Serum adiponectin regulates vascular O2- generation and NO bioavailability in patients with coronary atherosclerosis

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Adiponectin

Prevents insulin resistance

Endocrine

Vascular effects in animal models

Adipose tissue

Endothelium

NO synthesis

Antioxidant effects

TNF-α induced ADMA production

Expression of adhesion molecules

How valid are these effects for human vessels

C Antoniades, et al Obes Rev 2009;10;269-279
The adiponectin’s paradox:
Circulating adiponectin as a biomarker

Koenig et al, JACC 2006; 48:1369–77


Unresolved issues:

• What regulates adiponectin’s expression in humans?

• Does adiponectin have an antiatherogenic effect in humans?

• Which sites of adipose tissue in human body are responsible for the circulating adiponectin’s pool?

• Does adiponectin affect vascular redox in humans (and vice-versa)?
Aim of the study

• To evaluate the possible impact of adiponectin on endothelial function in patients with atherosclerosis.

• To examine whether circulating adiponectin predicts vascular redox state in these patients, and to explore the underlying mechanisms.

• To define the endocrine/paracrine effect of adiponectin on vascular redox and endothelial function in humans.
Study design (Part 1)

320 patients with CAD undergoing CABG

Day before surgery:
- Blood samples obtained
- FMD in the brachial artery (ultrasound)

CABG

SV/IMA segments
- Vasomotor studies (organ bath)
  - Vasorelaxations to ACh/SNP

Vascular O2-:
- eNOS coupling/ NADPH oxidase activity (chemiluminescence)

Adipose tissue
- Subcutaneous Mesothoracic Perivascular
- Culture for 4 hours

Adiponectin’s biosynthetic rate (ELISA)
### Study population

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>N (males/females)</td>
<td>320 (255/65)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>67 +/- 2.3</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>66</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td></td>
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<tr>
<td>Active smokers</td>
<td>22</td>
</tr>
<tr>
<td>Ex smokers</td>
<td>45</td>
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<tr>
<td>Diabetes mellitus (%)</td>
<td>32</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>75</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>55.0 +/- 3.3</td>
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<tr>
<td>Extend of CAD</td>
<td></td>
</tr>
<tr>
<td>1 vessel disease</td>
<td>25</td>
</tr>
<tr>
<td>2 vessels disease</td>
<td>102</td>
</tr>
<tr>
<td>3 vessels disease</td>
<td>193</td>
</tr>
</tbody>
</table>
Adiponectin and endothelial function (vasomotor responses of SVGs)

Vasorelaxation (% of PE contraction)

Log(Ach) [M]

High

Log(SNP) [M]

Low

Medium

High
Adiponectin and endothelial function (in vivo – FMD)

Serum Adiponectin (tertiles)

FMD (%)

P<0.01

NTG (%)

P=NS

High  Medium  Low

High  Medium  Low
Adiponectin and total vascular O2-

**SV**

- Low
- Medium
- High

**IMA**

- Low
- Medium
- High

P = 0.001
Adiponectin and eNOS coupling

**SV**
- High adiponectin: Uncoupled NOS $\Rightarrow O_2^-$
- Medium adiponectin: $\Rightarrow O_2^-$
- Low adiponectin: $\Rightarrow O_2^-$

**IMA**
- High adiponectin: Coupled NOS $\Rightarrow NO$
- Medium adiponectin: $\Rightarrow NO$
- Low adiponectin: $\Rightarrow NO$

P-values:
- SV: $P=0.028$
- IMA: $P=0.001$
Adiponectin and NADPH-oxidase

NADPH-induced O2- (RLU/Sec/mg)

Serum Adiponectin (tertiles)

- Low
- Med
- High

P=0.01

SV

P=0.008

IMA

Serum Adiponectin (tertiles)
Sources of circulating adiponectin

- **Mesothoracic AT**: $r=0.530$, $p=0.0001$
- **Subcutaneous AT**: $r=0.316$, $p=0.03$
- **Perivascular AT**: $r=-0.047$, $p=0.784$

**Log [serum adiponectin] (μg/ml)**
Perivascular adiponectin and vascular O2-

![Graph showing the relationship between tertiles of adiponectin in perivascular adipose tissue and vascular O2- induction with NADPH.]
Is there a causal association between adiponectin and vascular redox?
Study design (Part 2)

10 patients with CAD undergoing CABG

CABG

SV segments

Ex-vivo protocol

Control

Adiponectin 10μmol/L

6 hours incubation

Vascular O2--
eNOS coupling/ NADPH oxidase activity
Causal effect of adiponectin on vascular O$_2^-$
Subcutaneous, Mesothoracic, visceral

Adiponectin

Endocrine

Remote effects in human vessels

Paracrine

Adiponectin

Local defence mechanism?

Discusion

Atherogenesis

↓$O_2^-$ generation

↑NO bioavailability

↓NADPH-oxidase

↑eNOS coupling

$\uparrow$eNOS coupling

↓$O_2^-$ generation

$\uparrow$NO bioavailability
Conclusions

This is the first study demonstrating that adiponectin has a direct impact on NO bioavailability in human vessels, by suppressing vascular $O_2^-$ generation via improvement of eNOS coupling in patients with atherosclerosis.
Paradoxically, perivascular adiponectin production is enhanced in the presence of increased vascular O2-generation, suggesting that a “message” from the vascular wall to the perivascular fat may trigger the synthesis of adiponectin, possibly as a “paracrine defense mechanism”.

Further studies are required to explore this complex association.
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Antoniades C et al; J Am Coll Cardiol 2009

SUM=746

HEALTHY (BMI<28) n=130

OBESE (BMI≥28) n=74

CAD (NORMAL LV) n=283

IHD (IMPAIRED LV) n=225

HF (NO CAD) n=34

Serum Adiponectin (μg/ml)

P<0.05

P<0.0001

P=NS

P<0.0001

P<0.0001

P<0.0001