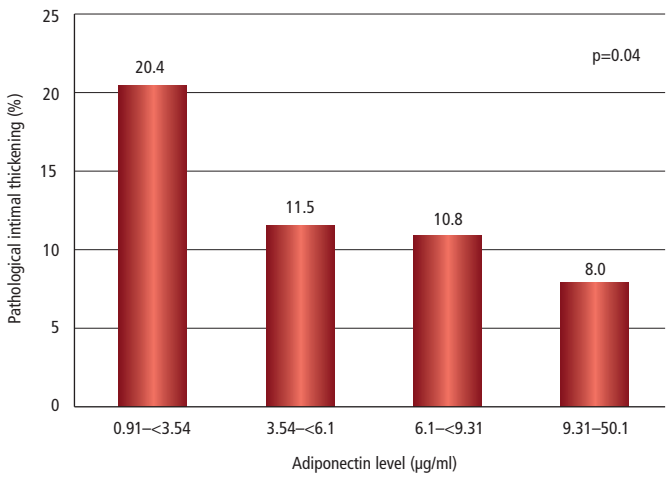


Figure 3: Association Between Quartiles of Adiponectin and Pathological Intimal Thickening in Non-diabetic Patients



Discussion

In this IVUS analysis from the Diabetes Genome Project, we found: correlations between adiponectin and quantitative IVUS measures of coronary atherosclerosis; a correlation between adiponectin and plaque lipid content; and a higher frequency of pathological intimal thickening in patients with lower adiponectin levels. These findings were seen mostly in non-diabetic patients. Our findings are also consistent with others[4] on the association between adiponectin and atherogenic dyslipidaemia, including elevated triglycerides, low HDL, and small dense LDL cholesterol.

Cardiovascular risk factors often precede the onset of diabetes. In addition to abdominal obesity, hypertension and hyperglycaemia, metabolic syndrome is characterised by low HDL cholesterol and high triglycerides.[7] In our study, adiponectin was associated with triglycerides and HDL cholesterol, suggesting a role for adiponectin in the development of atherosclerosis in patients with pre-diabetes.

Increasing presence of lipid is a distinguishing characteristic of coronary plaque classified as pathological intimal thickening.[8,9] Previously, Maahs and colleagues demonstrated low adiponectin levels to be associated with progression of coronary artery calcium in non-diabetic and type 1 diabetic patients.[10] In our cohort, pathological intimal thickening was more frequent in non-diabetic patients with lower adiponectin levels, thus supporting an indirect association between adiponectin and early atherosclerosis.

In summary, in a cohort of patients with coronary artery disease undergoing IVUS, lower levels of adiponectin are associated with atherosclerotic properties, especially in non-diabetic patients. These include small, dense LDL cholesterol, lipid accumulation in plaque and a higher prevalence of pathological intimal thickening – an early atherosclerotic plaque phenotype. ■

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