# ADIPONECTIN IS A STRONG MODIFIER OF THE DEATH RISK BY RESISTIN AND LEPTIN IN END STAGE KIDNEY DISEASE PATIENTS

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## *Objectives:*

The plasma concentrations of three major adipose tissue adipokines Adiponectin (ADPN), Leptin and Resistin are substantially raised in patients with End-Stage Kidney Disease (ESKD) but the relationship between these molecules and major clinical outcomes in this population is highly controversial. The interactions among these adipokines for the prediction of all-cause and cardiovascular (CV) mortality has never been analysed.

## *Methods:*

We studied an incident-prevalent cohort of 231 hemodialysis patients (age: 60±15 years; 127 M and 104 F) monitored for 57 months (range: 0.2 to 155 months) and, during this period, fatal cardiovascular events and death for other causes were accurately recorded.
Plasma concentrations of ADPN and Resistin were measured by ELISA and plasma Leptin by RIA.

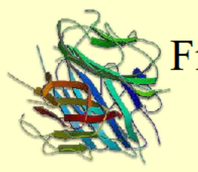


Fig. 1: MAIN CORRELATES OF ADPN

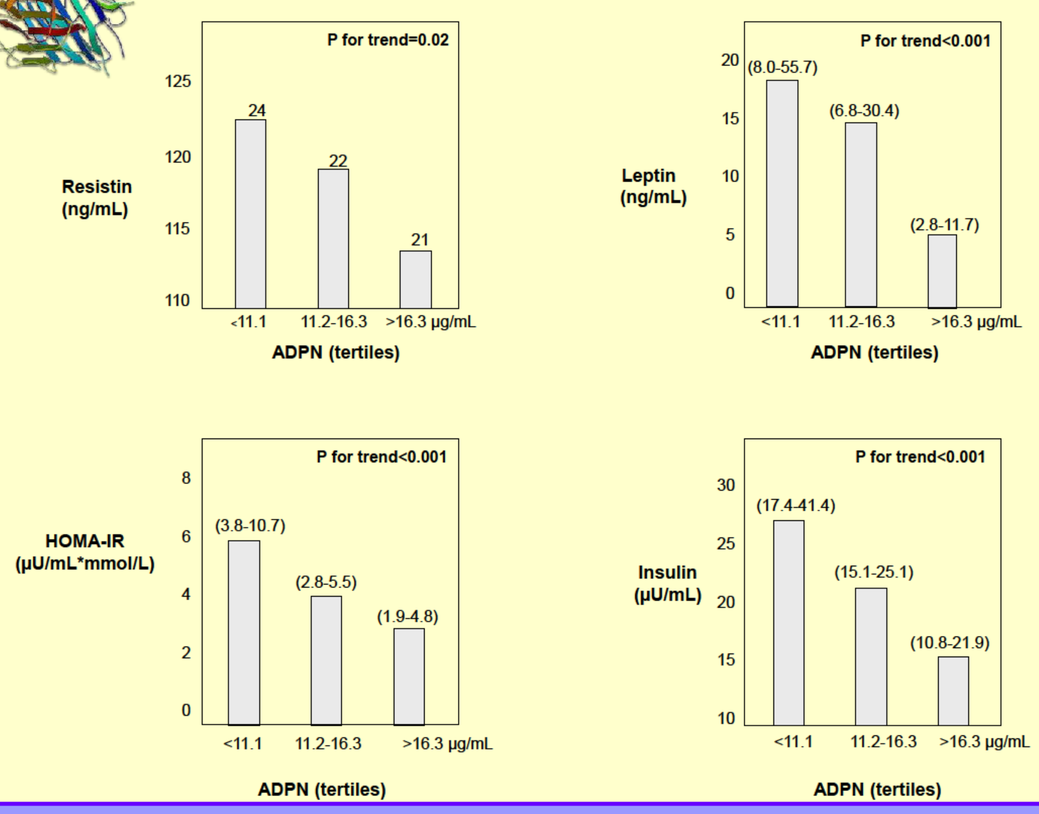
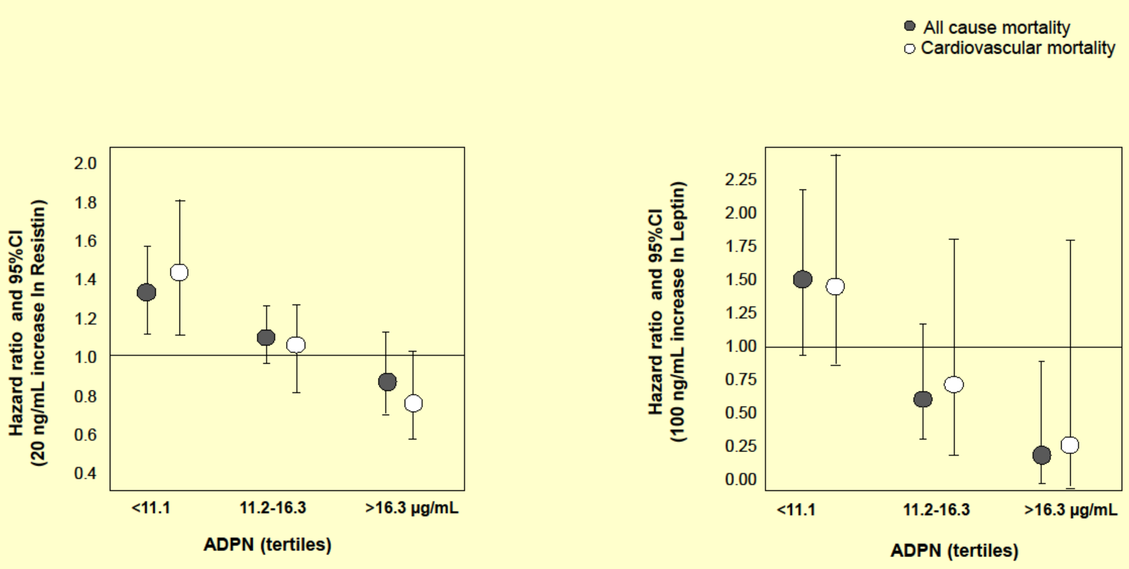



Fig. 2: INTERACTION ANALYSIS




## *Results:*

*Correlates of adipokines*

We categorized (tertiles) the study population according to the main ADPN levels. In this analysis, plasma ADPN was strongly and inversely related to plasma Resistin, Leptin, insulin and HOMA-IR index (**Fig.1**). Furthermore, plasma Resistin was directly related with C Reactive Protein (r=0.15, P=0.03) and plasma Leptin with insulin (r=0.29, P<0.001) and HOMA-IR index (r=0.38, P<0.001).

*Survival analysis*

During the follow-up period, 165 patients died (96 for CV causes). On univariate analysis, patients in the first ADPN tertile had higher all-cause and CV mortality rate (19 deaths/100 persons year; 13 CV deaths/100 persons year) when compared to those in the second (11 deaths/100 persons year; 6 CV deaths/100 persons year) and third ADPN tertile (17 deaths/100 persons year; 8 CV deaths/100 persons year) (p for trend=0.02). At variance, Resistin and Leptin failed to significantly predict all-cause and CV mortality (p=NS).

*Interaction analysis*

The interaction analysis showed that ADPN modified the Resistin-mortality link, both on unadjusted analysis (p ≤0.001) and after adjustment for traditional, peculiar of ESKD and emerging risk factors (p ≤0.004). The risk excess for all-cause and CV mortality portended by a fixed increase in Resistin (20 ng/mL) was maximal in patients in the first ADPN tertile (all-cause death, HR: 1.32, 95% CI: 1.11-1.58; CV death, HR: 1.42, 95% CI: 1.12-1.79), intermediate in those in the second tertile (all-cause death, HR: 1.09, 95% CI: 0.95-1.26; CV death, HR: 1.03, 95% CI: 0.85-1.25) and minimal (all-cause death, HR: 0.91, 95% CI: 0.72-1.14; CV death, HR: 0.75, 95% CI: 0.56-1.01) in patients in the third ADPN tertile (p for effect modification ranging from 0.001 to 0.01) (**Fig.2, left panel**).

Likewise, ADPN modified of the association between Leptin and all-cause mortality with a risk excess resulting from a fixed increase in Leptin (100 ng/mL), progressively lower from the first to the third ADPN tertile (ADPN, I tertile- HR: 1.40, 95% CI: 0.94-2.07; II tertile- HR: 0.55, 95% CI: 0.26-1.17; III tertile- HR: 0.22, 95% CI: 0.05-0.88) (p for effect modification P=0.009) (**Fig.2, right panel**).

Adiponectin also tended to modify the Leptin-CV mortality link, but this tendency did not attain the formal statistical significance (p= 0.09) (**Fig.2, right panel**).

## *Conclusions:*

In ESKD, ADPN is a strong modifier of the link between Resistin and Leptin with mortality. These data further highlight the role of the adipose tissue on clinical outcomes in this population and indicate that the analysis of interaction among these adipokines is fundamental to fully capture the relevance of their associations with adverse clinical outcomes.

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