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Adiponectin as a marker of peripheral insulin resistance in adolescents with Polycystic Ovarian Syndrome (PCOS) and as a tool to suspect insulin receptor defects

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<u>BACKGROUND:</u> Decreased serum adiponectin levels are associated with obesity and peripheral insulin resistance (IR). PCOS is characterized by hyperandrogenism and chronic anovulation and frequently is associated to IR. Some defects of Insulin Receptor have been proposed as mechanisms to explain ovarian hyperandrogenism in PCOS.

<u>OBJECTIVES:</u> To explore adiponectin levels in adolescents with PCOS.
To evaluate if adiponectin would identify potential patients with hyperandrogenism associated to defects in the insulin receptor or its intracellular signal pathway.

<u>PATIENTS AND METHODS:</u> Cross-sectional study. Twenty PCOS adolescents (16.4±2 years) diagnosed according to AES criteria and 10 healthy normal cycling adolescents (16.0±1.5 years) were studied. Fasting glucose, insulin, adiponectin, androgens (total and free testosterone -T and free T-, and androstenedione), were measured. HOMA-IR > 2.5 was used as surrogate of IR.
High molecular weight adiponenctin (HMW adiponectin) serum levels were measured by ELISA KAPME09-DIASource ®.

RESULTS

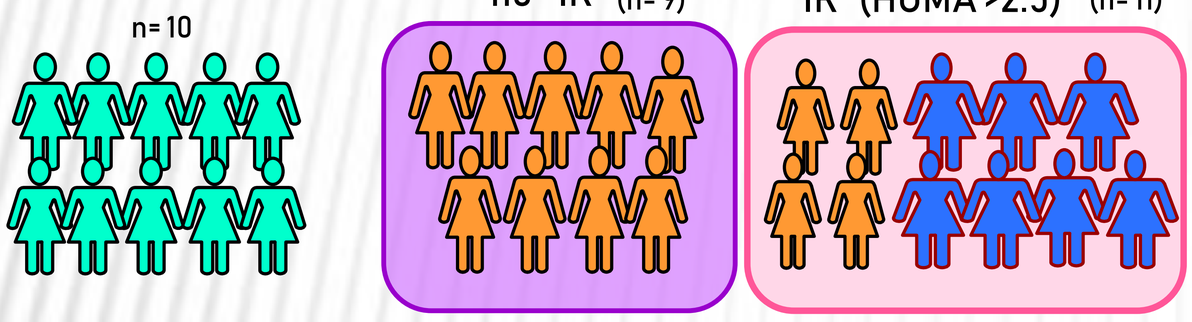
Control adolescents

n= 10

PCOS (n=20)

no- IR (n= 9)

IR (HOMA >2.5) (n= 11)

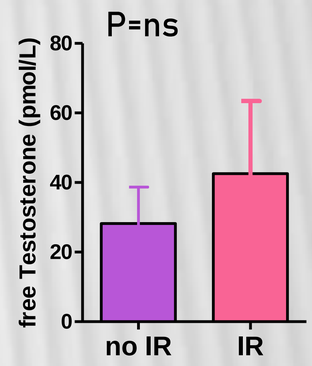


There were no differences between both groups no IR and IR in :

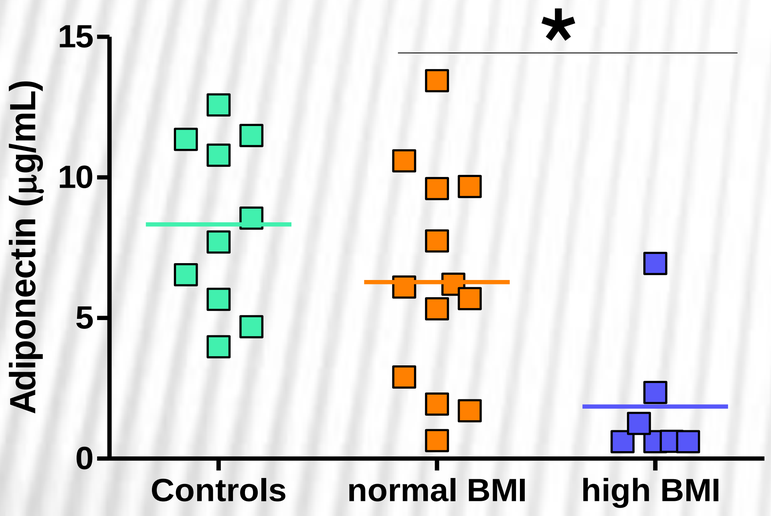
✓hirsutism score

✓menstrual cycle abnormalities

✓ levels of free T

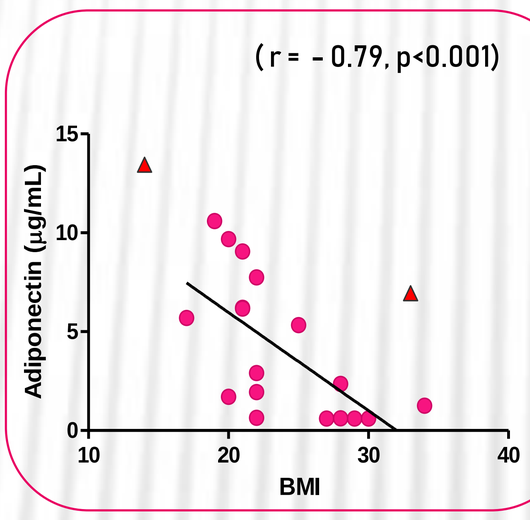


Adiponectin levels

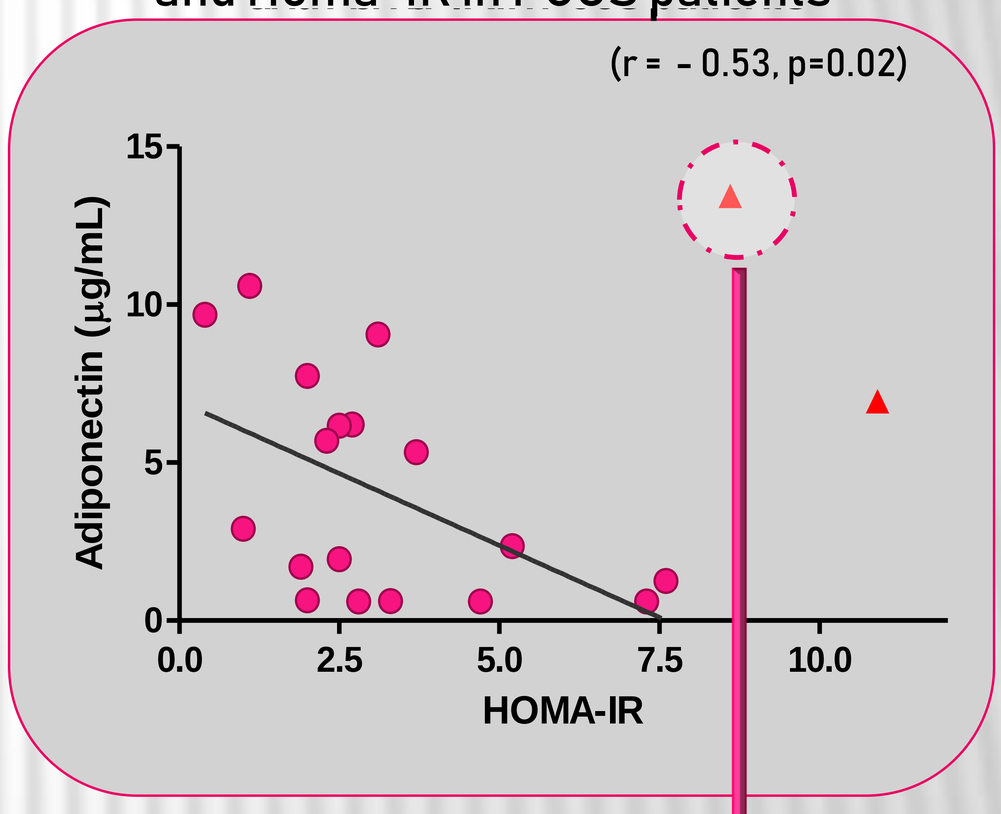


* Dunn's Multiple Comparison Test P<0.05

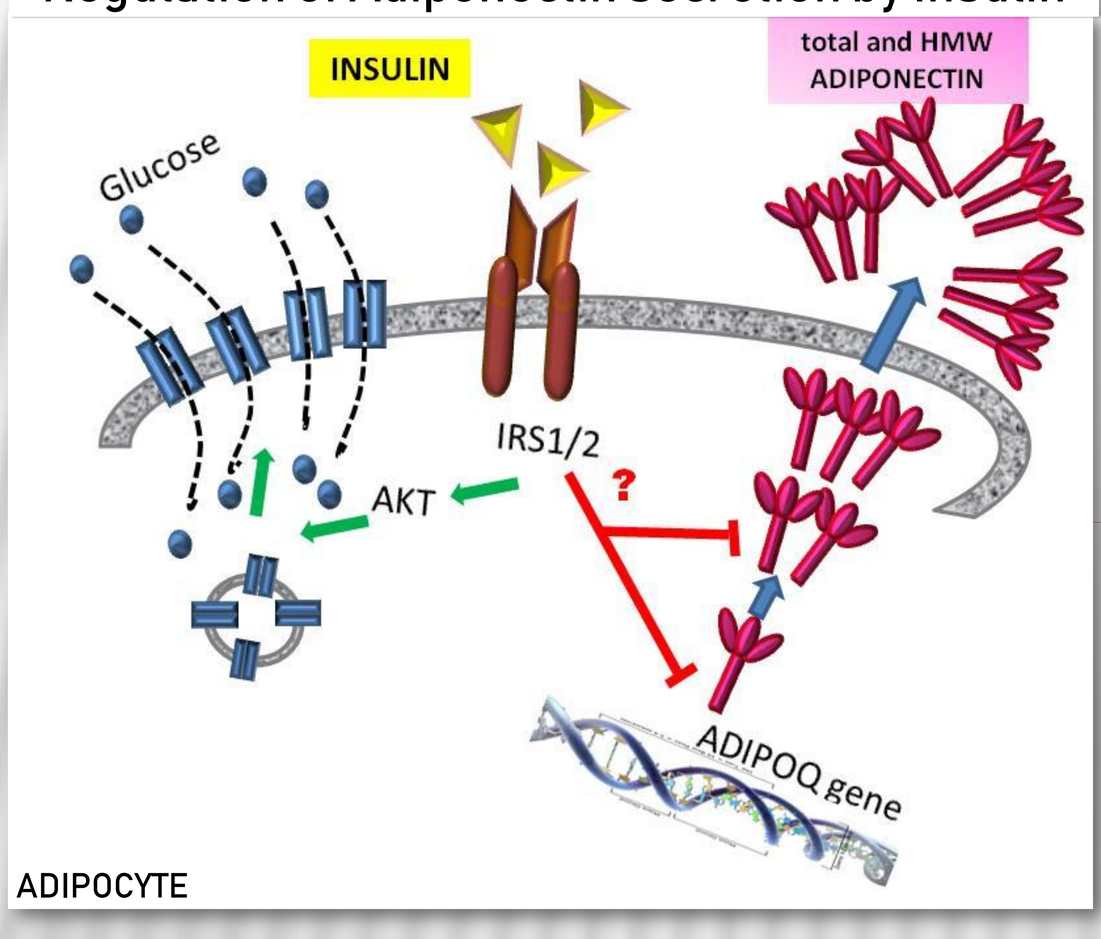
Correlation between Adiponectin levels and BMI in PCOS patients



Correlation between Adiponectin levels and Homa-IR in PCOS patients



Regulation of Adiponectin secretion by Insulin



A novel heterozygous missense variant in the tyrosine kinase domain of *INSR* gene was identified in one of the two patients that showed increased Adiponectin levels in spite of having severe insulin resistance.

Protein variant	cDNA variant	Classification ACMG
p.Leu1150Pro	c.3449T>C exon 19	Likely pathogenic

This aminoacid change could alter the dynamic flexibility of the activation loop of the insulin receptor and could cause loss of kinase activity.

(Exome analysis was performed using the Illumina TrueSight One assay in a NextSeq500 system)

CONCLUSIONS

Adiponectin levels are negatively associated with BMI and the severity of peripheral insulin resistance in PCOS adolescents,

Unexpectedly high levels of adiponectin in patients with PCOS who exhibit severe insulin resistance may help us select them towards molecular studies to rule out insulin receptor defects.