

# May Adiponectin be considered as a Novel Cardiometabolic Biomarker?

## Abstract

This study was designed to evaluate the interaction between total adiponectin (ADPN) and metabolic syndrome (MetS) on cardiac changes in 135 subjects with and without MetS, subgrouped according to normal or low ADPN. Left ventricular internal diameter (LVID/h), LV mass (LVM), LVM index (LVMI), interventricular septal thickness (IVST), relative wall thickness (RWT) and LV ejection fraction (EF) by echocardiography and diastolic parameters, by pulsed-wave Doppler were calculated.

BMI, LVM, LVMI, LVID/h, IVST and RWT values were significantly ( $p < 0.05$ ) higher in both groups with low ADPN. Prevalence of left ventricular hypertrophy ( $p < 0.001$ ) and coronary artery disease ( $p < 0.01$ ) was significantly higher in both low ADPN groups. LVMI correlated directly with BMI ( $p < 0.001$ ), ( $p < 0.001$ ), MetS ( $p < 0.001$ ) and inversely with ADPN ( $p < 0.0001$ ). ADPN and BMI resulted independently associated with LVMI. In conclusion, our data suggest that hypo adiponectinemia might be considered a novel "cardiometabolic biomarker". Accordingly, circulating ADPN might become a new target in the management of cardiometabolic syndrome.

## Keywords

Adiponectin; Metabolic syndrome; Left ventricular hypertrophy

## Short Communication

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## Abbreviations

ADPN: Adiponectin; MetS: Metabolic Syndrome; BMI: Body Mass Index; WHR: Waist to Hip Ratio; MBP: Mean Blood Pressure; HDL-C: High Density Lipoprotein Cholesterol; LDL: Low Density Lipoprotein cholesterol; TC: Total Cholesterol; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; LVM: Left Ventricular Mass; LVMI: Left Ventricular Mass/height<sup>2.7</sup>; LVID/h: Left Ventricular Internal Diameter/height; IVST: Interventricular Septal Thickness; RWT: Relative Wall Thickness; LVEF: Left Ventricular Ejection Fraction; E/A: Peak early transmitral flow/peak late transmitral flow; DTE: E Deceleration Time; IVRT: Isovolumic Relaxation Time; pts: patients; LVH: Left Ventricular Hypertrophy; CAD: Coronary Artery Disease; BP: Blood Pressure; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure

## Introduction

Accumulation of intra-abdominal visceral fat stands upstream of various risk factors and dysfunction of adipocyte is considered the cellular basis of metabolic syndrome (MetS) [1-4]. Adiponectin (ADPN) is an adipocyte-specific protein abundantly present in the plasma. Since its discovery, numerous experimental and clinical studies have demonstrated that ADPN has anti-atherogenic, anti-diabetic and anti-inflammatory properties. However, plasma adiponectin levels are low in subjects with visceral fat accumulation and it seems to play an important role in the pathogenesis of visceral fat syndrome [1-3]. Our previous data [4] and some clinical studies reported an inverse association between ADPN and left ventricular mass (LVM) [1,5]. Moreover, increased ADPN expression can attenuate left ventricular hypertrophy (LVH) induced by pathological stimuli and it is able to protect the ischemic heart from injury, through the activation of independent pathways [1,2,4,5].

Despite these data, the role of ADPN on cardiometabolic disease has been previously studied only in patients with preexisting diseases, such as type 2 diabetes, hypertension and obesity. The present study has been designed to explain the interaction between ADPN and MetS on the cardiac damage. Accordingly, cardiac parameters and prevalence of LVH and coronary artery disease (CAD) have been evaluated in patients with and without MetS, subgrouped according to normal or low ADPN levels. The main goal of the study was to evaluate whether hypo adiponectinemia might be considered a "novel cardiometabolic biomarker".

## Subjects and Methods

### Subjects

Subjects eligible for the study were screened at the centre of hypertension and metabolic disease at the Department of Internal Medicine, University of Palermo (Italy). The study population consisted of 135 patients, 55 of them affected by MetS, according to NCEP/ATPIII criteria [6] and 80 of them without MetS, utilized as control subjects.

Each patient gave a written consent after received a detailed description of study procedure. The study was approved by Ethics Committee of our Institution. For all participants the clinic examination included interviews, anthropometry, BP measurements, resting electrocardiogram. Information regarding medical history, drug use, and alcohol and cigarette consumption was collected during a face-to-face interview using a standardized questionnaire. Subjects with psychiatric problems or alcoholism were excluded. We enrolled only untreated or patients on stable treatment in order to have the best possible "real" correspondence between obtained clinical measurements

(BP, glycemia etc.), LVM and pharmacological treatment. Body height, weight and waist circumference were all taken in a standardized manner [1,4]. Body mass index was calculated as weight divided by squared height and expressed as kg/m<sup>2</sup> and WHR by waist/hip ratio [4]. Blood pressure (BP) was measured according to current recommendations with an appropriate large cuff in obese subjects. Systolic (SBP), diastolic (DBP) and mean (MBP) were determined. MBP was calculated by the sum of DBP plus one third of pulse pressure. According to ADA guidelines all subjects with fasting glycaemia  $\geq 126$  mg/dl or treated with antidiabetic drugs or insulin were considered diabetics [7]. The IR homeostasis model assessment (HOMA), was used as an index of IR. The following comorbidities were also evaluated.

### Left ventricular hypertrophy

Subjects were considered with LVH on the basis of echocardiographic measurement of LVM normalized for height to the 2.7 power (LVMI) [8]. Accordingly, all the subjects with LVMI  $\geq 50$  g/m<sup>2.7</sup> for men and  $\geq 47$  g/m<sup>2.7</sup> for women were considered to have LVH.

### Coronary artery disease

According to guidelines of European Society of Cardiology [9] the diagnosis of CAD was supported by history, symptoms of typical angina, cardiac markers and specific cardiac examinations.

## Methods

### Biochemical measurements

Routine biochemical parameters were detected through standardized methods. An immunoradiometric assay with an insulin RIA kit (Biosource, Belgium) was used to measure serum insulin. The HOMA-IR was calculated using the following equation: HOMA-IR= Fasting insulin (pmol/L X Fasting glucose (mmol/L)/22.5. IR was defined as an HOMA-IR in the highest quintile of its distribution [7]).

The concentration of ADPN was obtained by a radioimmunoassay using a human ADPN RIA kit (LINCO Research, Inc., Billerica, MA, USA) as previously described [4]. Patients with and without MetS were further subdivided in four groups, according to level of ADPN, higher than or equal to 6  $\mu$ g/mL (normal ADPN groups) and less than 6  $\mu$ g/mL (low ADPN groups) (Table 1). This cut-off value was related to the mean value  $\pm$  double standard deviation (2SD) of ADPN in young healthy control sample (without a family history of premature cardiovascular disease) from our laboratory. ADPN cut-off values are in agreement with those reported by others [3].

### Echocardiographic measurements

M and B-mode computerized echocardiography (ESAOTE, Italy) was used to calculate the following parameters:

Left ventricular internal diameter/height (LVID/h), and interventricular septum thickness (IVST). LVM was normalized for height to the 2.7 power (LVMI). We chose to investigate LVH as defined by LVM/h<sup>2.7</sup> cut-offs because body surface area

correction reduces variability due to body size and gender and underestimates LVM in the upper range of the body surface area distribution [8].

The relative wall thickness (RWT) by formula [(PWTd/LVIDd) x2] and left ventricular ejection fraction (LVEF) were also calculated. In our laboratory LVEF calculated over five consecutive beats permitted optimal reproducibility and accuracy [4]. Diastolic parameters, such as E/A ratio, Isovolumic relaxation time (IVRT) and the deceleration time of E velocity (DTE) by Echo-Doppler examination were also calculated.

### Statistical Analysis

Data are shown as mean  $\pm$  SD. The Chi-square and the Fisher exact test were used for contingency table analysis. The Mann-Whitney U test was used for comparison between groups. Z test was used for comparison between two proportions. Linear regression analysis was performed to study relationship among independent variables and LVMI. Multiple fractional polynomial analysis was performed to study the best power fit between each independent variable and the dependent one. A two tailed p value  $<0.05$  was used as cut-off for statistical significance. STAT/SE, version 9.2 for Windows (StataCorp College Station, Texas), was used to analyze the data.

## Results

Our study population consisted of 135 subjects with or without MetS, subgrouped according to normal (groups 1 and 3) and low (groups 2 and 4) ADPN. Prevalence of MetS in our sample was 39.2%, despite age  $< 60$  years old. Clinical characteristics of the study groups, echocardiographic parameters and prevalence of LVH and CAD are shown in (Table 1). All the groups were comparable with regard to sex and age. The two MetS groups were also comparable for the prevalence of subjects with visceral obesity, hypertension, diabetes, low HDL-C and hypertriglyceridemia.

BMI ( $p<0.005$ ) was significantly higher in both groups with low ADPN than in groups with normal ADPN. Both groups with low ADPN were characterized by a significant increase ( $p<0.05$ ) of LVM, LVMI, LVID/h, IVST and RWT values than those detectable in both groups with normal ADPN. Prevalence of LVH ( $p<0.001$ ) and CAD ( $p<0.01$ ) was significantly higher in low ADPN groups than normal ADPN groups. The higher prevalence of LVH and CAD was not different in subjects with MetS and low ADPN respect to patients without MetS but with low ADPN (Table 1). LVMI correlated directly with BMI ( $r=0.34$ ;  $p<0.001$ ), MBP ( $r=0.29$ ;  $p<0.001$ ), MetS ( $r=0.28$ ;  $p<0.001$ ) and inversely with ADPN ( $r= -0.57$ ;  $p<0.0001$ ).

### Multiple regression analysis

Regression models were used to explain the interaction between ADPN and MetS and to test the independent role of risk factors for LVMI. ADPN resulted independently associated with LVMI both In the first model, including MetS, ADPN, age and gender (Table 2), "Model 1" and in "Model 2", including the single components of MetS (BMI, MBP, Diabetes, C-HDL

**Table 1:** Clinical characteristics, metabolic profile, echocardiographic parameters and prevalence of LVH and CAD in patients with and without metabolic syndrome, subgrouped according to normal (groups 1 and 3) and low (groups 2 and 4) plasma adiponectin levels.

	MetS n. 53		No MetS n. 82	
	Group 1	Group 2	Group 3	Group 4
Cases n.	28	25	67	15
Sex (M/F)	15/13	12/13	38/29	9/6
Age (yr)	52.7 ± 10.1	48.1 ± 6.8	51.0 ± 9.5	48.4 ± 5.5
ADPN (µg/ml)	8.3 ± 1.4	4.95 ± 0.6	9.1 ± 2.2	5.3 ± 0.7
BMI (Kg/m <sup>2</sup> )	29.2 ± 4.4	32.3 ± 3.5 §	28.0 ± 5.1	31.7 ± 3.4 §
WHR	0.92 ± 0.09	0.95 ± 0.07	0.90 ± 0.08	0.93 ± 0.09
MBP (mmHg)	106 ± 8.5	110 ± 13.6	105 ± 8.2	108 ± 12.2
Tryglycerides (mg/dl)	120.1 ± 62.3	129.5 ± 80.2	117 ± 55.2	120 ± 58.6
HDL-C (mg/dl)	48.2 ± 11.2	45.9 ± 9.2	49.1 ± 10	47.1 ± 10
TC (mg/dl)	189.0 ± 35.8	192.7 ± 35.4	182 ± 34.3	186 ± 38
LDL-C (mg/dl)	110.3 ± 37.5	112.2 ± 37.3	110.2 ± 35.3	113 ± 36.3
HOMA-IR	2.5 ± 1.4	3.3 ± 1.9	2.6 ± 1.3	3.2 ± 1.4
LVM (gr)	155.7 ± 35.3	204.1 ± 41.7§	152. ± 25.6	198. ± 31.4 §
LVMI (gr/ h <sup>2.7</sup> )	38.4 ± 8.9	54.9 ± 7.6 §	39.2 ± 67.6	53.0 ± 4.4 §
LVID/h (mm/h)	2.88 ± 0.18	2.98 ± 0.21 §	2.82 ± 0.20	3.0 ± 0.15 §
IVST (mm)	9.1 ± 1.7	11.4 ± 1.5 §	9.4 ± 1.9	10.8 ± 1.7 §
RWT	0.38 ± 0.05	0.47 ± 0.09 §	0.39 ± 0.06	0.40 ± 0.08 §
LVEF (%)	64.8 ± 1.5	62.4 ± 3.1	64.4 ± 2.7	63.4 ± 2.1
E/A	1.6 ± 0.4	1.4 ± 0.6	1.5 ± 0.6	1.4 ± 0.7
DTE (ms)	188 ± 31	198 ± 38	190 ± 33	195 ± 30
IVRT (ms)	81 ± 11	78 ± 10	84 ± 15	80 ± 16
LVH pts (%)	14.3 (4/28)	76 (19/25)*	7.5 (5/67)	80 (12/15)*
CAD pts (%)	21.4 (6/28)	40 (10/25)**	6.0 (4/67)	40 (6/15)**

ADPN: total plasma adiponectin; MetS: Metabolic Syndrome; BMI: Body Mass Index; WHR: Waist to Hip Ratio; MBP: Mean Blood Pressure; HDL-C: High Density Lipoprotein Cholesterol; LDL: Low Density Lipoprotein cholesterol; TC: Total Cholesterol; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; LVM: Left Ventricular Mass; LVMI: Left Ventricular Mass/height<sup>2.7</sup>; LVID/h: Left Ventricular Internal Diameter/height; IVST: Interventricular Septal Thickness; RWT: Relative Wall Thickness; LVEF: Left Ventricular Ejection Fraction; E/A: Peak early transmitral flow/peak late transmitral flow; DTE: E Deceleration Time; IVRT: Isovolumic Relaxation Time; pts: patients; LVH: Left Ventricular Hypertrophy; CAD: Coronary Artery Disease;

ANOVA: § p<0.05 vs groups 1 and 3

Z Test: \*p<0.001 vs groups 1 and 3; \*\*p<0.01 vs groups 1 and 3

and Tryglycerides). In model 2 BMI was also independently associated with LVMI (Table 2, model 2).

## Discussion and Conclusion

Adiponectin has been reported as an important modulator of the adipovascular axis that affects the cardiometabolic risk profile, from the premetabolic syndrome, through the MetS to overt atherosclerosis. Hypoadiponectinemia alone may represent an early phenomenon that long precede the occurrence of all components of overt MetS [1-3].

In addition, reduced ADPN is common in subjects with MetS [1-3]. It is currently considered a predictor of future cardiovascular events and also plays an important role in myocardial remodeling [1,4,5]. Recent data reported positive, inverse or no statistically significant association between ADPN and LVM [5]. Our principal novel findings are twofold. First, circulating ADPN is inversely and independently associated to LVMI. To our knowledge, our work is the first study addressed the evaluation of the changes in left ventricular geometry and prevalence of LVH and CAD in subjects with MetS, subgrouped according to normal or low ADPN. Secondly, the lack of a significant difference in LVH and

CAD prevalence in both low ADPN groups (with or without MetS) might indicate that circulating ADPN, rather than MetS, is able to explain cardiovascular damage in these patients. These data appear interesting, suggesting that hypo adiponectinemia might be considered a “novel cardiometabolic biomarker”.

This opinion might be further supported by the role of ADPN on left ventricular geometry by us demonstrated. In fact, in our population LVMI correlated positively with BMI, MBP and MetS and negatively with ADPN. Multiple regression analysis indicated that the LVMI/ADPN and LVMI/BMI relationships remained independent also when adjusted for MetS or for its single components. These data suggest that increased risk of LVH due to a presence of MetS seems mediated mainly by adiposity and circulating adiponectin which works as a non haemodynamic factor.

It has been previously demonstrated that MetS had a greater impact on LVH and its effect was partly independent from the effect of several determinants of LVM but it was not able to predict LVH independently of increased adiposity [1,2]. The independent LVMI/BMI relationship by us reported in this study might support

**Table 2:** Independent risk factors for LVMI assessed by multiple regression analysis.

Model 1		
LVMI	$\beta \pm SE$	p=
Age	0.22 $\pm$ 0.075	0.004
Gender	0.88 $\pm$ 1.3	0.511
MetS	0.99 $\pm$ 1.4	0.490
ADPN	-16.0 $\pm$ 1.4	<0.001
Constant	26.4 $\pm$ 4.1	<0.001
Model 2		
ADPN	-15.4 $\pm$ 1.5	<0.001
Gender	4.6 $\pm$ 0.7	0.006
BMI	0.59 $\pm$ 0.2	0.005
MBP	0.15 $\pm$ 0.01	0.167
HDL-C	0.20 $\pm$ 0.02	0.205
Tryglicerides	0.24 $\pm$ 0.01	0.266
Diabetes	0.10 $\pm$ 1.7	0.951
Age	0.23 $\pm$ 0.7	<0.001
Constant	36.1 $\pm$ 10.4	<0.001

Model 1: Included age, gender MetS and ADPN as covariates.

Model 2: Included all model 1 variables except MetS.

In addition single components of MetS were included.

LVMI: Left Ventricular Mass/height<sup>2.7</sup>; MetS: Metabolic Syndrome; ADPN: total plasma adiponectin; BMI: Body Mass Index; WHR: Waist to Hip Ratio; MBP: Mean Blood Pressure; HDL-C: High Density Lipoprotein Cholesterol

this hypothesis and although WHR, as a single component, was not an independent determinant of LVH in our analysis, there are increasing evidences that regional fat distribution could contribute to cardiac remodeling and hypertrophy [1,2,5].

Hypoadiponectinemia or functional adiponectin resistance, perhaps secondary to down regulation of adiponectin receptors, may contribute to an exaggerated hypertrophic response to haemodynamic load and to inappropriate LVH [1,2]. Another interesting aspect is related to the pathophysiologic role of ADPN on LVH. The common belief is that the mechanisms able to increase LVM are not limited to haemodynamic changes [4,5]. Thus, non haemodynamic mechanisms are likely to contribute to increase in LVM and wall thickness. In this field an important role has been attributed to adiponectin [1-5]. The negative ADPN-LVMI relationship by us found may also contribute to this mechanism and a lack of protective effects of ADPN might cause an increase in LVM. It has been experimentally shown that decreased ADPN may lead to LVH by directly affecting LVM and that an increase in ADPN may be effective in correcting the pathologic change in cardiac structure. Accordingly, ADPN administration might have a practical clinical application to restore LVH [10].

Some limitations of this study must be taken into account. First, although our study is relevant for an important condition commonly found in "real life" medical practice, the bias attributable to this type of study have to be considered. Second, it has been designed to be a cross-sectional study. Evaluation of the cause-effect relationship between hypoadiponectinemia and LVMI would require a prospective study design with a cohort base and larger casistics. Therefore, we cannot prove causality or predictive ability, but only discern association.

In conclusion, our data seem to indicate that low circulating ADPN might be considered a novel "cardiometabolic biomarker". In a particular subset of patients, characterized by the contemporaneous presence of MetS and hypoadiponectinemia, circulating ADPN, more than MetS, is able to explain the development of LVH and CAD. However clinical long term follow-up with large number of participants is needed to confirm if it is the case, also evaluating whether the increase in ADPN might be able to restore LVH. According to emerging data [10], circulating ADPN might become a new target in the management and treatment of cardiometabolic syndrome.

### What is known about topic

- Adiponectin has been reported as an important modulator of the adipovascular axis that affects the cardiometabolic risk profile, from the premetabolic syndrome, through the Metabolic Syndrome to overt atherosclerosis.
- Hypoadiponectinemia alone may represent an early phenomenon that long precede the occurrence of all components of overt Metabolic Syndrome.
- Adiponectin has anti-atherogenic, anti-diabetic and anti-inflammatory properties and it has been considered as an important pathophysiological determinant of left ventricular hypertrophy.

### What this study adds

- Subjects with low adiponectin plasma levels were characterized by a significant higher prevalence of cardiometabolic comorbidities.
- Adiponectin, more than metabolic syndrome, is able to explain cardiac damage and it might become a new target to reduce cardiometabolic risk.
- Hypoadiponectinemia might be considered as a novel cardiometabolic biomarker.

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