



**Karolinska  
Institutet**

**Institutionen för medicinsk epidemiologi och biostatistik**

# **Adiponectin: Genetic determinants and relations with subclinical cardiovascular disease**

**AKADEMISK AVHANDLING**

som för avläggande av medicine doktorexamen vid Karolinska Institutet offentligen försvaras i Petrénsalen, Nobels väg 12B

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## ABSTRACT

Cardiovascular disease (CVD) is a major cause of morbidity and premature death in Sweden and globally, which besides the substantial individual suffering, puts large restraints on the public health system. Adiponectin is a highly heritable trait, which is strongly associated with metabolic disturbances such as obesity and insulin resistance. Previous studies indicate that adiponectin may play a fundamental role in the development of CVD. However, further knowledge about pathways linking circulating adiponectin, genetic loci, and markers of early CVD is needed. Therefore, the overall aim of this thesis was to assess the genetic determinants of adiponectin, and the role of adiponectin in the development of subclinical CVD.

In Study I, we investigated the association between adiponectin and cardiac geometry and function in two cross-sectional samples of elderly and found that high adiponectin levels were associated with poorer cardiac function in men. This association was dependent on N-terminal pro-brain natriuretic peptide and this was more pronounced in individuals with prior CVD, which could indicate a counter-active effect in response to decreased cardiac function, potentially mediated by natriuretic peptides.

In Study II, we examined the role of adiponectin in vascular pathology in a cross-sectional study design where higher adiponectin levels were associated with a lower lipid-content in plaques and higher vessel wall elasticity, indicating less arterial pathology.

In Study III, we assessed oxidative stress and inflammatory markers in relation to adiponectin, where adiponectin was positively associated with the anti-oxidant glutathione and inversely associated with lipid peroxidation as well as epidermal growth factor. Our findings suggest that adiponectin is associated with a more beneficial oxidative stress profile.

In Study IV, we explored the impact of rare genetic loci on circulating adiponectin levels on a genome-wide scale. Besides several independent variants around the adiponectin gene, we found a rare coding variant in a gene upstream of adiponectin receptor 2 that was associated with higher adiponectin levels. If replicated in an independent sample, these findings can provide new insight to adiponectin biology.

In conclusion, we found that individuals with poor cardiac function had higher levels of adiponectin and the results suggested that natriuretic peptides had an important role in a potentially counter-active mechanism. In contrast, high adiponectin levels were associated with a more beneficial arterial, oxidative stress and inflammation profile. Finally, rare variation around the adiponectin gene and a potentially novel locus upstream of the adiponectin receptor 2 gene was associated with adiponectin levels.

**Keywords:** adiponectin, cardiovascular disease, oxidative stress, inflammation, rare genetic variation.

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