Adiponectin levels in women with polycystic ovary syndrome: a systematic review and a meta-analysis

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BACKGROUND: Conflicting results regarding adiponectin levels in women with polycystic ovary syndrome (PCOS) have been reported. To evaluate adiponectin levels in PCOS, a systematic review of all studies comparing adiponectin levels in women with PCOS with healthy controls and a meta-analysis of those involving women with similar body mass index (BMI) were performed. The influence of possible effect modifiers, such as insulin resistance (IR) and testosterone, was investigated. The influence of obesity was investigated through a ‘nested’ meta-analysis after within-study BMI stratification and appropriate pooling.

METHODS: Literature search was conducted through MEDLINE, EMBASE, Cochrane CENTRAL (through June 2008), references from relevant studies and personal contact with the authors. Thirty-one studies, reporting data on 3469 subjects, were reviewed and 16 included in the main meta-analysis.

RESULTS: Women with PCOS demonstrated significantly lower adiponectin values [weighted mean difference (95% confidence interval) −1.71 (−2.82 to −0.6), P < 10−4], yet with significant between-study heterogeneity. Lower adiponectin levels are associated with the IR observed in women with PCOS, compared with controls. IR, but not total testosterone, was found significant among biological parameters explored in the meta-regression model. Hypoadiponectinaemia was present in both lean and obese women with PCOS when compared with non-PCOS counterparts. Data on high molecular weight (HMW) adiponectin are limited (three studies).

CONCLUSIONS: After controlling for BMI-related effects, adiponectin levels seem to be lower in women with PCOS compared with non-PCOS controls. Low levels of adiponectin in PCOS are probably related to IR but not to testosterone. Total adiponectin should not be used as a biomarker of PCOS severity. Further investigation is needed for HMW adiponectin levels in PCOS.

Key words: polycystic ovary syndrome / adiponectin / insulin resistance / testosterone / high molecular weight adiponectin
Introduction

The polycystic ovary syndrome (PCOS) is a common, heterogeneous endocrine disorder in women of reproductive age. It is characterized by a clustering of hyperandrogenism (either clinical or biochemical), chronic anovulation and polycystic ovaries (Franks, 1995) and it is frequently associated with insulin resistance (IR) and obesity (Ehrmann, 2005). Notwithstanding the known effects of excess adiposity on insulin sensitivity, evidence suggests that women with PCOS demonstrate an intrinsic form of IR that is unique to the disorder (Morales et al., 1996).

A possible link between adipose tissue and insulin sensitivity is provided through the mediation of adipokines, products of adipose secretory activity. Among them, adiponectin, a protein produced almost exclusively by adipocytes, is considered to exert insulin-sensitizing, anti-atherogenic and anti-inflammatory actions (Weyer et al., 2001; Kadowaki and Yamauchi, 2005). It has been suggested that adiponectin expression is down-regulated by obesity (Stefan and Stumvoll, 2002), whereas its plasma levels have been found reduced in a variety of states frequently associated with IR, such as diabetes, cardiovascular disease and hypertension (Matsubara et al., 2002; Trujillo and Scherer, 2005). Insulin-resistant states have also been associated with a reduction in high molecular weight (HMW) fraction of adiponectin (Hara et al., 2004; Lara-Castro et al., 2006), which is considered a potent mediator of insulin sensitivity (Pajvani et al., 2004). Furthermore, it has been reported that percentage composition of HMW adiponectin was decreased by testosterone in both animal (mice) and human (hypogonadal men after the testosterone replacement therapy) models (Xu et al., 2005).

Given the effects of excess adiposity and IR on adiponectin levels, a marked decrease of adiponectin levels in women with PCOS could be assumed. This assumption has been confirmed by the findings of numerous studies (Ducluzeau et al., 2003; Panidis et al., 2004; Sieminska et al., 2004; Spranger et al., 2004; Ardawi and Rouzi, 2005; Carmina et al., 2005, 2006, 2008a, b; Sepilian and Nagamani 2005; Escobar-Morreale et al., 2006; Beckman et al., 2007; Aroda et al., 2008; Glintborg et al., 2008; Thomann et al., 2008; Zhang et al., 2008); however, this was not the case in several other studies, where no significant difference was demonstrated (Orio et al., 2003, 2004; Panidis et al., 2003, 2004, 2005; Haap et al., 2005; Glintborg et al., 2006; Gulcelik et al., 2006, 2008; Tan et al., 2006; Bik et al., 2007; Moran et al., 2007; Shroff et al., 2007; Barber et al., 2008). In an attempt to further investigate the role of adiponectin in PCOS, many researchers examined the relationship between adiponectin and PCOS characteristics, such as adiposity, IR and androgen levels, yet with conflicting results.

Recently, low adiponectin levels have been associated with progression towards type 2 diabetes mellitus (Schwarz et al., 2006; Jalovaara et al., 2008) and have been suggested to reflect increased risk of cardiovascular disease in women (Zyriax et al., 2008). Both type 2 diabetes and cardiovascular disease are considered major long-term health risks for women with PCOS (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). Given the fact that low adiponectin levels could serve a predictor to the progression to type 2 diabetes and cardiovascular disease in women, adiponectin levels in PCOS might help identify high-risk PCOS patients or even impose a stricter follow-up and possibly an early treatment initiation. A definite answer to whether adiponectin levels are lower (as expected), higher or the same in women with PCOS and controls could provide useful implications for the pathogenesis of the syndrome and potentially its prognosis and physical history. An answer to whether hypoadiponectinaemia (if confirmed) is a result of the interactions between IR and hyperandrogenaemia or an intrinsic feature of PCOS is necessary for the interpretation of the former and might also provide inferences for the diagnosis of the syndrome. These two answers could help in deciding whether adiponectin measurement is of any potential value as biomarker of severity for a clinician confronting PCOS.

To investigate adiponectin levels in women with PCOS, a systematic review of all studies reporting total and HMW adiponectin levels in women with PCOS and a meta-analysis of the best available evidence were performed. To gain insights into the influence of IR and testosterone on adiponectin levels, appropriate categorical analyses and meta-regression modelling have been undertaken. To investigate the influence of obesity on adiponectin levels in PCOS, a ‘nested’ meta-analysis was undertaken after body mass index (BMI) stratification of subjects into subgroups within studies and appropriate pooling of them (Thompson and Higgins, 2005).

Methods

Search strategy

A preliminary search was conducted in electronic database MEDLINE on various combinations of the terms ‘polycystic ovary syndrome’ (MeSH), ‘hyperandrogenism’ (MeSH), ‘insulin resistance’ (MeSH), ‘adiponectin’ (MeSH) and ‘adipokines’ (MeSH) in order to evaluate the size of the relevant bibliography and to orientate to the keywords which would be used in the main search. To identify eligible studies, the main search was conducted in the electronic databases MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) from inception through June 2008, using the terms (‘Adiponectin’ [MeSH] OR ‘Adipokines’ [MeSH]) AND (‘Polycystic Ovary Syndrome’ [MeSH] OR ‘Hyperandrogenism’ [MeSH]) and restricted to English literature. The procedure was concluded by the perusal of the reference sections of all relevant studies or reviews, a manual search of key journals and abstracts from the major annual meetings in the field of endocrinology and a contact with experts on the subject, in an effort to identify relevant unpublished data. Finally, unpublished studies were also sought in the web sites isrcr.org, cahir.ca, action.org, UK clinical trials gateway and Welcome Trust.

The main search, as well as screening of titles, abstracts and full-text articles, was completed independently by two reviewers (K.A.T. and D.G.G.) with expertise in conducting systematic reviews. Chance-adjusted inter-rater agreement was calculated using Cohen’s k-statistics and found satisfactory. Any discrepancy was solved by consultation of a third reviewer, not involved in the initial procedure (I.P.).

Eligibility of relevant studies

Suitable for the systematic review were studies of any design, which reported adiponectin levels in women with PCOS [diagnosed consistently to either Rotterdam (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004) or National Institute of Health (NIH) criteria (Zawadzki and Dunaf, 1992)] compared with healthy controls. Eligible for the main meta-analysis were those studies included in the systematic review where BMI was similar between women with PCOS and controls. Eligible for the ‘nested’ meta-analysis were those studies included...
in the systematic review where adiponectin data on BMI subgroups were available. Studies were excluded from the systematic review and the meta-analyses if enrolled subjects had a disease other than PCOS, were on any kind of medication, were pregnant or were genetically related. Studies with no control group or control group including men were also excluded, as well as reviews, letters to the editor and studies published in language other than English.

Data extraction

Information from each study was extracted independently by two reviewers (K.A.T. and D.G.G.), using a standardized data extraction form. General characteristics of the study (author, journal, year of publication, design, ethnicity, study size and number of cases), characteristics of the PCOS and control groups (criteria, selection, age, BMI, insulin sensitivity status, androgen levels), methodology (PCOS definition, adiponectin measurement method, study quality) and results [total and HMW adiponectin means and standard deviation (SD), total adiponectin means and SDs after BMI stratification, subgroup and regression analyses] were recorded, where available, and double-checked. Where appropriate, data set was completed through communication with the authors. Pre-defined criteria [a modification of Newcastle–Ottawa Scoring for non-randomized studies (Wells et al., 2000)] were used independently by two reviewers to assess the quality of studies. The criteria were the comparability of subjects on the basis of BMI, the representativeness of subjects (selection of PCOS and control group), the validity of definitions and measurements and the lack of financial support from pharmaceutical industry. Inter-rater agreement was evaluated by means of k-test, and disagreement was resolved by consensus.

Institutional Review Board approval was not asked for this study, as no experiment or intervention was held on humans.

Statistical analysis

Total adiponectin, HMW adiponectin and total testosterone levels in each study were extracted as mean difference ± SD. When not reported, missing mean differences and SDs were estimated on the basis of reported confidence intervals (CIs), where available, and confirmation was sought through communication with the authors. Standard error of the mean was transformed into SD. Homeostasis Model Assessment of Insulin Resistance (HOMA2-IR) values were used as measures of insulin sensitivity. When not reported, missing HOMA2-IR values were estimated on the basis of reported mean glucose and insulin values, using the Oxford Diabetes Trials Unit calculator (www.dtu.ox.ac.uk).

Weighted mean differences (WMDs) in total plasma adiponectin were calculated for all eligible studies for the meta-analysis and combined using fixed or random-effects model (DerSimonian and Laird, 1986), where appropriate. Standardized mean differences (SMDs) in HMW adiponectin were calculated, as they were measured in different units across studies. Heterogeneity between the results of different studies was examined by weighted mean difference (WMD) in total plasma adiponectin was checked through restricted maximum likelihood (REML)-based random-effects meta-regression analysis. Univariate meta-regression analyses were performed first. Variables that were significant at the 0.1 level were entered into the multivariable model. Non-significant covariates (P > 0.05) in the multivariable model were deleted. The percentage of between-study variance explained by the model was estimated by the formula: tau^2 = 1 - tau2 (without covariates)/tau2 (model). To investigate the influence of obesity while securing reliable interpretation, categories of subjects on the basis of BMI within every study, included in the systematic review, were compared and then the results combined appropriately over studies (Thompson and Higgins, 2005) by means of a ‘nested’ meta-analysis. In specific, data within each study were stratified on the basis of BMI into three categories: lean (BMI < 25 kg/m²), overweight (BMI ≥ 25 and <30 kg/m²) and obese (BMI ≥ 30 kg/m²). WMDs were calculated for all three categories of each study. Thus, from each study, three additional WMDs were derived, one regarding lean PCOS and control women (subjects’ subgroup), one regarding overweight subgroup and one regarding obese subgroup, given that relevant data were available. To investigate adiponectin levels between lean women with PCOS and lean controls, a quantitative (meta-analysis) of the relevant WMDs was performed. This statistical procedure was repeated for the overweight and obese subjects as well.

Meta-analysis was conducted using Review Manager 4.2 software [Review Manager (RevMan), version 4.2 for Windows, Oxford, UK: the Cochrane Collaboration, 2002] and Stata/SE 9.0 for Windows (StataCorp LP, 4905 College Station, TX 77845, USA). The report of the study was complemented in adherence with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group standards for reporting meta-analysis of observational studies (Stroup et al., 2000).

Results

Search results

The search strategy identified 158 potentially relevant studies. A flow chart summarizing search results is provided in Fig. 1. Three unpublished studies were identified, two of them through the web site clinicaltrials.gov under the registry numbers NCT00173043 and NCT00667498 (currently active), and one by Panidis et al. (retrieved). Thirty-seven publications were excluded because it was clear from the title that they did not fulfil the selection criteria. Three of them were
Figure 1 Flow chart for the systematic review and the meta-analysis

read in full (K.A.T.) to check the validity of this selection procedure. From the remaining 121 publications, 64 were excluded on the basis of the abstract. Fifty-seven articles were read in full independently by two reviewers to assess their accordance with the selection criteria. Eight studies were excluded because no control group of women without PCOS was included (Lewandowski et al., 2005; Vrbikova et al., 2005; Majeri et al., 2007; Xita et al., 2007; Elkind-Hirsch et al., 2008; Jensterle et al., 2008; Veerakiet et al., 2008), one study was excluded because adiponectin was not measured in the control group (Xita et al., 2005) and one study was excluded because recruited women were with PCOS and had precocious puberty (Ibanez et al., 2004). In total, 26 studies were excluded because they did not fulfil the predefined selection criteria. Finally, 31 studies were included in the systematic review.

From the 31 studies included in the systematic review, 5 studies were excluded from the meta-analysis, because PCOS women and controls differed significantly in BMI (Panidis et al., 2004; Spranger et al., 2004; Haap et al., 2005; Carmina et al., 2008a; Zhang et al., 2008). Eight studies were excluded because no sufficient data were available: in three of them, results were presented only as medians or in figures (Sieminska et al., 2004; Bik et al., 2007; Carmina et al., 2008b); in five of them, only in subgroups and not in total (Ducluzeau et al., 2003; Orio et al., 2003; Ibanez and de Zegher, 2004; Ardawi and Rouzi, 2005; Panidis et al., unpublished data). In one study, all PCOS women had severe IR (Sepilian and Nagamani, 2005), forming a rather distinct population than the target. This was considered to introduce bias in the analysis, and, therefore, the study was excluded. Finally, a study was excluded (Carmina et al., 2006), as mean adiponectin values and mean BMI coincide with those in a previous study by the same authors (Carmina et al., 2005), suggesting sample overlap. Finally, 16 studies were included in the main meta-analysis.

**Systematic review**

The 31 studies were published between 2003 and 2008 and reported data on 3469 subjects (1776 women with PCOS and 1693 controls). In three of them, HMW adiponectin was also reported. Main data are summarized in Supplementary Material, Tables S1 and S2. The majority of studies was held in Europe (22 studies—70%), four in the USA, four in Asia and one in Australia. Eighteen studies (58%) applied the NIH criteria for the diagnosis of PCOS, 12 (39%) the Rotterdam consensus criteria, whereas one applied modified NIH criteria (Ibanez and de Zegher, 2004). Twenty-four studies (77%), using diverse methodology, reported that PCOS women were more insulin resistant than controls, whereas seven reported no difference. Seven studies (23%) were held in more than one centre and three were randomized to an insulin-sensitizing agent (baseline adiponectin was extracted). Overall, the reporting of studies was good: total numbers, inclusion criteria and reporting on baseline characteristics were generally clearly stated; however, methods of recruitment were poorly reported and reporting on adiponectin was also incomplete. No substantial differences were observed in the methodology applied to measure adiponectin. Almost half of them (15 out 31 studies) used radioimmunoassay (RIA) to quantify adiponectin levels, 13 studies (mostly more recent ones) applied enzyme-linked immunosorbent assays or enzyme immunoassay (1 study), 2 studies (by the same author) used time-resolved immunofluorometric assay, and in 1 study, no relevant information was reported. Many studies reported quality control measurements, although intra-assay and inter-assay coefficients of variation were high in some of them.

**Meta-analysis**

A meta-analysis of 16 studies, which included only subjects of similar BMI, was performed. Included studies reported data on 1186 women (660 PCOS and 526 controls), and their size ranged from 16 to 240 (median 49). In two of them, BMI was similar only on a subset of subjects; only these data were used in the meta-analysis, and their influence on the outcome was checked through sensitivity analysis.

Women with PCOS demonstrated significantly lower adiponectin values, yet with significant between-study heterogeneity [16 studies, random-effects WMD (95% CI) $-1.71 (-2.82$ to $-0.6); I² = 80.7%; Fig. 2]. Egger test for publication bias did not provide evidence of significant effect ($P = 0.139$). Sensitivity analysis, with the exclusion of the two studies where BMI was similar between PCOS patients and controls only in a subset of subjects, did not alter the result [14 studies, random-effects WMD (95% CI) $-1.71 (-2.85$ to $-0.57); $I^2 = 82.6\%$].

Quantitative synthesis of the data from three studies where HMW adiponectin was measured (Aroda et al., 2008; Barber et al., 2008;
Glintborg et al., 2008) demonstrated no significant difference in HMW adiponectin between women with PCOS and controls, yet with significant between-study heterogeneity [three studies, random-effects SMD (95% CI) = –0.59 (–1.33 to 0.16); $I^2 = 69.7\%$]. Unfortunately, this analysis had limited power to detect a true difference, as only three studies were included.

**Categorical analyses**

A priori hypotheses to explain potential heterogeneity between studies included: HOMA2-IR ratio (mean values in women with PCOS to controls in a single study), study size, total testosterone ratio (mean values in women with PCOS to controls in a single study) and study quality. Pooled WMDs in adiponectin between PCOS women and controls were calculated in four predefined categories, each covering a quartile interval (25% of studies) for the first two potential moderators (HOMA2-IR ratio and study size). Quartile intervals for HOMA2-IR ratio were <1.36, 1.36–1.7, 1.71–2.12, >2.12. For study size were <38, 39–49, 50–112, >113. For the last two moderators (testosterone ratio and study quality) and because of their distribution, study-level WMDs were categorized in three groups. For testosterone ratio, intervals were <1.68, 1.69–2.49, >2.5, and for study quality, intervals were studies with lower quality scores (<3), with medium quality scores (3–12) and with higher quality scores (>12). When relevant information (HOMA or testosterone ratio) was not possible to be extracted from a study (missing data), this study was classified into an additional separate category.

When HOMA2-IR ratio was used as a moderator in the categorical meta-analysis, WMD in adiponectin across relevant categories reflected a trend of a direct correlation with it. In studies with modest relative difference in IR between PCOS and control groups, no significant difference in adiponectin was observed. The $P$-value for between-groups heterogeneity was 0.001 (adjusted $P$-value $= k \times 0.001 = 0.004 < 0.05$, where $k$ is the number of designed comparisons, 23.75% of the total heterogeneity), indicating that the level of the relative difference in IR
Summary of categorical meta-analysis

Categorical meta-analysis on HOMA-IR ratio

Study ID
- HOMA ratio < 1.16
- Glueck (2006)
- Shorr (2007)
- Fawzi (2005)
- Omid (2005)
- Subtotal (I-squared = 54.3%, p = 0.04)
- HOMA ratio = 1.16 - 1.7
- Fawzi (2005)
- Tan (2006)
- Thomasson (2005)
- Subtotal (I-squared = 53.0%, p = 0.094)
- HOMA ratio > 2.12
- Monna (2007)
- Barber (2003)
- Subtotal (I-squared = 48.2%, p = 0.172)
- Heterogeneity between groups: p = 0.01
- Overall (I-squared = 89.7%, p = 0.003)

NOTE: Weights are from random-effects analysis

Categorical meta-analysis on Total Testosterone ratio

Study ID
- T ratio < 1.68
- Glueck (2006)
- Glueck (2009)
- Glueck (2009)
- Glueck (2009)
- Glueck (2009)
- Subtotal (I-squared = 82.7%, p = 0.001)
- T ratio = 1.69 - 2.49
- Shorr (2007)
- Adela (2007)
- Glueck (2009)
- Subtotal (I-squared = 91.3%, p = 0.001)
- T ratio > 2.5
- Panza (2005)
- Monna (2007)
- Tiet (2006)
- Fawzi (2005)
- Subtotal (I-squared = 87.9%, p = 0.028)
- T ratio unknown
- Fawzi (2005)
- Shorr (2007)
- Adela (2007)
- Glueck (2009)
- Subtotal (I-squared = 87.9%, p = 0.045)

NOTE: Weights are from random-effects analysis

Categorical meta-analysis on study size

Study ID
- Study size < 38
- Tan (2006)
- Usana (2009)
- Subtotal (I-squared = 78.9%, p = 0.001)
- Study size = 39 - 48
- Thomasson (2005)
- Shorr (2007)
- Subtotal (I-squared = 13.4%, p = 0.226)
- Study size > 48
- Glueck (2006)
- Monna (2007)
- Barber (2003)
- Subtotal (I-squared = 63.0%, p = 0.001)
- Heterogeneity between groups: p = 0.001
- Overall (I-squared = 63.0%, p = 0.001)

NOTE: Weights are from random-effects analysis

Categorical meta-analysis on study quality

Study ID
- Low quality score
- Panza (2005)
- Usana (2009)
- Subtotal (I-squared = 61.1%, p = 0.036)
- Medium quality score
- Glueck (2006)
- Thomasson (2005)
- Subtotal (I-squared = 63.0%, p = 0.001)
- High quality score
- Glueck (2006)
- Monna (2007)
- Shorr (2007)
- Usana (2009)
- Subtotal (I-squared = 84.7%, p = 0.001)

Heterogeneity between groups: p = 0.014
Overall (I-squared = 84.7%, p = 0.001)

NOTE: Weights are from random-effects analysis

Figure 3 Summary of categorical meta-analysis: categorical meta-analysis on HOMA-IR ratio; categorical meta-analysis on total testosterone ratio; categorical meta-analysis on study size; categorical meta-analysis on study quality.
between PCOS and control group (HOMA2-IR ratio) contributed significantly to the heterogeneity across studies. Results are summarized in Supplementary Material, Table S3A and visual inspection of them in Fig. 3.

When study size was used as a moderator in the categorical meta-analysis, WMD in adiponectin across relevant study size categories demonstrated evidence of inverse relation to it. In larger study categories, women with PCOS did not demonstrate any significant difference in adiponectin values compared with controls, in contrast to the smaller study categories, where adiponectin was found significantly lower in women with PCOS. The P-value for between-groups heterogeneity was significant (P-value < 0.001, adjusted P-value < 0.004, 42.66% of the total heterogeneity). Results are summarized in Supplementary Material, Table S3B and visual inspection of them in Fig. 3.

No evident pattern of correlation arose when categorical analysis was performed using total testosterone and study quality as moderators. WMD in adiponectin across categories did not seem to be explained by these two variables, as well as between-groups heterogeneity was not found to contribute significantly to total heterogeneity in the case of T-ratio (P-value = 0.014, adjusted P-value = 0.056, 13.68% of the total heterogeneity). However, the P-value for between-groups heterogeneity in the case of study quality was significant (P-value = 0.004, adjusted P-value = 0.016, 14.53% of the total heterogeneity). Results are summarized in Supplementary Material, Table S3C and D and visual inspection of them in Fig. 3.

**Meta-regression**

To further investigate the impact of the predefined study-level characteristics on WMD in adiponectin, an REML-based random-effects meta-regression analysis was performed. WMD was used as the dependent variable (logarithmic transformation was not possible for WMD, as negative values were included), and HOMA2-IR ratio, study size, total testosterone ratio and study quality were entered as explanatory covariates. REML estimate of the between-study variance (tau2) with no covariates in the model was 4.908. Univariate meta-regression analyses were performed first. HOMA2-IR ratio (15 studies, P = 0.086), study size (16 studies, P = 0.078), total testosterone ratio (13 studies, P = 0.278) and study quality (16 studies, P = 0.730) were assessed independently. Covariates whose regression coefficients were significant at the level of 0.1 in the univariate analysis, namely HOMA2-IR ratio and study size, were entered in the multivariate model. Regression coefficients for both HOMA2-IR ratio and study size were found significant at the level of 0.05 in the multivariate model. REML estimate of the between-study variance was reduced from 4.908 to 2.114, and the percentage explained by the multivariate model (tau_{exp}) was 56.92%. Results from the multivariate meta-regression analysis are presented in Table I. The possibility of a quadratic, cubic and logarithmic relationship between WMD and HOMA2-IR was explored in the multivariate model by relevant transformation of the covariate, but yielded no improvement to the model. Graphical display of the linear relationship between WMD and HOMA2-IR ratio is presented in Fig. 4.

**‘Nested’ meta-analysis on BMI**

Data regarding differences in adiponectin levels between lean women with PCOS and lean controls were available in 12 studies. WMDs regarding this subset (lean) in each study were combined and a pooled WMD derived [random-effects WMD (95% CI) −1.62 (−3.20 to −0.04), I^2 = 70.1%]. Data regarding differences in adiponectin between overweight women with PCOS and overweight controls were available in nine studies [fixed effects WMD (95% CI) −0.93 (−2.14 to 0.27), I^2 = 28.7%]. These subsets of studies had wide CIs and small number of subjects (less than 20 in 5 out of 9

**Table I Results of the multivariate meta-regression analysis**

<table>
<thead>
<tr>
<th>Fit of model without heterogeneity (tau2 = 0):</th>
<th>Number of studies = 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of variation due to heterogeneity</td>
<td>Q (12 df) = 27.0027</td>
</tr>
<tr>
<td>REML estimate of between-study variance:</td>
<td>Prob. &gt; Q = 0.008</td>
</tr>
<tr>
<td>WMD estimate</td>
<td>coef.</td>
</tr>
<tr>
<td>HOMA ratio</td>
<td>−2.50524</td>
</tr>
<tr>
<td>Study size</td>
<td>0.0277142</td>
</tr>
<tr>
<td>Cons</td>
<td>0.6025889</td>
</tr>
</tbody>
</table>

![Figure 4 Regression fit graph of adiponectin weighted mean difference (WMD) and HOMA2-IR ratio (scatterplot and 95% confidence intervals, 15 studies).](image)
Studies). Data regarding differences in adiponectin between obese women with PCOS and obese controls were available in 12 studies (random-effects WMD (95% CI) -1.22 (-2.41 to -0.03), $I^2 = 75\%$). Adiponectin was found lower in both lean and obese women with PCOS, when compared with healthy counterparts, suggesting that relative hypoadiponectinemia in women with PCOS compared with healthy controls is present, regardless of the degree of obesity.

**Discussion**

Systematic review and meta-analysis of relevant studies suggest that adiponectin is lower in women with PCOS compared with non-PCOS controls of similar BMI. Lower adiponectin levels are associated with the IR observed in women with PCOS compared with controls. It has been demonstrated that the more insulin-resistant women with PCOS recruited, the lower serum adiponectin levels were found. Total testosterone levels failed to account for any difference in adiponectin observed between groups. Relative hypoadiponectinemia in women with PCOS compared with healthy controls of similar BMI was present, regardless of the degree of obesity examined.

**Limitations of the study and alternative explanation of findings**

Certain limitations of the present meta-analysis might undermine the generalization of the findings or impose an alternative context for interpretation. First, the significant heterogeneity observed across study results ($I^2 = 80.7\%$) reduces the reliability of the result, suggesting different outcomes across studies with different design, patients, methods and measurements. This inconsistency was only partially explained ($\tau_{\text{exp}} = 56.92\%$) by predefined categorical and meta-regression analyses, which pointed out that in smaller studies and in studies where women with PCOS were markedly more insulin-resistant than controls, adiponectin was found significantly lower in women with PCOS. In contrast, in larger studies and in studies with modest difference in IR between groups, no difference was observed. Whereas there is a physiological rationale to explain the observed influence of IR on adiponectin levels, scientific rationale for explaining the influence of study size on adiponectin levels should be restricted to methodological aspects and could be found in the limited precision of smaller studies to evaluate differences in adiponectin levels.

Mean HOMA-IR values were chosen as a measure of IR in an effort to obtain a uniform comparator of IR. Despite the relative inferiority of HOMA to euglycaemic hyperinsulinaemic clamp and/or oral glucose tolerance test, as it does not correlate with any aspect of insulin-receptor binding (Matthews et al., 1985), HOMA2-IR values could be easily approximated (where missing) on the basis of reported mean glucose and insulin values (yet euglycaemic hyperinsulinaemic clamp and/or oral glucose tolerance test results could not), providing in this way this requisite uniform comparator of IR. Without that, the investigation of the influence of IR on adiponectin levels could not be feasible. On the other hand, this missing data manipulation integrated a certain degree of systemic bias in the expression of IR, which should be considered a limitation of the present analysis. In an effort to adjust for it, significance level in the meta-regression models could be set at 0.025, instead of 0.05. Even in that case, regression coefficient for HOMA2-IR in the multivariate model remains significant ($P = 0.015$), indicating a rather strong relationship, yet not establishing causality. On the other hand, total testosterone levels, which were used as a biochemical marker of hyperandrogenaemia on the basis of the availability, failed to show significant influence on adiponectin levels. An alternative explanation of this finding could be found in the inferiority of total testosterone to free androgen index as a marker of hyperandrogenaemia and the fact that in only 13 out of 16 studies testosterone data were available. It could also be attributed to the failure of testosterone assays to accurately and precisely detect levels of testosterone, especially below 100 ng/dl (3.47 nM) (Wang et al., 2004). From the 16 studies included in the main meta-analysis, 6 applied specific RIAs to measure total testosterone levels, 4 applied chemiluminescence immunoassays, and in 4, no data, no testosterone measurement or other methodology was reported. Subgroup analyses after BMI stratification failed to provide further insights, probably due to the small numbers included. The influence of visceral adiposity could not be checked, as waist circumference or waist-to-hip ratio was not available in the majority of studies. English language bias could potentially have introduced bias in the present analysis (Egger et al., 1997). Finally, insufficient data limit the generalization of HMW adiponectin findings, as only three studies reported HMW values, and in one of them, data extraction was implicated with missing data manipulation.

**Implications for clinical practice and research**

Data analysis suggests a direct relationship between IR and differences in adiponectin between PCOS patients and controls, which could be extrapolated to the assumption that adiponectin is not an intrinsic characteristic of PCOS. Interpreting the former in terms of clinical practice, adiponectin measurement in women with PCOS could not provide clinicians with additional information regarding the diagnosis, prognosis and physical history of the syndrome to that provided by an estimate of IR, and thus, it should not be used as a biomarker of PCOS severity. The effect of testosterone on adiponectin levels and, particularly, on HMW fraction should be further investigated. Anti-atherogenic, anti-inflammatory and insulin-sensitizing actions of adiponectin could be of potential research interest in PCOS.

**Conclusions**

After controlling for BMI-related effects, adiponectin levels seem to be lower in women with PCOS compared with non-PCOS controls. Low serum adiponectin levels in PCOS are probably related to IR, but not to testosterone. Further investigation is needed to clarify whether HMW adiponectin levels are also suppressed in PCOS.

**Supplementary data**

Supplementary data are available at http://humupd.oxfordjournals.org/.

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