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Adiponectin and Polycystic Ovary Syndrome

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Abstract

Introduction—Polycystic ovary syndrome (PCOS) has a prevalence of 5–8% in women of reproductive age. Women with PCOS have an increased risk of metabolic syndrome and associated comorbidities. Adiponectin is a circulating protein produced by adipocytes. Circulating levels of adiponectin are inversely related to adipocyte mass. Low levels occur with insulin resistance, type 2 diabetes, metabolic syndrome, and obesity-related cardiovascular disease. This article reviews the literature on the link between adiponectin and PCOS and the potential use of adiponectin as a biomarker for PCOS.

Method—Data-based studies on adiponectin and PCOS and adiponectin measurement were identified through the Medline (1950–2009) and ISI Web of Knowledge (1973–2009) databases.

Results—Fifteen studies related to adiponectin and PCOS met inclusion criteria and were included in this review. These studies present evidence that adiponectin is linked to insulin resistance, insulin sensitivity, body mass index (BMI), and adiposity. In women with PCOS, lower levels, as opposed to higher levels, of adiponectin occur in the absence of adiposity.

Conclusion—The relationships between adiponectin and insulin resistance and sensitivity, metabolic syndrome, and BMI in women with PCOS suggest that adiponectin potentially could serve as a marker for disease risk and provide opportunity for earlier intervention if knowledge is successfully translated from laboratory to clinical practice. However, further study of the relationship between adiponectin and PCOS is required before there can be direct application to clinical practice.

Keywords

adiponectin; PCOS; biomarker; metabolic syndrome; BMI

The prevalence of polycystic ovary syndrome (PCOS) in women of reproductive age ranges from 6.5% to 8%, and it is estimated that at least 4–5 million women are affected in the United States (Goodarzi & Azziz, 2006). Clinical presentation can vary but will include some combination of oligomenorrhea, hyperandrogenism, impaired glucose tolerance, predisposition to type 2 diabetes mellitus (T2DM), lipid abnormalities, and vascular disease (Ehrmann, 2005). The association of PCOS with metabolic and cardiovascular risk factors, most likely due to insulin resistance (Bethea & Nestler, 2008; Glintborg et al., 2006), puts women with PCOS at risk for T2DM and cardiovascular disease ([CVD]; Bethea & Nestler, 2008).

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There is a three- to fourfold increase in metabolic syndrome in women with PCOS compared with the general population (Cussons et al., 2008; Gulcelik, Aral, Serter, & Koc, 2008). Women with PCOS exhibit insulin resistance and androgen excess resulting in reproductive challenges and health consequences across the life span (Ehrmann, 2005). The insulin resistance in women diagnosed with PCOS is greater than that found in women without PCOS matched by body mass index (BMI) and body fat distribution (Ehrmann, 2005). Although obesity is common with this syndrome, the increased risk of metabolic syndrome and insulin resistance is not necessarily related to obesity in these cases (Svendsen, Nilas, Norgaard, Jensen, & Madsbad, 2008), suggesting a different mechanism may be present.

Adipose tissue is an active endocrine organ that produces a variety of proteins, one being adiponectin (Magkos & Sidossis, 2007). Adiponectin, which has three major multidimer forms, is a circulating protein. Low levels (hypoadiponectinemia) are associated with conditions such as obesity, insulin resistance, metabolic syndrome, T2DM, and CVD. Conversely, high levels of adiponectin (hyperadiponectinemia) have anti-atherogenic, anti-inflammatory and anti-diabetic effects (Matsuzawa, 2005).

Circulating levels of adiponectin are inversely related to adipocyte mass (Bloomgarden, 2005) and visceral adiposity (Matsuzawa, 2005). Plasma levels are lower in individuals with T2DM and are higher in individuals with insulin sensitivity (Bloomgarden, 2005; Matsuzawa, 2005). In insulin-sensitive individuals adipose tissue secretes high levels of adiponectin, but as adiposity increases, adiponectin secretion decreases (Rasouli & Kern, 2008). Decreased plasma levels and decreased adiponectin receptors occur with the development of insulin resistance, T2DM, metabolic syndrome, and obesity-related CVD (Kadowaki & Yamauchi, 2005). The specific role adiponectin plays in these metabolic conditions is not clear: it may have a causative role, or it could be regulated by insulin and serve as a marker for insulin resistance. Whichever function is correct; adiponectin is associated with insulin resistance and the metabolic syndrome (Pittas, Joseph, & Greenberg, 2004).

Adiponectin circulates in different multimer complexes and molecular weights (Ebinuma et al., 2007). Following translation, it can be modified into several forms: trimers, hexamers, and high molecular weight (HMW) formations, which have varying biological effects (Hill, Kumar, & McTernan, 2009). Women have higher levels of total and HMW adiponectin than men, and for women there are significant negative correlations between HMW isomers and body fat measures (Peake, Kriketos, Campbell, Shen, & Charlesworth, 2005).

Adiponectin levels have been examined in women diagnosed with PCOS, but delineation of a role for the protein in diagnosis and/or treatment has not occurred. The purpose of this article is to review the literature to determine what is known about the connection of adiponectin with PCOS and the potential application to clinical practice.

Method

Studies eligible for this review were published in the English language and were retrospective, prospective, case–control, cohort, or randomized controlled trials (RCTs) containing original data related to adiponectin levels in women and PCOS. I located studies via searches in Medline (1950–2009) and ISI Web of Knowledge (1973–2009) using the terms *adiponectin, metabolic syndrome, measurement, biomarker, polycystic ovary syndrome* without limits or restrictions. I examined the abstracts of the articles that appeared in the search results and retrieved and reviewed all articles that were pertinent to the topic and met the inclusion criteria. After combining searches from the two databases, I found that

15 articles pertaining to adiponectin and PCOS met the criteria. In addition, I reviewed 16 data-based studies nonspecific to PCOS to assess measurement of adiponectin.

Results

Adiponectin in Women With PCOS

Adiponectin is produced or expressed by adipose tissue, and levels are lower when there is obesity and insulin resistance (Tan et al., 2006). In women without PCOS, adiponectin levels decrease as BMI increases (Vardhana et al., 2009). What appears to be different in PCOS is that there is an independent effect of PCOS on insulin sensitivity—an effect unrelated to obesity that has been identified in lean women (BMI < 25 kg/m^2; Svendsen et al., 2008). Lean women with PCOS have a higher trunk-to-peripheral fat ratio than lean women without PCOS. This effect may account for the lack of association between body weight and insulin sensitivity in these women. Even when obese women with PCOS have similar trunk/peripheral fat ratios to women without PCOS they have lower insulin sensitivity (Svendsen et al., 2008).

Lewandowski et al. (2005) conducted serial measurements of adiponectin during glucose tolerance testing in 19 women with PCOS. They discovered that adiponectin levels increased in some of the women during the testing. The authors were unable to explain this variation between women. BMI was not the explanation and they speculated that it may be related to resistin, a protein that was negatively correlated with adiponectin during the glucose tolerance test.

Many of the symptoms women with PCOS experience, such as changes in menstrual cycles and infertility, are a result of androgen excess (Pasquali, Gambineri, & Pagotto, 2006). For these women, development of hyperandrogenism happens in part because high insulin levels and free insulin growth factor stimulate the ovary to increase the production of androgens (Gambineri, Pelusi, Vicennati, Pagotto, & Pasquali, 2002). Compounding the effect of insulin, increases in fat tissue create an imbalance in sex steroids, specifically androgens and sex hormone binding globulin (SHBG). There is a decrease in SHBG that results in an increase in free androgens and is related to increasing hyperinsulinemia. Consequently, abdominal obesity alone can create a hyperandrogenic environment. Thus, for women with PCOS, hyperandrogenism is exacerbated by obesity, and the hyperandrogen state in turn contributes to insulin resistance. In this manner, a vicious cycle is set up (Gambineri et al., 2002).

There are two membrane receptors for adiponectin that mediate its glucose-lowering effect as well as its anti-inflammatory effects: adiponectin receptor 1 (adipoR1) and adiponectin receptor 2 (adipoR2; Tan et al., 2006). Normally, there is decreased expression of these receptors with obesity (Kadowaki & Yamauchi, 2005). However, in women with PCOS these receptors are upregulated in both subcutaneous and visceral fat tissue compared to women without PCOS. There is expression of these receptors in both subcutaneous and visceral fat, though expression is higher in subcutaneous fat tissue (Tan et al., 2006). In all women, expression of adipoR1 is positively correlated with insulin, androgen index (testosterone/SHBG × 100), and testosterone in both types of fat and negatively correlated with SHBG. Of interest, treating tissue with testosterone and estradiol increases the expression of these receptors. Prior studies demonstrated that high levels of sex steroids (testosterone and estradiol; Kalish, Barrett-Connor, Laughlin, & Gulanski, 2003) and low levels of SHBG (Haffner, Valdez, Morales, Hazuda, & Stern, 1993) correlate with insulin resistance. Consequently, high levels of androgen are a plausible explanation for why women with PCOS have higher expression of these receptors than women without PCOS, even while their BMI and adiponectin concentrations are similar. It is plausible that the

upregulation of the receptors may be a compensatory mechanism to achieve some insulin sensitivity in women with PCOS (Tan et al., 2006).

Further examination of fat tissue in women with PCOS has shown that adiponectin messenger RNA (mRNA) expression is significantly lower in women with PCOS compared with weight-matched women without PCOS (Carmina et al., 2008). This decreased expression, which occurs in both subcutaneous and visceral fat tissue, is consistent with the lower levels of circulating adiponectin levels that are seen in women with PCOS.

The results of several studies support the finding that adiponectin levels are associated with insulin resistance (Aroda et al., 2008; Ducluzeau et al., 2003; Jensterle et al., 2008; Spranger et al., 2004) and are negatively correlated with insulin sensitivity in women with PCOS (Ehrmann, 2005; Escobar-Morreale et al., 2006; Glintborg et al., 2006; see Table 1). The majority of studies provide support for low levels of adiponectin occurring in women with PCOS irrespective of the BMI level (Ardawi, Rouzi, Ardawi, & Rouzi, 2005; Aroda et al., 2008; Carmina et al., 2005; Escobar-Morreale et al., 2006; Glintborg et al., 2006), although some studies have reported the converse (Orio et al., 2003; Panidis et al., 2003; Spranger et al., 2004). Possible explanations for this discrepancy is that when overweight and obese women were grouped together, findings were nonsignificant (Spranger et al., 2004); or when women with PCOS were compared to women without PCOS, they were not matched by BMI (Panidis et al., 2003).

Adiponectin as a Biomarker

PCOS has a familial pattern. Signs begin to appear before puberty, although diagnostic clinical features such as clinical hyperandrogenism, oligoamenorrhea, and insulin resistance are not evident until adulthood (Sir-Petermann et al., 2007). It is possible that the metabolic abnormalities of PCOS are present prior to hyperandrogenism and that adiponectin could be used as a susceptibility biomarker for girls at risk for development of PCOS. Sir-Petermann et al. (2007) conducted a case–control study of 53 prepubertal and 22 pubertal girls who were daughters of women diagnosed with PCOS and 32 prepubertal and 17 pubertal girls with mothers without PCOS. Groups were similar in terms of age, BMI, and waist circumference. Adiponectin levels were significantly lower ($p = .0004$) in the prepubertal girls whose mothers were diagnosed with PCOS compared with controls, but levels in pubertal girls were similar across groups. Absolute changes in adiponectin occurred only in the control group, where adiponectin levels decreased from prepuberty to puberty. The authors concluded that the lower-than-expected levels of adiponectin, given BMI levels, in prepubertal daughters of women with PCOS could be related to visceral fat levels. The cross-sectional nature of this study did not allow for determination of which girls went on to develop PCOS, nor was there measurement of fat type (i.e., subcutaneous vs. visceral fat), which could be an explanation for the different adiponec-tin levels noted in daughters of women with PCOS. A longitudinal study involving a similar sample and including genetic biomarkers would provide valuable insight into the heritable aspects of this syndrome. It could provide evidence for how adiponectin might be useful in determining which girls are at high risk for development of PCOS, creating an opportunity for early intervention to decrease the health risks associated with the syndrome.

For adiponectin to be used as a biomarker in PCOS, the pathway of disease and an understanding of measurement options and potential measurement confounders are needed. Adiponectin can be measured in serum or plasma as total adi-ponectin or its isomers, primarily HMW. Various assays have been used to measure adiponectin, and numerous methodologies have been developed to increase the ease over, yet maintain the accuracy provided by, the gold standard, Western blot analysis.

Challenges of Using Adiponectin as a Biomarker

The initial challenge to using adiponectin as a marker for PCOS is the determination of what form of adiponectin to measure. Total adiponectin is an option because enzyme-linked immunoassay systems (ELISAs) have been developed and tested against long-standing laboratory methods such as radioimmunoassay (Kaplan et al., 2007; Risch et al., 2006), and total adiponectin is stable over time (Kaplan et al., 2007), which is an important criterion for usage in clinical practice.

Although total adiponectin is an option, observations suggest that adiponectin variations are primarily related to changes in HMW concentrations and that it alone or in relation to total adiponectin is a better biomarker for insulin resistance and metabolic syndrome (Magkos & Sidossis, 2007). ELISAs for HMW adiponectin have also been developed and tested against standards such as the Western blot (Ebinuma et al., 2006; Liu et al., 2009), making this a viable alternative. In one study of women with PCOS and controls matched by age and BMI, HMW adiponectin levels were found to be decreased. This decrease was independent of BMI and correlated with insulin resistance (Aroda et al., 2008). This is consistent with reports indicating HMW adiponectin is the biologically active form (Magkos & Sidossis, 2007; Peake et al., 2005) and is correlated with metabolic disorders (Hill et al., 2009).

The ratio of HMW to total adiponectin (HMWR) was assessed in one study and demonstrated to be a better predictor of insulin resistance than total adiponectin alone (Hara et al., 2006). As such, this measure offers the possibility of a sensitive and specific predictor of PCOS prior to development of clinical indicators. However, HMWR has not been examined in studies of PCOS. In one study, Xita et al. (2007) examined the adiponectin/letpin ratio as well as total adiponectin levels in 74 women with PCOS. They found a negative correlation between adiponectin and BMI in women with PCOS. In addition, they found that the adiponectin/leptin ratio was independently negatively correlated with BMI, insulin resistance, and lipoprotein profile in normal-weight and obese women with PCOS. These results support the conclusion that the adiponectin/leptin ratio is a superior marker for women with PCOS but confirmatory research is needed.

All forms of adiponectin have been examined using either serum or plasma samples, and it appears that serum is the better option for adiponectin measurement (Banga et al., 2008; Tanita, Miyakoshi, & Nakano, 2008). Plasma levels, but not serum levels, are affected by sodium fluoride and chelating agents mixed with plasma at the time of collection, which can affect results (Banga et al., 2008).

An internal factor that potentially affects adiponectin levels is body composition (Cassidy et al., 2009; Drolet et al., 2009; Kaser et al., 2008; Vardhana et al., 2009; Yannakoulia et al., 2003). In one study, both subcutaneous and visceral fat contributed to adiponectin levels in women with a BMI < 25 kg/m^2. However, there was decreased expression in the visceral fat of women whose BMI was >25 kg/m^2, whereas subcutaneous fat expression remained unchanged (Drolet et al., 2009). In another study, Kaser et al. (2008) found that HMW and total adiponectin were lower in subjects with a BMI > 30 kg/m^2. In this case, it was the visceral fat area that predicted the decrease in HMW concentration and the negative correlation of HMW adiponectin with BMI. What is suggested by these findings that visceral fat may have a greater impact than subcutaneous fat on adiponectin levels is that, when measuring adiponectin levels, researchers may need to take into account the predominant type of fat and make adjustments for the variation that is due to type of fat rather than amount of fat.

Additional findings suggest that dietary intake influences adiponectin levels in women. Dietary factors such as fruit and vegetable intake and dieting, measured using food

frequency questionnaires, are positively associated with adiponectin levels, whereas a high-fat diet is negatively associated, suggesting that diet intake has a modest influence on adiponectin levels (Cassidy et al., 2009). Dietary intake in the Nurses' Health Study was measured with the Alternate Healthy Eating Index (AHEI), which measures adherence to healthy eating patterns based on nine components such as fruit and vegetable intake, white vs. red meat, trans fats, and so on. In this study, adiponectin levels were positively associated with higher scores on the AHEI, indicating healthier diets (Fargnoli et al., 2008). Consequently, it might be important to control for diet when measuring adiponectin levels, at least when there has been a change in dietary patterns, as that alone could change adiponectin levels. Further study could determine whether the effect of diet on adiponectin levels is strong enough to warrant inclusion of this variable.

The validity of adiponectin as a biomarker can be examined in terms of content, construct, and criterion validity. An inverse relationship of adiponectin with body fat or BMI is consistently reported across studies, and adiponectin is one of several adipokines involved in glucose and lipid metabolism, insulin sensitivity, and cardiac function (Hill et al., 2009). Adiponectin is inversely related to insulin resistance, or positively with insulin sensitivity, in a pattern consistent with what is seen in diseases such as diabetes where insulin resistance and obesity are tied together. It is also associated with metabolic syndrome: a group of metabolic risk factors including obesity, dyslipidemia, and insulin resistance, all of which increase disease risk due to the body's inability to use insulin efficiently. Only one study that I reviewed (Hara et al., 2006) provided adequate reports of criterion information such as sensitivity, specificity, and predictive values of adiponectin and that was in relation to the HMW/total adiponectin ratio as a predictor of insulin resistance and metabolic syndrome.

Adiponectin is a stable protein, diurnal in nature, linked to insulin sensitivity/resistance, the metabolic syndrome and BMI, though the actual linkage mechanism is unknown. Measurement of total and/or HMW adiponectin can be accomplished using serum and ELISA techniques. Criterion information such as sensitivity and specificity are lacking and further delineation is needed to effectively use adiponectin as a biomarker.

Discussion

There is evidence that adiponectin is linked to insulin resistance, insulin sensitivity, BMI, and adiposity. This linkage is evident in women with PCOS with the exception that adiponectin levels can be low in this group in the absence of adiposity. Mechanisms of adiponectin regulation and the importance and role of this protein in health and disease have yet to be determined. The predominant use of cross-sectional studies has assisted in determination and identification of relationships but has not enabled determination of cause and effect. It is unclear whether adiponectin is a single marker with a direct effect or whether there are multiple pathways, whether it is an intermediate marker, a mediator, or whether it is in the direct pathway for disease. Adiponectin as a bio-marker for PCOS holds potential, but prospective, longitudinal examination is necessary to gain an understanding of causal pathways. For example, to identify the usefulness of measuring adiponectin in prepubertal girls who seemingly are at risk due to heritable factors, longitudinal follow-up of which girls actually develop PCOS is needed.

The link of adiponectin to PCOS is challenging to sort out because the variation in adiponectin levels occurs irrespective of adiposity, which is unlike what occurs in women without PCOS. The apparent relationship of adiponectin with androgen levels suggests a unique relationship in PCOS. The suggestion that upregulation of adiponectin receptors in the adipose tissue of women with PCOS is a compensatory mechanism to counteract the

insulin resistance provides additional information that something unique is happening in PCOS because normal levels of adiponectin and receptor expression decrease with obesity.

There are gaps and weaknesses in the current literature assessing the relationship of adiponectin with PCOS. All of the studies delineated the selection of cases and controls, however, the criteria for defining PCOS varied, with some studies using well-defined, standard disease classifications and others using less rigorous definitions, which could contribute to misclassification and erroneous findings. A generally consistent requirement that control subjects have regular menstrual cycles was applied across studies, though in some studies there was minimal or no description of the control subjects. Potential confounders such as BMI, age, waist circumference, and fat mass were not consistently accounted for in studies of women with PCOS. None of the reviewed PCOS studies considered or controlled for diet or medications, whereas most incorporated factors related to insulin resistance. Serum and plasma were both used for adiponectin levels. The majority of studies used total adiponectin, not HMW or HMWR, though these have the potential to be more useful for prediction of insulin resistance or disease syndromes. There were no discussions of race or other social variables that could affect generalizability.

With the emergence of the genomic era, there have been attempts to identify the genetic basis for PCOS. It is becoming clear that PCOS is a multifactorial, complex disease and the mode of inheritance is not Mendelian (Nam Menke & Strauss, 2007). PCOS is likely a product of incomplete penetrance, polygenetic inheritance, and epigenetic factors, and the clinical presentation could be the result of multiple mechanisms that lead to a common pathway. Genes have been identified that are involved in steroidogenesis, hormonal activity, insulin action, energy homeostasis, and inflammation (Prapas et al., 2009). Furthermore, an adiponectin gene has been identified, but it does not appear to be in the causal pathway of PCOS. It does, however, seem to have a role in phenotype variation and may be reflective of the metabolic disturbances (Prapas et al., 2009).

The majority of genetic studies done on adiponectin have been linkage analysis or examination of candidate genes (Nam Menke & Strauss, 2007). More recently, a combination of linkage and whole genome analysis was used to identify genes correlated to adiponectin. *ADIPOQ* was identified as the locus with the most influence on adiponectin variation: several single nucleotide polymorphisms (SNPs) within the gene were significantly associated with adiponectin levels (Ling et al., 2009). However, there has been no replication of this recent genome-wide association study, which is essential to determine whether this is a true effect.

Future Research

Further research is required before adiponectin can be used as a biomarker for PCOS in clinical practice. The relevant “dose” for risk and where adiponectin falls in the pathway for disease are essential pieces of knowledge for determining the range of utility. Differing adiponectin levels in women diagnosed with PCOS compared with “healthy” controls suggest biomarker application, especially as noted for prepubescent girls. Determination of “normal” ranges of adiponectin in the population and/or standardization of ranges for given ages or BMIs is essential, as is delineation of what level of adiponectin is reflective of imminent or actual disease. These standards would be extremely valuable if it turned out that adiponectin could serve as a marker for risk prior to development of the disorder. Such early detection would, in turn, aid in the development of treatment modalities to prevent PCOS, itself, or at least some of the negative consequences of the disorder. An understanding of the underlying biological mechanism/mechanisms of PCOS would enable development of new treatment options along the continuum of the disorder.

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Table 1

Studies Involving Adiponectin and Polycystic Ovary Syndrome (PCOS)

Author	Type of Study	Subjects	Biomarker (Adiponectin)	Outcome
Ardawi et al., 2005	Case–control	• 90 PCOS women • 45 BMI >30 kg/m^2 • 45 BMI < 25 kg/m ^{2} • 90 non-PCOS women • 45 BMI > 30 kg/m ^{2} • 45 BMI < 25 kg/m ^{2}	Plasma Collection: fasting AM blood draw early follicular phase or 2–5 days after spontaneous menses Sample handling: not reported Assay: commercial ELISA kit Unit of measure: total adiponectin Intra-assay CV: 4.9% Inter-assay CV: 6.3%	Adiponectin levels decreased in PCOS both in obese and in nonobese women compared to equivalent controls. Conclusions: Hypoadeponectinemia is evident in obese and lean women with PCOS, and insulin resistance may be involved in the control of adiponectin in PCOS.
Aroda et al., 2008	Case–control	• 31 PCOS obese women • 6 control women • Matched: age, BMI	Serum Collection: fasting AM blood draw in early/ midfollicular phase Sample handling: centrifuged and stored $^{-}70^{\circ}$C Assay: commercial RIA, all samples assayed in duplicate. Multimerization = Western Blot Unit of measure: total adiponectin, HMW, MMW, LMW Intra-assay CV: 7% Inter-assay CV: 11% Adipose tissue biopsy: cells extracted and stored at −70°C	Insulin action and adiponectin significantly less in PCOS. Correlation between glucose tolerance, insulin action, and adiponectin in all participants. Adiponectin protein decreased in subcutaneous cells in PCOS. PCOS less circulating HMW adiponectin. Glucose intolerant with PCOS had decreased HMW adiponectin. Conclusions: Circulating adiponectin and HMW adiponectin decreased in PCOS independent of obesity. Adiponectin differences are correlated with glucose intolerance and insulin resistance.
Carmina et al., 2005	Case–control	• 52 PCOS women • 45 normal ovulatory women • Matched: age, weight	Serum Collection: fasting AM blood draw during follicular phase Sample handling: not reported Assay: ELISA Unit of measure: total adiponectin Intra-assay CV: < 6% Inter-assay CV: < 15%	Adiponectin levels lower in PCOS. Negative correlation with BMI Conclusions: PCOS group had altered adipocyte secretion.
Ducluzeau et al., 2003	Case–control	• 16 nonobese hirsute PCOS women • 10 nonobese women (only for glucose disposal references)	Plasma Collection: morning blood draws after overnight fasting Sample handling: not reported Assay: RIA kit Unit of measure: total adiponectin CV: not reported	Adiponectin levels correlated with WHR but not BMI in PCOS. Adiponectin (low levels) correlated with insulin resistance (glucose disposal). Conclusions: Adiponectin is a marker of abdominal fat tissue.
Escobar-Moreale et al., 2006	Case–control	• 76 PCOS women • 40 healthy controls • Matched: BMI, degree of obesity	Serum and/or plasma Collection: not reported Sample handling: not reported Assay: commercial immunoassay-RIA kit Unit of measure: total adiponectin CV: not reported	PCOS: Reduced adiponectin levels independent of degree of obesity and increased WHR. Conclusion: Hypoadiponectinemia in PCOS irrespective of obesity level.

Glintborg et al., 2006	Case–control	• 51 PCOS women • 63 control women • Matched: age, BMI	Serum or plasma Collection: fasting AM blood draw follicular phase or random day Sample handling: not reported Assay: in-house immunofluorometric assay Unit of measure: total adiponectin CV: not reported	PCOS obese lower adiponectin than obese controls. Adiponectin negatively correlated with insulin when adjusted for WHR or central fat mass (determined by DEXA scan) as well as BMI. Conclusions: PCOS lower levels of adiponectin suggest high risk for metabolic syndrome. Correlations between adiponectin, ghrelin, and leptin were different for PCOS than controls, suggesting regulation is different in PCOS.
Gulcelik et al., 2008	Case–control	• 60 PCOS women • 60 control women • Matched: age	Serum Collection: fasting AM blood draw within 2–5 days of menses Sample handling: not reported Assay: ELISA Unit of measure: total adiponectin CV: not reported	Significantly more PCOS had metabolic syndrome than controls. PCOS with abdominal obesity had lower adiponectin levels and also lower levels of insulin resistance. Best cutoff value of adiponectin to identify metabolic syndrome 8160 ng/ml (sensitivity 85%; specificity 65%). Conclusions: Metabolic syndrome associated with adiponectin and adiponectin levels predictive of metabolic syndrome in PCOS. Hypoadiponectinemia independently association with metabolic syndrome in PCOS.
Jensterle et al., 2007	Case only	• 50 PCOS women < 25 years old	Serum Collection: fasting blood sample Sample handling: centrifuged and stored at ⁻40°C. Run in the same batch within 6 months of collection. Assay: RIA Unit of measure: total adiponectin Intra-assay CV: 2.8–5.0% Inter-assay CV: 3.5–8.2%	Mean adiponectin level (8.4 ± 3.3mg/L) slightly below normal reference range (10–12 mg/L). Participants with insulin resistance had significantly lower adiponectin levels. Conclusions: Adiponectin is no better than the existing homeostatic model assessment currently in use as a marker for insulin resistance in PCOS.
Lewandowski et al., 2005	Case only	• 19 PCOS women	plasma Collection: at 0, 60, and 120 min after a 75 g OGTT Sample handling: placed on ice, sent to laboratory, centrifuged and frozen at −30°C. Assay: commercial RIA Unit of measure: total adiponectin Intra-assay CV: 4.8% Inter-assay CV: 5.7%	Negative correlation between adiponectin and resistin independent of age or BMI. Variable increase in adiponectin during OGTT while resistin unchanged. Conclusions: Negative correlation with resistin—adiponectin/ resistin ratio might be useful in prediction of future risk in PCOS
Orio et al., 2003	Case–control	• 60 PCOS women • 30 normal weight • 30 obese • 60 non-PCOS women • Matched: age, BMI	Serum Collection: fasting AM blood draw during follicular phase Sample handling: not reported Assay: commercial RIA kit Unit of measure: total adiponectin CV: not reported	Adiponectin levels lower in obese compared to normal-weight PCOS and controls. Inverse correlation between adiponectin and BMI. Conclusion: Adiponectin levels change depending on fat mass in all women.
Panidis et al., 2003	Case–control	• 70 PCOS women • 35 overweight or obese • 35 normal weight • 15 normal-weight non-PCOS women	Serum Collection: fasting AM blood draw between Days 3 and 6 of menstrual cycle Sample handling: not reported Assay: commercial RIA Unit of measure: total adiponectin Intra-assay CV: 5.2%	Adiponectin levels lower in PCOS þ BMI > 25 kg/ m^2. Adiponectin levels similar for non-PCOS and PCOS BMI < 25 kg/m^2. Conclusions: Adiponectin not likely involved in pathogenesis of PCOS.

Sir-Petermann et al., 2007	Case–control	• Girls with PCOS mothers • 53 prepubertal girls • 22 pubertal girls • Girls with non-PCOS mothers • 32 prepubertal • 17 pubertal girls	Serum Collection: fasting AM blood draw (post menarche between Days 3 and 7 of men- strual cycle: premenarche when feasible) Sample handling: not reported Assay: RIA Unit of measure: total adiponectin Intra-assay CV: 1.8% Inter-assay CV: 9.0%	Adiponectin levels significantly lower in normal- weight prepubertal daughters of PCOS women compared with daughters of normal women. Prepubertal daughters of PCOS women have lower levels of adiponectin than would be expected based on their BMI. Lower adiponectin was associated with increased poststimulated insulin levels—possible relationship with insulin resistance. Adiponectin levels were similar in all pubertal girls—prepubertal PCOS-parented girls had lower adiponectin levels that stayed low into puberty whereas prepubertal girls of normal mothers had higher levels that decreased at puberty (considered the normal pattern).
Spranger et al., 2004	Case–control	• 62 PCOS women • 35 non-PCOS women	Plasma Collection: fasting AM blood draw within first 10 days after menses Sample handling: stored at −20°C until analysis Assay: RIA Unit of measure: total adiponectin Intra-assay CV: 0.1–6.2% Inter-assay CV: 5.0%	Stratification by obesity level: adiponectin levels lower in obese groups (PCOS and non-PCOS), but no difference between PCOS and non-PCOS. Conclusions: PCOS women adiponectin is independently associated with markers of obesity and insulin resistance.
Tan et al., 2006	Case–control	• 8 PCOS women • 8 non-PCOS women	Plasma Abdominal subcutaneous tissue Omental tissue Collection: Serum—morning fasting Tissue—early follicular phase collection. Sample handling: plasma stored at −80°C Tissue: methodologies included adipocyte isolation, RNA extraction, cDNA synthesis, real-time RT-PCR, Western blot Assay: serum-RIA Adiponectin intra-assay CV: 5.7%	Expression of adiponectin receptors in corresponding tissue demonstrating upregulation of receptors (ADIPOR1/R2) in both subcutaneous and omental tissue in PCOS adipocytes with no difference in BMI, WHR, and plasma adiponectin concentrations compared to controls.
Xita et al., 2007	Case only	• PCOS women • 38 normal weight • 36 overweight and obese	Serum Collection: fasting AM blood draw Sample handling: centrifuged and stored at −70°C Assay: ELISA kit Unit of measure: LMW, MMW & HMW adiponectin & leptin (no indication of what was used as analysis unit) Adiponectin intra-assay CV: 2.5–4.7% Adiponectin inter-assay CV: 5.8–6.5% Leptin intra-assay CV: <4.8% Leptin inter-assay CV: <4.3%	Adiponectin negatively correlated with BMI. Lep- tin positively correlated with BMI. Inverse correlation between adiponectin and leptin independent of BMI. Strong independent association of adiponectin–leptin ratio with adiposity and insulin resistance. Conclusions: Adiponectin/leptin ratio a biomarker of insulin resistance.

Note. ADIPO R1/R2 = adiponectin receptors 1 and 2; BMI = body mass index; CV = coefficient of variation; ELISA = enzyme-linked immunosorbent assay; HMW = high molecular weight; LMW = low molecular weight; MMW = middle molecular weight; OGTT = oral glucose tolerance test; RIA = radioimmunoassay; RT-PCR = reverse transcription polymerase chain reaction; cDNA = complementary DNA; WHR = waist–height ratio.