Insulin-like growth factor binding protein-1 in PCOS: a systematic review and meta-analysis

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Background: Despite extensive research, the pathogenesis of polycystic ovary syndrome (PCOS) remains unclear. Putatively, an elevated circulating concentration of insulin inhibits the production of insulin-like growth factor binding protein-1 (IGFBP-1), thus increasing the level of free IGF-I in serum and stimulating ovarian androgen production. Decreased IGFBP-1 has been reported in PCOS and in obesity; however, there are inconsistencies in the evidence. This systematic review and meta-analysis aimed to determine whether IGFBP-1 is decreased in PCOS when controlling for the influence of BMI.

Methods: Articles published between 1988 and 2008 were searched using MEDLINE, PubMed, SCOPUS and Web of Knowledge. Unpublished literature, trials in progress, and recent reviews were also searched. Original articles were selected by two investigators. To be included, the study must have compared serum IGFBP-1 in two populations: either PCOS versus controls, or an overweight subgroup versus the normal weight subgroup in either population. From 617 identified articles, 12 were included in the meta-analysis. Data were abstracted by two reviewers independently and standardized for errors.

Results: The population difference is presented as the Weighted Mean Difference (95% CI). PCOS subjects had a significantly lower serum concentrations of IGFBP-1 compared with controls [P < 0.00001; −36.6 (−52.0, −21.2) µg/l]. Overweight PCOS subjects also had lower IGFBP-1 levels compared with normal weight PCOS subjects [P < 0.006; −30.6 (−52.3, −8.8) µg/l]. No significant difference was found between overweight PCOS patients and overweight controls [P = 0.23; −5.1 (−13.5, 3.2) µg/l] or between normal weight PCOS patients and normal weight controls [P = 0.50; −3.8 (−14.9, 7.3) µg/l]. Overweight controls had significantly lower IGFBP-1 concentrations than normal weight controls [P = 0.03; −18.0 (−34.4, −1.5) µg/l].

Conclusion: These data indicate that a decreased serum level of IGFBP-1 is unlikely to be a mechanism for ovarian hyperandrogenism in PCOS. BMI may be the major determinant of serum IGFBP-1.

Keywords: polycystic ovary syndrome / insulin-like growth factor binding protein-1 / systematic review / meta-analysis / obesity
Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder of unknown aetiology. Characteristically, the spectrum of PCOS includes clinical and morphological ovarian features, intermittent or absent menstrual cycles, and clinical or biochemical hyperandrogenism. Hyperandrogenism is widely believed to play a pivotal role in the definition of PCOS despite the Rotterdam consensus (Azziz et al., 2006).

PCOS is believed to be strongly associated with insulin resistance and hyperinsulinaemia (Dunaif, 1997), which has been shown in some studies to be independent of the obesity that is also prevalent among PCOS women (Burghen et al., 1980; Dunaif et al., 1989). The evidence that insulin stimulates ovarian thecal and stromal androgen production in vitro (Barbieri et al., 1986; Bergh et al., 1993) and the demonstration of a positive correlation between fasting insulin and circulating androgens (Burghen et al., 1980) gave rise to the hypothesis that hyperinsulinaemia promotes hyperandrogenaemia in PCOS. This was supported clinically by the reported reduction in serum testosterone and amelioration of hyperandrogenic symptoms after insulin-sensitizing therapy (Nestler and Jakubowicz, 1996).

It was proposed that insulin stimulates ovarian androgen synthesis through its interaction with the insulin-like growth factor (IGF) system and that IGF-I potentiates LH-stimulated ovarian androgen synthesis. The action of IGF-I action is modulated by the IGF-binding protein-1 (IGFBP-1; Rajaram et al., 1997), which has been reported to correlate inversely with the serum level of free IGF-I (Thierry van Dessel et al., 1999). Insulin has also been shown to regulate the serum level of IGFBP-1 (Suikkari et al., 1988), decreasing its production by the liver (Brismar et al., 1994). Serum IGFBP-1 has been found to be decreased in women with PCOS (Conway et al., 1990; Iwashita et al., 1990; Thierry van Dessel et al., 1999). It was therefore hypothesized that hyperinsulinaemia in PCOS inhibits the production of IGFBP-1, causing an increase in the level of free IGF-I in the serum and potentiating LH-stimulated androgen production.

The relationship between serum IGFBP-1, PCOS and BMI has been the focus of many studies. Several have reported that the serum level of IGFBP-1 is significantly lower in PCOS women than in healthy (Pekonen et al., 1989; Conway et al., 1990; Morris and Falcone, 1996; Thierry van Dessel et al., 1999) and anovulatory (Homburg et al., 1992) control subjects. However, other studies have failed to demonstrate a significant difference in IGFBP-1 between the two groups (Suikkari et al., 1991; Buyalos et al., 1995).

There is a strong inverse relationship between BMI and serum IGFBP-1 in the general population (Sandhu et al., 2004). This could confound the comparison of PCOS and non-PCOS yet obese women, and contribute towards discrepancies in the available evidence. Given the increased prevalence of overweight and obesity in PCOS (Pasquali and Casimirri, 1993), it is necessary to control for BMI in order to establish the independent effects of BMI and PCOS. This approach has been adopted by a number of studies (Buyalos et al., 1995; Morales et al., 1996; Morris and Falcone, 1996); however, there are various inconsistencies in the evidence.

Despite these inconsistencies in the literature there is a consensus that serum IGFBP-1 is significantly lower in PCOS women (Poretsky et al., 1999; Wang and Wang, 2003) which suggests a role for IGFBP-1 in the pathogenesis of PCOS. However, many have arrived at this conclusion based on selective evidence obtained from a group of studies which are generally of small sample size, in diverse populations and using different methodologies. It is possible that these factors have contributed to the discrepancies noted or confounded the results.

In light of these points, a definitive conclusion on the role of IGFBP-1 in PCOS has yet to be reached. This highlights the need for an investigation into the serum level of IGFBP-1 in PCOS and control women, controlling for the influence of BMI.

To date, meta-analyses have largely been used for dichotomous data, and to pool the results of interventional trials. However, the method also lends itself to continuous data. In order to determine the verity of the current consensus and address the impact of BMI on IGFBP-1, we carried out a systematic review and meta-analysis of all the studies that compared the serum level of IGFBP-1 in a PCOS and control population. Further, we investigated the influence of the assay used and of various population differences.

Methods

The systematic review and meta-analysis were conducted according to a detailed protocol. Our null hypothesis was that serum IGFBP-1 was not significantly different in PCOS compared with control subjects. A secondary null hypothesis was that serum IGFBP-1 is not significantly different in overweight and obese subjects compared with normal weight subjects.

After inspection of the data, we hypothesized that population differences affect serum IGFBP-1 and contribute towards the heterogeneity between studies. This factor was therefore investigated by several post hoc analyses.

Selection of studies

We searched the following electronic databases: MEDLINE via Ovid SP (1950 to October 2008), PubMed, SCOPUS and Web of Knowledge. Further, Google Scholar was used to maximize identification of relevant studies by free-text searching. Unpublished literature was searched using the System for Information on Grey Literature in Europe (SIGLE). Relevant trials in progress were investigated on the UK Clinical Research Network portfolio database (UKCRN). The reference sections of five recent review articles on IGFBP-1 were hand-searched (Poretsky, 1991; Poretsky et al., 1999; Lee et al., 1997; Fowler et al., 2000; Wang and Wang, 2003). Searches were limited to literature published during the past 20 years (1988–2008).

The search terms were ‘PCOS’, ‘IGF-I’ and ‘IGFBP-1’, including all acronyms and synonyms. Wild cards were used to allow for variation in punctuation and suffixes. We were unable to include articles that were not written in English due to cost limitations. We included studies that measured fasting serum IGFBP-1 levels in PCOS women and non-PCOS controls, or that compared overweight and normal weight subgroups of either population. We accepted PCOS women on the basis of a clinical diagnosis (Table I). Studies were excluded if subjects were post-menopausal. Control subjects were defined as non-PCOS. The definition of ‘control’ used in each study is described in Table I. Subjects were subgrouped according to their BMI. Normal BMI status was defined as ≤25 kg/m². Overweight was defined as a BMI > 25 kg/m².

Articles were excluded from the analysis if it was stated that subjects were taking hormone therapy or drugs known to affect carbohydrate metabolism. If it was explicit that subjects were tested in a non-fasting state, the study was excluded from the analysis. In the absence of specific mention of fasting, a measurement of ‘fasting glucose/insulin’ or description of a glucose tolerance test was accepted as proof of an overnight fast. Where either fasting or drugs were not mentioned, the study was...
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<tr>
<th>Study</th>
<th>PCOS definition</th>
<th>Control definition</th>
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<tr>
<td>Carmina et al. (1995)</td>
<td>NIH</td>
<td>Ovulatory women (menstrual cycles not defined)</td>
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<tr>
<td>Buyalos et al. (1995)</td>
<td>Clinical and biochemical evidence of PCOS&lt;br&gt;Perimenarchal onset of oligo-/amenorrhoea&lt;br&gt;At least facial hirsutism&lt;br&gt;Absence of virilism</td>
<td>‘Regular’ menses (27–32 days)&lt;br&gt;No hirsutism</td>
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<tr>
<td>Morris and Falcone (1996)</td>
<td>A-/oligomenorrhoea&lt;br&gt;And hirsutism (Grade 2 or higher, on face and abdomen)&lt;br&gt;Serum testosterone and androstenedione 1.5 SD above those of a group of 55 controls with proven fertility.</td>
<td>Healthy&lt;br&gt;No history or clinical evidence of any endocrine or reproductive abnormality&lt;br&gt;‘Normal cycles’ (not defined)&lt;br&gt;‘Regular’ menstrual cycles (not defined)&lt;br&gt;Normal ovarian morphology on ultrasound&lt;br&gt;No features of hyperandrogenism&lt;br&gt;‘Regular’ menstrual cycles (not defined)</td>
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<tr>
<td>Liu et al. (2008)</td>
<td>No definition given</td>
<td>Healthy</td>
</tr>
<tr>
<td>Kowalska et al. (2001)</td>
<td>Ultrasound features of PCOS plus two of the following criteria:&lt;br&gt;Oligo-/amenorrhoea&lt;br&gt;Hirsutism&lt;br&gt;Serum androgens in upper limit of normal/elevated</td>
<td>Healthy women needing contraception&lt;br&gt;No more than one of the PCOS features described&lt;br&gt;Menstrual cycles not defined</td>
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<tr>
<td>Laatikainen et al. (1990)</td>
<td>Evidence of Polycystic ovaries</td>
<td>N/a</td>
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<tr>
<td>Suikkari et al. (1991)</td>
<td>At least four of the following features:&lt;br&gt;Menstrual disturbances&lt;br&gt;Obesity&lt;br&gt;Hirsutism&lt;br&gt;LH/FSH &gt; 2.5&lt;br&gt;Hyperandrogenaemia&lt;br&gt;PCO on ultrasound</td>
<td>Healthy women needing contraception&lt;br&gt;No more than one of the PCOS features described&lt;br&gt;Menstrual cycles not defined</td>
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<tr>
<td>Tiitinen et al. (1993)</td>
<td>On the basis of clinical symptoms, laboratory findings, and the typical appearance of the ovaries in vaginal ultrasonography</td>
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<tr>
<td>Iwashita et al. (1990)</td>
<td>All of the following:&lt;br&gt;Menstrual disturbances&lt;br&gt;PCO by ultrasound&lt;br&gt;Hyperandrogenaemia&lt;br&gt;LH/FSH &gt; 2.5</td>
<td>Healthy adult women&lt;br&gt;Regular 28–32 day menstrual cycles&lt;br&gt;No family history of disordered glucose metabolism</td>
</tr>
<tr>
<td>Carmina et al. (1999)</td>
<td>NIH</td>
<td>Normal, ovulatory women. Menstrual cycles not defined</td>
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<tr>
<td>Insler et al. (1993)</td>
<td>Clinical, sonographic and hormonal criteria</td>
<td>N/a</td>
</tr>
<tr>
<td>Conover et al. (1992)</td>
<td>N/a</td>
<td>Healthy women. Menstrual cycles not defined</td>
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NIH, National Institutes of Health.
IGFBP-1 was significantly lower in PCOS subjects than in control subjects ($P < 0.00001$).

There was statistically significant heterogeneity between these studies ($\chi^2 = 86.8, df = 4, P < 0.00001, I^2 = 95.4\%$). In the sensitivity analysis, the WMDs (95% CI) ranged from $-24.4 (-37.1, -11.7)$ to $-44.9 (-69.2, -20.5)$ and the upper limits of the confidence intervals never crossed zero. This showed that the exclusion of any one study did not affect the overall direction of the result.

Secondary analyses
Comparison 2: overweight PCOS versus normal weight PCOS
There were five studies which compared the serum IGFBP-1 levels in an overweight PCOS and a normal weight PCOS population (Fig. 3; Laatikainen et al., 1990; Insler et al., 1993; Tiitinen et al., 1993; Buyalos et al., 1995; Morris and Falcone, 1996). In the overweight PCOS population, the IGFBP-1 mean (SD) ranged from 2.2 $\mu$g/l (1.8) to 24.3 $\mu$g/l (17.5). There was a wider range of mean IGFBP-1 values among the Normal Weight PCOS subjects; from 6.2 $\mu$g/l (5.3) to 70.8 $\mu$g/l (41.5). Four of the five included studies showed IGFBP-1 to be significantly lower in the overweight subjects in comparison to the controls (Laatikainen et al., 1990; Insler et al., 1993; Tiitinen et al., 1993; Morris and Falcone, 1996), whereas Buyalos et al. (1995) indicated that there was no significant difference between the two populations. This discrepancy may be explained by the anomalously low mean value for IGFBP-1 in Buyalos’ normal weight PCOS population.

Meta-analysis of all trials confirmed that IGFBP-1 is significantly lower in overweight PCOS than in normal weight PCOS women ($P = 0.006$). The summary WMD (95% CI) was $-30.6 \mu$g/l ($-52.3, -8.8$).

There was significant heterogeneity between these studies ($\chi^2 = 54.3, df = 4, P < 0.00001, I^2 = 92.6\%$). A sensitivity analysis was undertaken. The WMDs (95% CI) ranged from $-27.2 \mu$g/l ($-49.6, -4.7$) to $-38.6 \mu$g/l ($-47.0, -30.2$) and the upper limits of the confidence intervals never crossed zero.

Comparison 3: overweight PCOS versus overweight control
There were three studies which compared overweight PCOS and control populations (Fig. 4; Buyalos et al., 1995; Morris and Falcone, 1996; Kowalska et al., 2001). In the overweight PCOS subjects, the mean (SD) IGFBP-1 ranged from 2.2 $\mu$g/l (1.8) to 13.7 $\mu$g/l (5.4). Among the overweight control population the range was much wider; 1.8 $\mu$g/l (1.3) to 50.6 $\mu$g/l (21.0). Kowalska et al. (2001) and Buyalos et al. (1995) found no significant difference between the two populations; WMD (95% CI) = $-2.3 \mu$g/l ($-7.4, 2.8$) and $0.4 \mu$g/l ($-1.0, 1.8$), respectively. Conversely, Morris and Falcone (1996) reported that IGFBP-1 was significantly greater in overweight control subjects than in overweight PCOS subjects, WMD (95% CI) = $-36.9 (-57.8, -15.99)$, $P < 0.01$.

Meta-analysis showed no significant difference between the IGFBP-1 level in overweight PCOS subjects compared with overweight control subjects ($P = 0.23$). The summary WMD (95% CI) was $-5.1 \mu$g/l ($-13.5, 3.2$).

The test for heterogeneity was significant ($\chi^2 = 13.1, df = 2, P = 0.001, I^2 = 84.7\%$). In the sensitivity analysis the WMDs (95% CI) ranged from 0.2 ($-1.2, 1.6$) to $-18.1 (-51.8, 15.7$). The sensitivity

Results

Results of the systematic literature review
The systematic retrieval process to identify eligible studies is summarized in Fig. 1. The characteristics of the included studies and their subjects are summarized in Table II.

Primary analysis
Comparison 1: PCOS versus control
Five studies compared the serum IGFBP-1 levels in a PCOS and a control population (Fig. 2; Suikkari et al., 1991; Carmina et al., 1995; Morris and Falcone, 1996; Carmina et al., 1999; Liu et al., 2008). The mean (SD) IGFBP-1 level in the PCOS populations ranged from 6.4 $\mu$g/l (7.1) to 26.9 $\mu$g/l (16.3). In the control populations, the range was 26.1 $\mu$g/l (6.2) to 124.0 (38.0). With the exception of Suikkari et al. (1991), all studies showed a significant mean difference between the IGFBP-1 levels in PCOS and control subjects. The summary WMD (95% CI) was $-36.6 \mu$g/l ($-52.0, -21.2$). Serum
analyses confirmed that IGFBP-1 is not significantly different in overweight PCOS and overweight control subjects.

Comparison 4: normal weight PCOS versus normal weight control
There were three studies which compared the serum IGFBP-1 levels in Normal Weight PCOS and Normal Weight control populations (Fig. 5; Iwashita et al., 1990; Buyalos et al., 1995; Morris and Falcone, 1996). The mean IGFBP-1 value (SD) in the Normal Weight PCOS population ranged from 6.2 μg/l (5.3) to 51.7 μg/l (31.5). There was also a wide range in the Normal Weight controls: 4.5 μg/l (3.5) to 70.7 μg/l (34.4). None of the included studies found a significant difference in mean IGFBP-1 between the two populations. This was reflected by the summary WMD (95% CI): 0.47 μg/l (–3.8, 4.8). There was no significant difference between normal weight PCOS and normal weight control subjects ($P = 0.83$). These studies were shown to be homogenous ($\chi^2 = 3.53$, df = 2, $P = 0.17$, $I^2 = 43.3\%$).

Comparison 5: overweight control versus normal weight control
There were four studies which compared overweight and normal weight control populations (Fig. 6; Conover et al., 1992; Buyalos et al., 1995; Morris and Falcone, 1996; Kowalska et al., 2001). The mean IGFBP-1 values (SD) were wide-ranging for both overweight control and normal weight control subjects; 1.8 μg/l (1.3) to 50.6 μg/l (21.0) and 4.5 μg/l (3.5) to 70.7 μg/l (34.4), respectively. IGFBP-1 was significantly lower in overweight controls in three of the studies (Conover et al., 1992; Buyalos et al., 1995; Kowalska et al., 2001).
<table>
<thead>
<tr>
<th>Study, year</th>
<th>Setting</th>
<th>Sample size by study group</th>
<th>Assay</th>
<th>Fasting</th>
<th>BMI (standard deviation), kg/m²</th>
<th>Mean age (standard deviation), years</th>
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<td></td>
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<td>PCOS</td>
<td>O-PCOS</td>
<td>NW PCOS</td>
<td>O-Control</td>
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<td>10</td>
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<td>Morris and Falcone (1996)</td>
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<td>8</td>
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<td>11</td>
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PCOS, all PCOS subjects (not stratified by BMI); Control, all control subjects (not stratified by BMI); O-PCOS, overweight PCOS; O-Control, overweight control; NW PCOS, normal weight PCOS; NW Control, normal weight control. The method of the assay was defined as ‘In-House’ (IH), i.e. a specific protocol determined by the study authors was used; or ‘commercial’ (com), where the samples were assayed by a commercial laboratory or a specific commercially available kit was used. IRMA, immunoradiometric assay; RIA, radioimmunoassay; ELISA, enzyme-linked immunosorbent assay.
et al., 2001), while Morris and Falcone (1996) found no significant difference between the two populations [WMD (95% CI) = −20.1 (−52.9, 12.7)]. From the meta-analysis, the summary WMD (95% CI) was −18.0 μg/l (−34.4, −1.5), demonstrating that IGFBP-1 is significantly lower in overweight control subjects compared with normal weight controls (P = 0.03). The test for heterogeneity was significant (χ² = 57.2, df = 3, P < 0.00001, I² = 94.8%). A sensitivity analysis was undertaken (Fig. 7).
The WMDs (95% CI) ranged from $-13.4 \mu g/l (-30.3, 3.52)$ to $-25.2 \mu g/l (-30.6, -19.7)$. If Morris and Falcone, Kowalska et al. or Conover et al. were excluded from the analysis, the summary WMD would become non-significant.

### Subgroup analyses

Methodological heterogeneity was investigated by subgroup analysis according to the assay used. The studies included in the comparison of normal weight PCOS and normal weight controls were homogenous; therefore a subgroup analysis was not performed.

#### PCOS versus control

Two separate subgroup analyses were possible from the primary analysis. Suikkari et al. (1991) and Morris and Falcone (1996) used an in-house RIA method (Fig. 8). This supported the primary analysis, demonstrating a significantly lower IGFBP-1 level in PCOS subjects compared with controls, WMD (95% CI) = $-27.0 \mu g/l (-39.4, -14.5); P < 0.0001$). These studies were homogenous ($\chi^2 = 0.37, df = 1, P = 0.54, I^2 = 0\%$). A second subgroup analysis of the studies using a commercial IRMA (Carmina et al., 1995; Liu et al., 2008) was conducted (Fig. 9), which also showed a significant difference between the populations, WMD (95% CI) = $-23.7 \mu g/l (-40.8, -6.47); P=0.007)$. However, the test for heterogeneity was significant ($\chi^2 = 44.33, df = 1, P < 0.00001, I^2 = 97.8\%$).

#### Overweight PCOS versus normal weight PCOS

Of the original five studies of overweight compared with normal weight PCOS subjects, three studies used an in-house RIA and were analysed separately (Laatikainen et al., 1990; Tiitinen et al., 1993; Morris and Falcone, 1996; Fig. 10). The result supported the initial analysis. By subgroup analysis, there was a significant mean difference between the overweight and normal weight PCOS groups ($P < 0.00001$), with difference being $-35.1 \mu g/l (-47.4, -22.8)$. The test for heterogeneity was not significant ($\chi^2 = 1.37, df = 2, P = 0.50, I^2 = 0\%$).

A post hoc analysis from all three originally included studies was performed to investigate the effect on heterogeneity of excluding Morris and Falcone (1996), the only significant WMD in the original analysis (Fig. 12). The WMD (95% CI) remained non-significant; $0.21 \mu g/l (-1.15, 1.56); P = 0.77$). However, the studies were homogenous; $\chi^2 = 1.01, df = 1, P = 0.31, I^2 = 1.4\%$).
Figure 7  Sensitivity analysis: IGFBP-1 levels in overweight control versus normal weight control subjects. WMD, weighted mean difference.

Figure 8  IGFBP-1 levels in PCOS versus control subjects: in-house RIA method. N, number of subjects in group; SD, standard deviation; WMD, weighted mean difference; CI, confidence interval; BP-1, IGFBP-1; df, degrees of freedom.

Figure 9  IGFBP-1 levels in PCOS versus control subjects: commercial IRMA method. BP-1, IGFBP-1; N, number of subjects in group; SD, standard deviation; WMD, weighted mean difference; CI, confidence interval; BP-1, IGFBP-1; df, degrees of freedom.
Overweight control versus normal weight control

A subgroup analysis of the three studies which used an RIA assay to study overweight and normal weight controls was conducted (Conover et al., 1992; Morris and Falcone, 1996; Kowalska et al., 2001; Fig. 13). This supported the original analysis, indicating that IGFBP-1 is significantly lower among overweight controls, WMD (95% CI) = -25.2 μg/l (-30.6, -19.7). The test for heterogeneity was non-significant ($\chi^2 = 1.59$, df = 2, $P = 0.45$, $I^2 = 0\%$).

Discussion

The mechanism for excess androgen production in PCOS is yet to be fully elucidated. One theory is that an elevated serum concentration of insulin could act directly via the IGF-I receptor to increase androgen production (Barbieri and Rayan, 1983). However, the IGF-I receptor has a greater affinity for IGF-I than for insulin (Froesch and Zapf, 1985). In healthy individuals (Grégoire Nyomba et al., 1997) and in diabetic patients (Brismar and Hall, 1993), the administration of
insulin has been shown to reduce serum IGFBP-1. Thus, insulin may act indirectly on the IGF-I receptor by influencing free levels of IGF-I. It was concluded that insulin resistance increases bio-available IGF-I levels in PCOS women, contributing to the abnormalities in IGF-I. It was concluded that insulin resistance increases bio-available IGF-I levels in PCOS women, contributing to the abnormalities in ovarian steroidogenesis (Morales et al., 1996). However, this is confounded by evidence from a large population study which indicates that IGFBP-1 is lower in obese subjects in the general population, independent of fasting insulin levels (Sandhu et al., 2004). Since obesity is highly prevalent in PCOS, IGFBP-1 must be consistently lower in PCOS women than in controls across the BMI spectrum to prove a role for IGFBP-1 in the pathogenesis of PCOS. The evidence from published studies is inconsistent in this regard. In this meta-analysis, we have examined all the studies that have compared serum IGFBP-1 in PCOS and non-PCOS women, to determine whether IGFBP-1 is decreased in PCOS and to investigate the effects of BMI. We also investigated the influence of assay on the overall effect.

Obesity is not an integral part of the PCO syndrome. Rather, it is a separate disease entity that tends to be more prevalent among PCOS suffers compared with the rest of the population. The presence of obesity is likely to confound the results of any study investigating PCOS. This may explain the inconsistency in the literature. Further, the prevalence of obesity in PCOS patients is likely to be influenced by the prevalence of obesity in the general population from which the study sample was taken.

The populations of the studies included in this systematic review came from the four corners of the globe; namely the USA (4), Finland (3), Canada (1), Japan (1), Poland (1), China (1) and Israel (1). The degree of ethnic diversity in each of these countries will be different. In particular, the USA and Israel are likely to be more ethnically homogeneous. This may be responsible for some variation in the results.

However, the effect of population background and ethnicity on the IGF-system is not clear. Ethnic differences in IGFBP-3 and IGF-II have been reported between white Caucasian and Asian women from the Indian subcontinent in the UK (Hopkins et al., 1996). In another study, a rich soy foods and low protein diet was related to lower IGF-I among Japanese and Hawaiian women (Takata et al., 2006). Despite the scarcity of such studies, it is evident that both diet and ethnic background are likely to influence the IGF-system. Although it was not possible to investigate these effects within this systematic review, their potential impact should be kept in mind until further evidence becomes available.

Since insulin resistance alters the IGF-I to IGFBP-1 ratio (Grégoire Nyomba et al., 1997), the prevalence of insulin resistance in the study population will have great impact on the outcome of that study. African and Hispanic Americans have higher insulin resistance than whites after adjusting for BMI (Haffner et al., 1994; Haffner et al., 1996; Diaz et al., 2005). Further, individuals of South Asian and Asian descent have a higher risk of insulin resistance and type 2 diabetes mellitus compared with those of European origin with a similar BMI (Deurenberg et al., 1998; Lear et al., 2003; WHO Expert Consultation, 2004).

Our comparison of PCOS and control populations irrespective of BMI suggests that serum IGFBP-1 is significantly lower in the overall PCOS population. Although crude, this supports the general consensus (Poretsky et al., 1999; Wang and Wung, 2003). However, when adjusting for BMI, the picture changes. IGFBP-1 is significantly lower in overweight and obese individuals than in normal weight subjects, in both the PCOS and control populations. This highlights the influence of BMI on IGFBP-1 in the population as whole. However, having no data regarding the insulin resistance status of subjects in these studies, we cannot determine whether this effect is independent of insulin resistance. The similarity in IGFBP-1 levels between the PCOS and control populations that has been demonstrated when adjusting for BMI suggests that PCOS per se does not determine the relationship between BMI and IGFBP-1. These findings indicate that IGFBP-1 is unlikely to play a major role in the pathogenesis of PCOS.

There was significant statistical heterogeneity between the studies included in many of the meta-analyses (Figs 2, 3, 4 and 6). Methodological variation between the included studies may have contributed to the significant statistical heterogeneity observed. There is evidence that the sensitivity of different assays is not consistent (Koistinen et al., 1987). We therefore stratified the studies according to the IGFBP-1 assay used, and re-analysed. Three of the four RIA subgroup analyses achieved homogeneity, confirming the strong effect the assay method had on the result. However, the subgroup analysis of studies that compared the PCOS and Control subjects using IRMA (Fig. 9) showed statistically significant heterogeneity. There were only two studies included in this analysis, one from the USA and one from China. We believe that population differences are the likely cause of the heterogeneity in this analysis, although the picture would be clearer if other studies using IRMA were available to include.
The diagnostic criteria for PCOS are another cause of the lack of consistency in the literature. Prior to the Rotterdam criteria (Rotterdam ESHRE/ASRM, 2004), there had been two different sets of criteria upon which the diagnosis of PCOS was made, the NIH (Zawadski and Dunaf, 1992) and the European criteria (Adams et al., 1985). The formerly accepted hyperandrogenism and oligo/anovulation as the main criteria for the diagnosis whereas the latter had the radiological morphological appearance of the ovaries as mandatory to the diagnosis. Neither set of criteria were deemed adequate, hence the Rotterdam consensus. However, even the Rotterdam consensus has been the subject of criticism; mainly from those who believe that hyperandrogenism should be the cornerstone of PCOS diagnosis (Azziz et al., 2006). Several subsets or phenotypes of PCOS have emerged as a result of the introduction of the Rotterdam criteria (Welt et al., 2006). Given such disagreement, the variation in PCOS definitions is likely to be a contributor to the heterogeneity in our meta-analyses.

**Conclusion**

This meta-analysis suggests that a decreased serum level of IGFBP-1 does not have a role in the pathogenesis of PCOS but is likely to result from the high prevalence of obesity in the PCOS population. However, we are limited by the retrospective nature of the included studies. Since they did not address temporality, we cannot exclude the possibility of reverse causality between obesity and IGFBP-1.

Although homogeneity was not achieved in all the analyses, we identified assay method as a potential source of heterogeneity and adjusted for this factor. The inherent variation in the PCOS phenotype, ethnic differences and the prevalence of obesity and insulin resistance are likely sources of heterogeneity which cannot be avoided in a meta-analysis. Prospective studies are needed to fully investigate the impact of these factors.

**Authors’ roles**

C.J.K.: Acquisition of data, analysis and interpretation of data, drafting the article. S.R.S.: Acquisition of data, analysis and interpretation of data. H.L.: Conception and design of article, analysis and interpretation of data, revising the article for intellectual content.

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