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**Markers of insulin resistance in Polycystic ovary syndrome women: An update**

Amisi CA. Markers of insulin resistance in PCOS

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**Abstract**

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders, affecting 5%-10% of women of reproductive age. The importance of this syndrome lies in the magnitude of associated comorbidities: infertility, metabolic dysfunction, cardiovascular disease (CVD), plus psychological and oncological complications. Insulin resistance (IR) is a prominent feature of PCOS with a prevalence of 35%-80%. Without adequate management, IR with compensatory hyperinsulinemia contributes directly to reproductive dysfunction in women with PCOS. Furthermore, epidemiological data shows compelling evidence that PCOS is associated with an increased risk of impaired glucose tolerance, gestational diabetes mellitus and type 2 diabetes. In addition, metabolic dysfunction leads to a risk for CVD that increases with aging in women with PCOS. Indeed, the severity of IR in women with PCOS is associated with the amount of abdominal obesity, even in lean women with PCOS. Given these drastic implications, it is important to diagnose and treat insulin resistance as early as possible. Many markers have been proposed. However, quantitative assessment of IR in clinical practice remains a major challenge. The gold standard method for assessing insulin sensitivity is the hyperinsulinemic euglycemic glucose clamp. However, it is not used routinely because of the complexity of its procedure. Consequently, there has been an urgent need for surrogate markers of IR that are more applicable in large population-based epidemiological investigations. Despite this, many of them are either difficult to apply in routine clinical practice or useless for women with PCOS. Considering this difficulty, there is still a need for an accurate marker for easy, early detection and assessment of IR in women with PCOS. This review highlights markers of IR already used in women with PCOS, including new markers recently reported in literature, and it establishes a new classification for these markers.

**Key Words:** Markers; Insulin resistance; Polycystic ovary syndrome; Emerging markers; Impaired glucose tolerance

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**Core Tip:** Diagnosing insulin resistance in Polycystic ovary syndrome is of crucial importance for better management and prevention of complications. Seeking of an easy-to-detect surrogate marker of insulin resistance represents a promising approach for maximizing treatment outcomes. This review highlights markers of insulin resistance already used in women with Polycystic ovary syndrome, including new markers recently reported in literature, and establishes a new classification of them.

**INTRODUCTION**

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder, affecting 5%-10% of women of reproductive age.

According to the Rotterdam consensus[1], it is defined by at least two of the following abnormalities: oligo- and/or anovulation, clinical and/or biological hyperandrogenism, and polycystic ovaries.

The importance of this syndrome lies in the magnitude of associated complications[2,3]: Reproductive complications: menstrual dysfunction, infertility, hyperandrogenism, increased pregnancy complications, amongst others; Metabolic complications: insulin resistance and increased risk factors for type 2 diabetes (T2D) mellitus and cardiovascular disease (CVD); Oncological complications: Endometrial, ovarian and breast cancers; Psychological complications: Heightened anxiety, depression.

Insulin resistance (IR), the most common metabolic feature, is found in almost 35%-80% of PCOS women and is independent of body mass index (BMI) and body fat distribution[4-7].

IR is usually defined as a pathological condition characterized by a decreased responsiveness or sensitivity to the metabolic actions of insulin. It is an established predictor of a range of disorders. In women with PCOS, IR plays an important role in the development and persistence of this disorder[8,9] and is recognized to lead to many of the metabolic abnormalities associated with metabolic syndrome. PCOS patients with IR are likely to have chronic subclinical inflammation and impaired fasting plasma glucose levels, which in turn enhance the prevalence of the more atherogenic, low-density cholesterol (LDL-c) particles[10].

Given this high prevalence, the need for accurate screening of IR in women with PCOS is obvious.

Early recognition and management of IR in women with PCOS would offer important preventive measures[11].

**Markers of direct measurement of insulin resistance IN PCOS WOMEN**

***Hyperinsulinemic euglycemic clamp***

The hyperinsulinemic euglycemic clamp technique is the gold standard method for assessing beta-cell sensitivity in humans, quantifying the amount of glucose metabolized by the body following a controlled hyperglycemic stimulus[12]. It has been used in cross-sectional and prospective studies designed to test insulin sensitivity in women with PCOS[9,13-17] and the effect of interventions such as pharmacological treatment and lifestyle management (weight loss, weight gain, or diet changes)[18-26].

However, the glucose clamp is irrelevant for clinical practice. It is ill-suited for large-scale investigations because of extensive requirements in procedure, cost, time and technical expertise. Therefore, it is rarely used.

**SURROGATE MARKERS OF INSULIN RESISTANCE IN WOMEN WITH PCOS**

Since the glucose clamp is difficult to apply in large-scale investigations because of the chaotic procedure, surrogate markers are obviously needed. Over the years, simple markers have been developed and used in clinical practice. They include anthropometric and biological indices.

**ANTHROPOMETRIC MARKERS**

Anthropometry has been widely and successfully used for assessing health and nutritional risk. Several hundred papers have been published in the past five decades that have reported the close relation between different measures of body size and one or another cardiovascular risk factors[27-34]. Most of them have attempted to assess the robustness and nature of these associations. Thus, several measures have been described and proposed as surrogate markers of IR. Anthropometric markers could be divided into fat anthropometric markers and bone anthropometric markers. To date, bone anthropometric markers have been reported as the best anthropometric marker for insulin resistance.

***Fat anthropometric markers***

**BMI:** BMI is the ratio of weight to the square of height, initially described by Keys in 1976[35]. BMI has traditionally been the chosen method to measure body size in epidemiological studies. It is used as a measure of overall adiposity and a good marker of variability in energy reserves in individuals with a sedentary lifestyle[35-41]. The positive association between obesity and the risk of developing T2D has been repeatedly observed, both in cross‐sectional studies and in prospective studies[36-40].

Over the years, BMI has been shown to be an accurate marker for detecting cardiovascular risk. BMI > 25 kg/m² is a major risk factor for a wide range of chronic diseases and metabolic abnormalities, including T2D and IR[35-40].

In women with PCOS, BMI is an independent predictor of IR[41-44]; however, it is not routinely used as a surrogate marker of IR. Indeed, since IR in PCOS is independent of body fat, it could not accurately be predicted by BMI in lean PCOS women. BMI correlates more closely with IR in overweight and obese women than in lean PCOS women.

**Waist circumference:** First suggested by Lean *et al*[45], to be more strongly associated with metabolic risk than BMI, the stronger positive association between cardiovascular risk factors and abdominal adiposity measured by anthropometric measurements of abdominal circumference has been confirmed by several studies[45].

According to the World Health Organization (WHO), waist circumference (WC) is measured at the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest[46].

WC is an easy surrogate marker of visceral adiposity and is commonly used in daily medical practice to detect IR clinically. Increased visceral adiposity is associated with a range of metabolic abnormalities, including decreased glucose tolerance, reduced insulin sensitivity and adverse lipid profiles, which are risk factors for T2D and CVD. Moreover, WC is the core component of the definition of metabolic syndrome. It is specifically required for diagnosing metabolic syndrome according to the International Diabetes Federation and the 2003 Rotterdam consensus[1,47].

A considerable correlation has been found between WC and insulin resistance assessed by the hyperinsulinemic euglycemic clamp technique[48]. A wide WC > 80 cm has been shown to be associated with IR in women with PCOS[49]. Therefore, WC is now considered the most clinically relevant approach for the measurement of IR[50].

However, the use of WC, a fat anthropometric marker, for the assessment of IR in women with PCOS is limited because IR is independent of visceral adiposity[5,7,44]. Several studies have failed to show an association between WC and IR in lean women with PCOS [51]. WC could predict IR in overweight and obese PCOS women but not in lean PCOS women[5,51]. Consequently, it is not a good anthropometric surrogate marker for assessing IR in women with PCOS[44].

**Waist-to-hip ratio:** The waist-to-hip ratio (WHR) is an anthropometric index that combines waist and hip measurements. It is used as a measure of body fat distribution. According to the WHO, WHR is calculated as waist circumference divided by hip circumference[46]. WHR > 0.8 corresponded with a BMI overweight range of 25-29.9 kg/m².

Since it measures abdominal obesity, which in turn is attributed to the presence of visceral adipose tissue that promotes insulin resistance, WHR is used as a predictor of IR and metabolic risk. However, it has been described in several papers as a less accurate marker of adiposity that could predict cardiovascular and metabolic risk[27,44,52].

In PCOS assessment, its used has been practically abandoned[27,44,52].

**Waist-to-height ratio:** In the middle of the 1990s, the use of waist-to-height ratio (WHtR) was first proposed by Lee *et al*[32], for detecting abdominal obesity and associated health risks[53].

WHtR is calculated as waist divided by height.

Several studies have found a strong association of WHtR with cardiovascular risks. Indeed, it has been reported as the best anthropometric marker to assess T2D, metabolic syndrome, cardiovascular events, and altered blood pressure[53-57]. According to Ashwell *et al*[54], WHtR is one of the best alternative measures in predicting chronic diseases. In a systematic review comparing WC to WHtR, they found that the use of WHtR provided better results over WC for CVD outcomes, as well as for T2D and hypertension. In addition, Huxley *et al*[27] conducted a systematic review and meta-analysis of the anthropometric indices of cardiometabolic risk factors, involving 32 studies, to determine which of the four indices (BMI, WC, WHR and WHtR) is the best discriminator of major cardiovascular risk factors. They found that measures of central obesity were superior to BMI as discriminators of risk of T2D, and therefore of IR. Huang *et al*[58], concluded that WHtR is one of the most representative marker to assess insulin resistance. The superiority of WHtR over BMI for detecting cardiovascular risk factors has been reported in a meta-analysis[59].

In women with PCOS, a few articles using WHtR as a marker are available. In a study conducted by Costa *et al*[60], in Brazilian women with PCOS, WHtR was the marker that presented significant positive correlations with the highest number of cardiovascular risk factors. They proposed the inclusion of this easily-measured parameter in the clinical assessment for the screening of women with PCOS and cardiovascular risk factors. Similarly, the results of a study by Gateva *et al*[61], indicated that both WHtR and WC, but not WHR, were good markers of adverse metabolic profiles in women with PCOS. More recently, Bhattacharya *et al*[62], suggested that WHtR could be used as an inexpensive and noninvasive screening tool for the early prediction of PCOS and IR among PCOS patients. Amisi *et al*[44], comparing several anthropometric markers, found that WHtR and WC showed similar performance but were less predictive of IR than wrist circumference.

***Bone anthropometric markers***

**Wrist circumference:** Wrist circumference (Wrc)was first proposed as a marker of insulin resistance in young obese people by Cappizzi *et al*[63]. His team was inspired by the findings of Karsenty *et al*[64], on the involvement of the bone system in glucose metabolism *via* osteocalcin (OC) effects on insulin[65-67]. Hyperinsulinemia has been associated with increased bone mass[68-70], and wide WrC has been associated with IR[71-74]. Esmaeilzadeh *et al*[75], found a positive correlation between WrC and PCOS status.

Amisi *et al*[44], showed that WrC is the best anthropometric marker known to date for the assessment of insulin resistance in women with PCOS. In their study, they reported a significantly higher correlation of nondominant WrC with IR than other anthropometric markers.

The novelty of WrC as a marker of IR is that it is based on the assessment of IR on bone, not on fat, as other anthropometric markers.

WrC is, to date, the only anthropometric marker that can assess IR in both obese and lean women. WrC is, consequently, the only useful clinical measure for assessing IR in lean women with PCOS. Given that most women with PCOS are insulin resistant, which is independent from fat and characterized by hyperinsulinemia, fat anthropometric markers are not suitable[44].

However, there are few publications on WrC as a marker of IR in women with PCOS.

**BIOLOGICAL MARKERS**

***Markers using insulin and/or glucose***

**Oral glucose tolerance test:** The oral glucose tolerance test (OGTT) is a frequently used index of glucose tolerance. It is commonly used in medical practice to detect IGT and T2D. Moreover, OGTT is the only means of identifying people with IGT[76]. The WHO recommends the test as a valid way to diagnose diabetes.

According to the WHO, the OGTT technique involves the oral administration of 75 g of glucose after 8 to 10 h of fasting. At 0, 30, 60 and 120 min following the oral glucose load, blood glucose levels are measured to determine how rapidly it is cleared from the bloodstream.

In PCOS women, the Androgen Excess Society in consensus with the European Society of Human Reproduction and Embryology (ESHRE) and the American Society of Reproductive Medicine (ASRM) have recently recommended a 2 h OGTT in all women with PCOS, with annual or biannual rescreening, depending on the risk factors[11,77,78]. The Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS consensus Workshop Group recommended screening for IGT and T2D when presented with the following conditions: hyperandrogenism with anovulation, acanthosis nigricans, obesity (BMI > 30 kg/m²) in women with a family history of T2D or gestational diabetes mellitus[78].

However, OGTT provides useful information about glucose tolerance but not insulin resistance. In addition, it is more time-consuming and labor intensive to perform.

**Glucose/insulin ratio:** The glucose/insulin ratio (G/I) has long been employed as an index of IR[4,79-82].

It has been described by Legro *et al*[83], as a useful measure of insulin sensitivity in obese PCOS women and has both high sensitivity and specificity for detecting IR in women. In addition, the G/I ratio reflects profound peripheral IR and hepatic IR, which are found in obese women.

Furthermore, Quon confirmed the same in his editorial published in 2004, explaining how the G/I ratio correlates with insulin sensitivity in nondiabetic patients with PCOS[84]. In healthy subjects with normal fasting glucose levels, elevations in fasting insulin levels correspond to increased IR. Since fasting glucose levels are similar for all subjects, the G/I ratio is functionally equivalent to 1/insulin, which is a well-known proxy for insulin sensitivity. It decreases as a subject becomes more insulin resistant and their fasting glucose rises[84].

However, the use of the fasting G/I ratio is limited in PCOS women with abnormal fasting glucose levels because, as demonstrated by Quon, this leads to erroneous results. Indeed, the G/I ratio is similar to 1/insulin in nondiabetic subjects, but it increases paradoxically in diabetic subjects and in PCOS women with abnormal glucose levels[84]. Consequently, the fasting G/I ratio has been considered a potentially flawed index of insulin sensitivity[84].

**Fasting insulin:** Numerous studies have investigated and proposed fasting insulin concentrations as the simplest index for assessing IR[85-87] because it has been shown to correlate well. High fasting insulin level in individuals with normal glucose tolerance has been found to reflect IR. Furthermore, high insulin concentrations presage the development of diabetes in the future[88].

In nondiabetic subjects with normal fasting glucose levels, the rise of fasting insulin levels corresponds to insulin resistance. In this population, insulin sensitivity, which decreases as subjects become more insulin resistant, can be substituted by 1/fasting insulin.

In women with PCOS, many authors have recommended fasting insulin as a simple office-based method to assess insulin resistance[77,89,90].

Recently, after comparing the prevalence of IR using published methods in a cohort of women with PCOS, Lunger *et al*[91], suggested the use of fasting insulin as a simple screening test. This can reduce the number of OGTTs needed to routinely assess IR in women with PCOS, as proposed by the Androgen Excess Society.

However, the use of fasting insulin for assessing IR in women with PCOS could be limited by a lack of adequate laboratories and the cost of insulin assays, especially in developing countries.

**Minimal model analysis of frequently sampled intravenous glucose tolerance test:** The frequently sampled intravenous glucose tolerance test (FSIVGTT) is an alternative method sought to simplify the clamp procedure. It provides information on both insulin sensitivity and β-cell function. The minimal model was developed by Bergman *et al*[92], in 1979 as a method to obtain an indirect measurement of insulin sensitivity or insulin resistance.

The standard technique of FSIVGTT includes multiple blood sampling for insulin and glucose. Baseline blood samples for insulin and glucose were taken at 15, 20, 25, and 30 min following the placement of an intravenous catheter. Glucose was then infused intravenously as a bolus over 1 min, followed by the extraction of blood samples for glucose and insulin measurements at 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 25, 30, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160 and 180 min after the start of the glucose injection.

Plasma glucose and insulin concentrations collected during the test were subjected to minimal model analysis using the computer program MINMOD to generate an index of insulin sensitivity (Si).

Parameters derived from minimal model analysis have been found to correlate with those from euglycemic clamps[93].

Although FSIVGTT is minimally invasive and easier than euglycemic clamp, it is not suitable for large epidemiological studies. The complexity of the sampling procedure, the number of samples required and especially the corresponding higher cost make it unsuitable for clinical use.

**Homeostasis model assessment:** The Homeostasis Model Assessment (HOMA) is a method used to quantify insulin resistance from basal glucose and insulin levels, first described in 1985 by Matthews *et al*[94]. HOMA is a mathematical model of the relationship of insulin and glucose concentrations for a wide range of possible combinations of insulin resistance and β-cell function. It assumes the principle of interactions between β-cell deficiency, insulin resistance and fasting hyperglycemia. Consequently, any given decrease in insulin sensitivity and β-cell dysfunction is associated with fasting steady-state insulin and glucose concentrations. Using a computer-solved mathematical model of basal insulin and glucose interactions, the authors plotted a wide range of basal plasma insulin and glucose concentrations expected for possible combinations of insulin resistance and β-cell deficiency, to obtain the first model of HOMA. The early model was later updated using nonlinear solutions[95]. The approximating equation for insulin resistance has been simplified, and insulin resistance values can be derived from basal insulin and glucose concentrations as follows: HOMA-IR = insulin (mU/L) × glucose (mmol/L)/22.5.

The β-cell function is calculated as: HOMA β-cell = 20 x insulin (mU/L)/[glucose (mmol/L) - 3.5].

A strong linear correlation of HOMA-IR has been found with the euglycemic-hyperinsulinemic clamp[96,97]. However, HOMA-IR is determined from fasting concentrations of glucose and insulin. It provides an estimation of hepatic insulin sensitivity and could, therefore, assume the important limitation of identifying hepatic and peripheral insulin sensitivity. However, this is not the case in reality.

In women with PCOS, HOMA-IR has been used in various studies of distinct populations to assess insulin resistance[7,44,98-101]. Furthermore, the HOMA has proven to be a robust clinical and epidemiological tool for assessing IR. Similarly, HOMA β-cell has been used as a marker of basal insulin secretion by pancreatic β-cells[98].

In Sub-Saharan African women and in developing countries in general, HOMA-IR has been successfully used[7,44]. However, although the HOMA index has proven to be an accurate means to assess insulin resistance, it is difficult to perform in developing and low-resource countries because of the cost of insulin measurements, as well as the lack of adequate laboratories and equipment.

**Log (HOMA-IR):** To more accurately reflect the physiology, other modifications have been made to the Homeostasis Model Assessment for insulin resistance (HOMA-IR). Using a computer program, log transformed HOMA-IR [Ln(HOMA-IR)] was obtained[96,102] and it correlates well with the eugylcemic clamp method[96].

Comparing Log(HOMA-IR) and HOMA-IR with the Minimal model, Log(HOMA-IR) correlated more strongly than HOMA-IR in nondiabetic subjects[103]. Log(HOMA-IR) has been found to be more convenient than HOMA-IR for the assessment of IR in mild to moderate diabetes and glucose intolerance. Moreover, Log(HOMA-IR) is a better predictor of insulin sensitivity than HOMA-IR[ 103].

Similar to HOMA-IR, log(HOMA-IR) has been extensively used in large epidemiological studies and in clinical research[103,104].

However, log(HOMA-IR) has been used in few studies for assessing IR in women with PCOS[42,105,106].

**Fasting insulin resistance index:** The fasting insulin resistance index (FIRI) was proposed by Duncan *et al*[107], in 1989.

FIRI is calculated as: FIRI = (glucose x insulin)/25.

However, in women with PCOS, FIRI has not been extensively used, similar to HOMA-IR[108,109].

**Quantitative insulin sensitivity check index:** Quantitative insulin sensitivity check index(QUICK) is an index of insulin sensitivity that provides a consistent and precise index of insulin sensitivity with better positive predictive power[110-111]. It is calculated from basal glucose and insulin concentrations obtained from a single fasting blood specimen. QUICKI is similar to HOMA and is simply its variation, as it interprets the data by taking both logarithms and the reciprocal of the fasting glucose-insulin product. Consequently, it is more accurate than HOMA in calculations over a wide range of insulin sensitivities.

QUICKI = 1/[log insulin (µU/mL) + log glucose (mg/dL)].

This formula implies that the lower the QUICKI value, the lower the insulin sensitivity.

QUICKI has been strongly correlated with measurements made by the euyglycemic clamp technique, especially in obese and diabetic subjects[112]. However, its performance was less satisfactory in subjects with normal glucose tolerance. Therefore, the revised QUICKI, which incorporates the fasting plasma free fatty acid concentration (FFA) into the equation, has been proposed[113-114]:

Revised QUICKI = 1/[log insulin (µU/mL) + log glucose (mg/dL) + log FFA (mmol/L)].

QUICKI has been shown to be appropriate and effective for use in large epidemiological or clinical research studies[111,115].

In a large meta-analysis of insulin-resistant subjects, Hanley *et al*[115], demonstrated that QUICKI is a simple surrogate index with the best positive predictive power for determining the development of diabetes.

In women with PCOS, QUICKI is among the most thoroughly evaluated surrogate indices for insulin sensitivity. It has been validated as a simple, inexpensive, useful, and minimally invasive surrogate index of insulin sensitivity[116-118].

***Derived surrogate markers from OGTT***

Some studies, carried out in other clinical conditions, suggested that surrogate indices derived from the OGTT could perform better than those obtained from fasting values[119-122].

**Matsuda index:** Additionally, called “the composite index”, the Matsuda index was described by Dr Masafuni Matsuda and Prof Ralph DeFronzo in 1999. The Matsuda index, or the composite whole-body insulin sensitivity index (WBISI), is an index of IR derived from the OGTT that evaluates whole-body physiological insulin sensitivity. It is determined by insulin and glucose values obtained from the OGTT[120].

In women with PCOS, Rizzo *et al*[123], found that the Matsuda index correlates well with the HOMA-IR and QUICKI, indicating that it may be a reliable substitute in the detection of IR and subsequent intervention required to improve outcomes in women with PCOS. Ciampelli *et al*[90], observed that the Matsuda index obtained the best correlation coefficients with the euglycemic clamp in menopausal women.

**Stumvoll index:** Another index derived from the OGTT has been described by Stumvoll *et al*[121]. From demographic data (age, BMI, WHR), as well as insulin and glucose values obtained from the OGTT, they found a new index to predict insulin sensitivity and beta cell function.

However, in PCOS, only a few published studies have used the Stumvoll index[121,124-126].

In a recent study, Lewandowski *et al*[124], found that the correlation between various IR indices is highly variable when comparing surrogate methods based on fasting insulin and either fasting glucose (HOMA-IR and QUICKI) or triglycerides (McAuley Index), with IR indices derived from glucose and insulin during an OGTT (Belfiore, Matsuda and Stumvoll indices). They suggested that the clinical application of surrogate indices for the assessment of IR in PCOS must therefore be viewed with extreme caution[124].

Tosi *et al*[119], evaluated the performance of several surrogate markers of insulin resistance in identifying individual PCOS subjects with impaired insulin sensitivity, as defined by the euglycemic clamp, and found that all surrogate indices were highly correlated with hyperinsulinemic euglycemic clamp values. However, their ability to identify insulin-resistant individuals was limited in terms of sensitivity, especially in normal-weight subjects. ROC analysis showed similar performances of these indices (AUC values 0.782-0.817). They concluded that surrogate indices of insulin action show a low sensitivity in identifying insulin-resistant subjects, which causes many subjects to be erroneously diagnosed as insulin sensitive[119].

**Avignon index:** Avignon *et al*[127], also used OGTT values to try and develop another insulin sensitivity index. They compared sensitivity indices obtained from baseline fasting insulin and glucose levels (Sib), and at the end of the second hour of the OGTT (Si2h), a third insulin sensitivity index (SiM) was calculated by averaging Sib and Si2h. They observed that sensitivity indices obtained were useful to obtain a single test that could be used to determine both glucose tolerance and an estimate of insulin sensitivity.

In the study conducted in women with PCOS and menopausal subjects, which aimed to verify the validity of several indices of insulin sensitivity by comparing the data obtained by indices to those of the euglycemic clamp, Ciampelli *et al*[90] found that the best correlation with clamp studies was obtained with the Avignon Insulin Sensitivity Index in PCOS. The Matsuda index obtained the best correlation in menopausal patients[90].

**Gutt index:** In the search for a simple measure of insulin sensitivity, Gutt *et al*[122], also explored the use of OGTT values.

They devised a formula for an insulin sensitivity index, ISI (0, 120), that uses the fasting (0 min) and 120 min post oral glucose (OGTT), insulin and glucose concentrations. They found that ISI (0, 120) correlates well when applied prospectively in comparative studies, with the insulin sensitivity index obtained from the euglycemic hyperinsulinelic clamp[122].

In PCOS, Tosi *et al*[119], demonstrated the substantial pitfalls of derived surrogate indices, including the Gutt index, in identifying insulin-resistant individuals among PCOS women. Collectively, these indices showed a high PPV (90%-96%) but a low NPV (36%-45%). In other words, many subjects with insulin resistance were not recognized by any of these surrogate markers[119].

**Insulinogenic index:**The insulinogenic index (IGI) is derived from the OGTT to evaluate β-cell function.

IGI = [(30 min insulin - fasting insulin)/30 min glucose]

IGI is used to estimate the level of insulin secretion during glucose administration. The insulinogenic index has been commonly used during the first 30 min of the OGTT as a surrogate measure of first-phase insulin responses to a glucose challenge[128].

In women with PCOS, IGI is frequently used to express β-cell function[9,129-132].

**Homa-M120:** Morciano *et al*[133], first reported the aim of developing and validating a specific simple measure of insulin sensitivity using oral glucose tolerance test (OGTT) values for lean PCOS women because their cardiometabolic impairment is more frequently misunderstood. They showed that a temporarily delayed assessment of glucose and insulin concentrations during OGTT is more predictive of IR than a standard fasting evaluation, such as with HOMA-IR[133].

They then compared HOMA-M120 with other OGTT-derived indices and concluded that the 120-minute glucose and insulin evaluation (HOMA-M120) was the best IR index in lean PCOS women[133] .

Song DK *et al*[126], made the same observation that lean women with PCOS, even when β-cell function is matched, showed higher values for HOMA-M120 but not HOMA-IR than matched controls.

***Markers using lipid and lipoproteins***

Abnormal lipid metabolism is one of the main characteristics of women with PCOS, with a prevalence of up to 70%[134-136]. Insulin resistance is closely associated with lipid disorders: elevated triglycerides (TGs), low-density cholesterol (LDL-c) levels and low high-density cholesterol (HDL-c) levels[136-142]. Increased serum concentrations of LDL-c and TG, as well as decreased HDL-c, are recognized as risk factors for cardiovascular disease[143-145]. Several epidemiologic studies have reported that lipid ratios are better predictors of atherosclerosis and cardiovascular disease than any other single lipid marker[144]. The superior ability of lipid ratios to predict the risk of cardiovascular disease than single lipid markers is of particular clinical interest.

Seeking a simple, effective and economic method to investigate IR, many researchers have suggested lipid ratios as surrogate indices[138-142].

Moreover, in PCOS patients, several studies have shown that the serum lipoprotein ratio has a significant positive correlation with IR and could be employed as a simple reliable indicator to determine IR[134-142,146].

**TG/HDL-c:** In overweight individuals with normal glucose tolerance, the TG/HDL-c ratio has shown the ability to identify IR with similar sensitivity and specificity to those of fasting plasma insulin concentration. It has been proposed as a marker of insulin resistance[147]. Furthermore, low serum HDL-c combined with increased serum TG concentrations predicts the development of T2D[148].

In women with PCOS, Barrios *et al*[149], evaluated the relationship between the TG/HDL-c ratio and IR indices. They found that women with PCOS showed significantly higher TG/HDL-c ratios and HOMA-IR values, but lower QUICKI values. They proposed the TG/HDL-c ratio as a useful and practical method of assessing IR[149]. The same observation was made by Xiang *et al*[139]. The TG/HDL-c ratio seems to be the best index that directly correlates with insulin levels and can therefore be used as a marker of IR[138-140,149].

However, the problem with all markers using TG levels is that they could not be used efficiently in the African population because of the presence of TGs. Indeed, the Sub-Saharan African population presents what has been called the “TG paradox”: Normal TG levels in the presence of IR[150]. This fact emphasized the previous need for a normal threshold of TG in the African population.

**TC/HDL-c:** Several epidemiologic studies have demonstrated that total cholesterol (TC)/HDL-c is a better predictor of atherosclerosis and cardiovascular disease than TC or HDL-c alone[144]. Furthermore, the TC/HDL-c ratio was shown to correlate negatively with insulin concentrations[151]. Subsequently, normal subjects with standard weight or overweight, as well as an increased TC/HDL-c ratio, have shown insulin resistance, increased TG concentrations, and hyperinsulinemia[152].

In women with PCOS, upon comparing the three lipid ratios commonly used as surrogate markers of IR (TG/HDL-c, TC/HDL-c, LDL-c/HDL-c), Xiang *et al*[139], found that the area under the ROC curve of TC/HDL-c was the largest, with the highest sensitivity and specificity. However, these findings were not confirmed in a similar study that reported the largest area under the ROC curve of TG/HDL-c[140].

**LDL/HDL-c:** Another index using lipoprotein is LDL/HDL-c ratio. It has also been found to correlate well with cardiovascular diseases.

In women with PCOS, it has been shown that LDL/HDL-c is an effective diagnostic marker for insulin resistance[139-140].

***Emerging markers***

Scientific evidence has disclosed strong influences between inflammatory mechanisms and IR. Some studies have shown that insulin resistance itself amplifies chronic inflammation[153]. PCOS is now recognized as a proinflammatory state associated with elevations in a number of circulating inflammatory mediators[154]. Therefore, it is not surprising that inflammatory markers have gained popularity in IR assessment, with several being proposed as surrogate markers of IR.

**Interleukin-6:** Interleukin-6 (IL-6), a major proinflammatory cytokine, has been shown to be closely associated with IR[155].

In women with PCOS, low-grade chronic inflammation has been reported and is involved in the pathogenesis of T2D and CVD[156]. However, conflicting results regarding IL-6 Levels in women with PCOS have been reported.

To evaluate IL-6 Levels in women with PCOS, a systematic review and meta-analysis were performed[157]. High levels of IL-6 have been reported to be related to IR. Interestingly, IL-6 levels have been reported to be high in both lean and obese women with PCOS. Indeed, IL-6 has been found to be related to IR and androgen levels but not to BMI.

However, Escobar-Morreale did not find statistically significant differences between PCOS and controls regarding IL-6 concentrations[154].

**C-Reactive protein:** C-Reactive protein (CRP) is one of the markers of systemic subclinical inflammation[158,159]. The relationship of CRP and several measures of IR has been described[160]. However, CRP alone could not predict IR.

It is well known that women with PCOS exhibit an elevation in circulating CRP that is independent of obesity[161]. Moreover, in a meta-analysis, circulating CRP was found to be 95% higher in women with PCOS than in controls[154]. This finding corroborates the existence of low-grade chronic inflammation in women with PCOS[156,161].

Nonetheless, in women with PCOS, elevation of CRP seems to be a PCOS effect rather than a result of IR. This fact limits its use as a good marker of IR.

**Soluble CD 36:** Soluble CD36 (SCD36) was initially described by Handberg *et al*[161], as a novel marker of IR. It has been found to be distinctly elevated in patients with IR and T2D[161].

In PCOS, a study conducted by Glintborg *et al*[162], reported that SCD36 correlated with measures of insulin sensitivity independent of central fat mass. Furthermore, pioglitazone treatment reduced SCD36 while improving insulin-stimulated glucose metabolism[162].

Nonetheless, more studies need to be conducted in PCOS to ascertain this association.

**C3 complement:** Recently, Muscari *et al*[163], reported a strong link between C3 complement (C3) and IR in an elderly population, independent of the components of metabolic syndrome. Some researchers have described the insulin-like properties of C3. Indeed, activation of C3 complement has been proven to have insulin-like properties. It affects glucose transmembrane transport and promotes the synthesis of TG in adipocytes[164].

In PCOS, Yang *et al*[165], reported a strong association of serum C3 complement with insulin resistance. Lewis RD *et al*[166], observed a similar phenomenon. However, in a study conducted by Dehdashtihaghighat *et al*[167], such an association was not found.

Even so, this observation needs to be further investigated.

**Ferritin:** Ferritin, a major intracellular iron storage protein, has been proposed as a new marker of IR. High levels of ferritin have been associated with hyperinsulinemia and hypertriglyciridemia[168].

In PCOS women, elevated serum ferritin levels have been found to be associated with increased insulin resistance and the risk of diabetes in obese women but not in nonobese women[169]. Moreover, in both obese and nonobese PCOS women, higher serum ferritin levels have been correlated with a greater risk of hypertriglyceridemia.

In addition, elevated ferritin levels have been reported as a result of insulin resistance and hyperinsulinism but not reduced menstrual losses secondary to oligomenorrhea or amenorrhea[170,171].

Nevertheless, more studies are needed to better clarify its applicability as a marker of IR in women with PCOS.

**Adiponectin:** Adiponectin is a protein produced by adipocytes with direct insulin sensitizing activity, plus vascular protective and anti-inflammatory effects. Adiponectin reduces glucose production by the liver and increases fatty acid oxidation in skeletal muscle. In addition to its antidiabetic effects, adiponectin possesses direct antiatherogenic properties[172,173]. In a variety of conditions frequently associated with IR, such as diabetes, hypertension and CVD, its plasma concentration has been found to be reduced[174,175]. Moreover, a reduction in high molecular weight (HMW) adiponectin levels, a fraction of adiponectin that is considered a potent mediator of insulin sensitivity, has been reported in IR states[176]. HMW is also decreased by testosterone[177]. It has recently been proposed that the ratio of HMW/total adiponectin, but not the absolute amounts of adiponectin, determines insulin sensitivity[178].

In women with PCOS, low serum adiponectin and HMW levels have been reported to be associated with IR[8,179-181]. It has been suggested that adiponectin may serve as the common denominator that connects obesity, IR and altered lipid metabolism in PCOS patients[177]. Furthermore, serum adiponectin levels have been suppressed in patients with both metabolic syndrome and IR. Consequently, the use of serum concentrations of adiponectin as a biomarker for insulin resistance has been suggested to distinguish PCOS patients at a higher risk of diabetes and cardiovascular morbidity[182].

However, the assumption that adiponectin is an intrinsic characteristic of IR in women with PCOS remains controversial. In addition, the effect of testosterone levels on adiponectin levels should be further investigated.

**Tumor necrosis factor-α:**Tumor necrosis factor-α (TNF-α) is an inflammatory cytokine produced mainly by monocytes and macrophages. Several studies have shown a relation between TNF-α and IR in the general population[183].

In women with PCOS, multiple studies have demonstrated elevated levels of TNF-α[184,185].

TNF-α has been shown to impact ovarian function, including follicular development, ovulation, and corpus luteum regression[186]. Furthermore, it has been suggested that TNF-α promotes IR in women with PCOS and is implicated in the pathophysiology of PCOS[185].

However, Escobar-Morreale *et al*[154], in a meta-analysis cited above, found that TNF-α levels were not significantly different in women with PCOS compared to controls.

Therefore, the association of TNF-α and IR in women with PCOS remains controversial.

**Glycosylated hemoglobin:** Glycosylated hemoglobin (HbA1c) is the most common marker of chronic hyperglycemia and has long been considered the most practical approach used to review long-term glycemic control in diabetic patients. However, in 2010, the American Diabetes Association (ADA) included a glycated hemoglobin A1(c) (A1C) level as a component of diagnostic criteria of 'increased risk for diabetes'[187]. Since then, some researchers have conducted studies to examine the relationship of 'elevated A1C' (≥ 5.7%) with 'increased risk for diabetes' in women with PCOS to generalize its use as a screening test of prediabetes[188-192]. Indeed, increased HbA1c levels in the range of 5.7%-6.4% have been found to reflect IR or some component of metabolic syndrome[193].

However, the results reported in the current literature are controversial. A high prevalence of elevated A1C in nonobese patients with PCOS and an increased risk of elevated A1C have been associated with PCOS. Therefore, assessment of A1C as a useful new approach to screening for diabetes has been recommended[188,194]. Conversely, many studies do not support the recommendation that HbA1c can be used for the screening of prediabetes in women with PCOS because it failed to identify IR, though it was diagnosed in many PCOS patients by HOMA or fasting insulin levels[190,195].

**Leptin:** Leptin is an adipocyte-derived hormone that regulates a broad spectrum of homeostatic functions. It was the first adipokine to be identified[195,196]. One homeostatic function modulated by leptin is the regulation of insulin secretion by pancreatic β-cells and the regulation of insulin action and energy metabolism in adipocytes and skeletal muscle[197]. Leptin suppresses food intake and promotes energy expenditure mainly *via* its direct effects on hypothalamic neurons, and it is thus considered an antiobese hormone. Leptin levels decrease with fasting and increase with food intake[198,199].

A positive relationship between leptin, fat mass and BMI has been reported. Leptin levels are increased in obesity and significantly correlated with IR[200].

In women with PCOS, several prospective studies have confirmed that an increased leptin level is associated with insulin resistance and an elevated risk of obesity and diabetes[201-203]. Leptin has been found to have a strong positive correlation with HOMA-IR[204]. However, many studies failed to report any significant differences in serum leptin levels in women with PCOS when compared with age- and weight-matched controls[205-207]. The relationship between leptin and IR is thus still a matter of debate. Wang *et al*[208], did not observe significant differences in serum leptin between PCOS with IR and PCOS without IR. However, Yildizhan *et al*[202], observed an association between serum leptin levels and IR in young women with PCOS. Further investigation is needed to clarify the link between leptin and IR in women with PCOS.

**Resistin:** First found by Steppan *et al*[209], resistin is an adipokine that exerts an inhibitory effect on adipocyte differentiation and exerts resistance to insulin in mice. It has been suggested that resistin could be the potential link between obesity and diabetes[209,210]. Moreover, resistin seems to be an important adipokine that is involved in obesity, IR and PCOS[211].

However, these are hypotheses that need to be ascertained in humans. Data regarding the association between resistin and IR remain controversial. Many studies failed to recognize any association between resistin and IR[212-213], while a few studies indeed discovered a significant positive correlation[214-215].

In women with PCOS, conflicting results have also been reported[216-218]. Munir *et al*[216], reported increased concentrations of serum resistin levels in women with PCOS in comparison to controls. However, no significant difference was found in circulating resistin levels between PCOS and controls in most studies[217,218].

**Vaspin:** Elevated serum and omental adipose tissue levels of visceral adipose tissue-derived serine protease inhibitor (vaspin) in overweight PCOS women and *ex vivo* regulation of vaspin, predominantly by glucose, were reported, for the first time, by Tan *et al*[219]. A similar result was found by Dogan *et al*[220]. However, Franik G *et al*[221], did not observe correlations between plasma vaspin levels and serum glucose and insulin concentrations or HOMA-IR values.

**Apelin:** Apelin is a peptide expressed in several organs and in visceral and subcutaneous tissues[222].

Controversial results have been reported by different authors. Several authors reported elevated apelin, while others reported low serum levels of the same[223-228]. Polak *et al*[8], in their recent review of the literature, concluded that discrepant findings among the published studies may be attributed to the differences in ethnicity, age, study design, sample size, genetic characteristics of populations, and assessment methodology. Further studies are necessary to elucidate the role of apelin in insulin resistance in PCOS.

**Copeptin:** Copeptin, a vasoactive peptide, has been reported to play an important role in CVD and metabolic disorders. Enhanced copeptin levels in PCOS patients are positively associated with fasting insulin, HOMA-IR, androgenic profile, triglycerides and carotid intima media thickness, indicating that copeptin may play an important role in cardiometabolic consequences in PCOS[8,229-231].

However, to date, few studies have been performed to assess copeptin as a marker of IR in women with PCOS.

Further data from large-scale longitudinal studies are required for its validation.

**Irisin:** Irisin is a myokine identified as a new marker of IR[8,232-234].

In PCOS, a significant positive correlation between circulating irisin, IR and dyslipidemia has been found.Li *et al*[233], demonstrated that irisin levels were significantly higher in PCOS subjects than in controls, as well as in overweight and obese patients than in lean women. Similar results were obtained by Li *et al*[234].

Further studies are necessary to confirm these findings.

**Zinc-α2-glycoprotein:** Zinc-α2-glycoprotein (ZAG) has been proposed to play a role in the pathogenesis of insulin resistance[235].

In women with PCOS, Lai *et al*[236], found that women with PCOS and high ZAG had fewer metabolic syndrome, IGT and polycystic ovaries than those with low ZAG. Taken together, circulating ZAG levels are reduced in women with PCOS. They concluded that ZAG may be a cytokine associated with insulin resistance in women with PCOS[236,237]. Pearsey *et al*[238], arrived at a similar conclusion.

Zheng *et al*[238], performed a study to investigate changes in ZAG levels after exenatide or metformin treatment. The results showed that circulating ZAG was significantly lower in women with PCOS than in healthy women. After 12 wk of exenatide or metformin treatment, there were significant increases in circulating ZAG in both treatment groups[238].

Therefore, more research is needed before robust conclusions can be drawn[8].

**Plasminogen activator inhibitor-1:** Numerous studies have reported the association between IR and plasminogen activator inhibitor-1 (PAI-1), a glycoprotein involved in the coagulation system[8,239-241].

PAI-1 has been found to be linked to insulin resistance in PCOS subjects[8,239-242].

Further data from large-scale longitudinal studies are required for its validation.

**CONCLUSION**

This article is an attempt to summarize existing markers of IR and their usefulness in women with PCOS. There is no recommended screening method for assessing IR in women with PCOS despite evidence of the high prevalence of this metabolic disturbance.

A host of methods have been described for assessing insulin resistance. Each method has its own merits and disadvantages.

The euglycemic clamp remains the gold standard for direct measurement of insulin sensitivity.

Concerning anthropometric surrogate markers, wrist circumference could revolutionize the assessment of IR in women with PCOS if validated through large-scale studies.

Regarding biological surrogate markers, HOMA-IR is the best and extensively validated marker.

Biological markers using lipids and lipoproteins are inconsistent in the Sub-Saharan African population and hence in Sub-Saharan African PCOS women.

Conflicting data concerning emerging markers in women with PCOS limit their use in the clinical setting.

Finally, an easy-to-detect marker for assessing IR in women with PCOS is urgently required.

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