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

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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
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.[33-40].

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 hyperinsulinenic 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[5,44]. 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 use 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[33].

WHR 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. [38], 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[39].

In women with PCOS, a few articles using WHtR as a marker are available. In a study conducted by Costa et al. [40], 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 WHR and WC, but not WHtR, 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]. Esmaeizadeh 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.
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[83].

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-hyperinsulinenic 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\(^\text{[96,102]}\) and it correlates well with the euglycemic clamp method\(^\text{[96]}\).

Comparing Log(HOMA-IR) and HOMA-IR with the Minimal model, Log(HOMA-IR) correlated more strongly than HOMA-IR in nondiabetic subjects\(^\text{[105]}\). 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\(^\text{[103]}\).

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

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

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

FIRI is calculated as: \(\text{FIRI} = \frac{\text{glucose} \times \text{insulin}}{25}\).

However, in women with PCOS, FIRI has not been extensively used, similar to HOMA-IR\(^\text{[108,109]}\).

**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\(^\text{[110-111]}\). 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.

\[
\text{QUICKI} = \frac{1}{\log \text{insulin} (\mu U/mL) + \log \text{glucose} (mg/dL)}
\]

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

QUICKI has been strongly correlated with measurements made by the euglycemic clamp technique, especially in obese and diabetic subjects\(^\text{[112]}\). 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\(^\text{[113-114]}\):

Revised QUICKI = \(\frac{1}{\log \text{insulin} (\mu U/mL) + \log \text{glucose} (mg/dL) + \log \text{FFA} (mmol/L)}\)

QUICKI has been shown to be appropriate and effective for use in large epidemiological or clinical research studies\(^\text{[111,115]}\).

In a large meta-analysis of insulin-resistant subjects, Hanley et al\(^\text{[115]}\), 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\(^\text{[116-118]}\).

**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\(^\text{[119-122]}\).

**Matsuda index:** Additionally, called “the composite index”, the Matsuda index was described by Dr Masafumi 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\(^\text{[120]}\).

In women with PCOS, Rizzo et al\(^\text{[122]}\), 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\(^\text{[90]}\), 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\(^\text{[121]}\). 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\(^\text{[121,124-126]}\).

In a recent study, Lewandowski et al\(^\text{[124]}\), 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\(^\text{[124]}\).
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 hyperinsulinemic 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.

\[
IGI = \frac{(30 \text{ min insulin} - \text{fasting insulin})}{30 \text{ min glucose}}
\]

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[134-142]. 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 concent-
Markers of insulin resistance in PCOS

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 CD36:** 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 Glinborg 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 Dehdashtighaghid 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 hypertriglyceridemia[168].

In PCOS women, elevated serum ferritin levels have been found to be associated with increased insulin resistance and the risk of obesity 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[223-226]. 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[235], 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.

### FOOTNOTES

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### REFERENCES

1. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to Polycystic ovary syndrome (PCOS). *Hum Reprod* 2004; 19: 41-47 [PMID: 14688154 DOI: 10.1093/humrep/deh098]
2. Bates GW, Legro RS. Longterm management of Polycystic Ovarian Syndrome (PCOS). *Mol Cell Endocrinol* 2013; 373: 91-97 [PMID: 23261983 DOI: 10.1016/j.mce.2012.10.029]
3. Palomba S, Santagni S, Falbo A, La Sala GB. Complications and challenges associated with Polycystic ovary syndrome : current perspectives. *Int J Womens Health* 2015; 7: 745-763 [PMID: 26261426 DOI: 10.2147/IJWH.S70314]
4. Carmina E, Lobo RA. Use of fasting blood to assess the prevalence of insulin resistance in women with Polycystic ovary syndrome. *Fertil Steril* 2004; 82: 661-665 [PMID: 15374711 DOI: 10.1016/j.fertnstert.2004.01.041]
5. Dunaiif A, Segal KR, Futterweit W, Dobrjansky A. Profound peripheral insulin resistance, independent of obesity, in Polycystic ovary syndrome. *Diabetes* 1989; 38: 1165-1174 [PMID: 2670645 DOI: 10.2337/diabetes.38.9.1165]
6. Mayer SB, Evans WS, Nestler JE. Polycystic ovary syndrome and insulin: our understanding in the past, present and
Amisi CA. Markers of insulin resistance in PCOS

future. *Women's Health (Lond)* 2015; 11: 137-149 [PMID: 25756288 DOI: 10.2217/WHE.14.73]

Amisi C, Mputa M, Mboloko E, Bielci E, Pozzili P. [Biological insulin resistance in Congolese woman with Polycystic ovary syndrome (PCOS)]. *Gynecol Obstet Fertil* 2013; 41: 707-710 [PMID: 24200988 DOI: 10.1016/j.gyobfe.2013.08.002]

Polak K, Czyzyk A, Simoncini T, Meczakalski B. New markers of insulin resistance in Polycystic ovary syndrome. *J Endocrinol Invest* 2011; 34: 1-8 [PMID: 21743787 DOI: 10.1007/s40618-011-0523-z]

Amato MC, Vesco R, Vigneri E, Ciresi A, Giordano C. Hyperinsulinism and Polycystic ovary syndrome (PCOS): role of insulin clearance. *J Endocrinol Invest* 2015; 38: 1319-1326 [PMID: 26294351 DOI: 10.1007/s40618-015-0372-x]

Singh B, Saxena A. Surrogate markers of insulin resistance: A review. *World J Diabetes* 2010; 1: 36-47 [PMID: 21537426 DOI: 10.4239/wjd.v1.i2.36]

Wild RA, Carmina E, Diamanti-Kandarakis E, Dokras A, Escobar-Morreale HF, Futterweit W, Lobo R, Norman RJ, Talbott E, Dumesic DA. Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the Polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic ovary syndrome (AE-PCOS) Task Force. *J Clin Endocrinol Metab* 2014; 99: 2038-2049 [PMID: 23075205 DOI: 10.1210/jc.2010-2724]

DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* 1979; 237: E214-E223 [PMID: 382871 DOI: 10.1152/ajpendo.1979.237.3.E214]

Ciardali TP, Aroda V, Mudaliar S, Chang RJ, Henry RR. Polycystic ovary syndrome is associated with tissue-specific differences in insulin resistance. *J Clin Endocrinol Metab* 2009; 94: 157-163 [PMID: 18854391 DOI: 10.1210/jc.2008-1492]

Svendsen PF, Nilas L, Norgaard K, Jensen JE, Madsbad S. Obesity, body composition and metabolic disturbances in Polycystic ovary syndrome. *Hum Reprod* 2008; 23: 2113-2121 [PMID: 18586679 DOI: 10.1093/humrep/den211]

Goodarzi MO, Quiñones MJ, Aziz R, Rotter JJ, Hsuaw WA, Yang H. Polycystic ovary syndrome in Mexican-Americans: prevalence and association with the severity of insulin resistance. *Fertil Steril* 2005; 84: 766-769 [PMID: 16169421 DOI: 10.1016/j.fertnstert.2005.01.051]

Park HR, Choi Y, Lee HJ, Oh JY, Hong YS, Sung YA. The metabolic syndrome in young Korean women with Polycystic ovary syndrome. *Diabetes Res Clin Pract* 2007; 77 Suppl 1: S243-S246 [PMID: 17619085 DOI: 10.1016/j.diabres.2007.01.065]

Vrbíková J, Cibulá D, Dvorákovi K, Staníček S, Sindelka G, Hill M, Fanta M, Vondra K, Skrha J. Insulin sensitivity in women with Polycystic ovary Metab 2004; 89: 2942-2945 [PMID: 15181081 DOI: 10.1210/jc.2003-03178]

Lemieux S, Lewis GF, Ben-Chetrit A, Steiner G, Greenblatt EM. Correction of hyperandrogenemia by laparoscopic ovarian cautery in women with polycystic ovarian syndrome is not accompanied by improved insulin sensitivity or lipid-lipoprotein levels. *J Clin Endocrinol Metab* 1999; 84: 4278-4282 [PMID: 10566685 DOI: 10.1210/jcem.84.11.6140]

Arslanian SA, Lewy V, Danadian K, Saad R. Metformin therapy in obese adolescents with Polycystic ovary syndrome and impaired glucose tolerance: amelioration of exaggerated adrenal response to adrenocorticotropic with reduction of insulinemia/insulin resistance. *J Clin Endocrinol Metab* 2002; 87: 1555-1559 [PMID: 11932281 DOI: 10.1210/jc.2002-020997]

Fulghesu AM, Ciampelli M, Muzi G, Belosi C, Selvaggi L, Ayala GF, Lanzone A. N-acetyl-cysteine treatment improves insulin sensitivity in women with Polycystic ovary syndrome. *Fertil Steril* 2002; 77: 1128-1135 [PMID: 12657717 DOI: 10.1016/S0014-4079(01)01333-3]

Morin-Papunen L, Vauhkonen I, Koivunen R, Ruokonen A, Martikainen H, Tapanainen JS. Metformin vs ethinyl estradiol-cyproterone acetate in the treatment of nonobese women with Polycystic ovary syndrome : a randomized study. *J Clin Endocrinol Metab* 2003; 88: 148-156 [PMID: 12519844 DOI: 10.1210/jcem.84.11.6140]

Michi D, Sumarac-Dumanovic M, Kendereski A, Cvijovic G, Zoric S, Pejkovic D, Micic J, Milic N, Dieguez C, Casanueva FF. Total ghrelin levels during acute insulin infusion in patients with Polycystic ovary syndrome. *Am J Physiol Endocrinol Metab* 2010; 300: 820-827 [PMID: 18075283 DOI: 10.1152/ajpendo.2009.21422]

Aroda VR, Ciardali TP, Burke P, Mudaliar S, Clonton P, Phillips S, Chang RJ, Henry RR. Metabolic and hormonal changes induced by pioglitazone in Polycystic ovary syndrome: a randomized, placebo-controlled clinical trial. *J Clin Endocrinol Metab* 2009; 94: E249-E257 [PMID: 18984667 DOI: 10.1210/jc.2008-13133]

Hutchison SK, Stepto NK, Harrison CL, Moran LJ, Teede HJ. Effects of exercise on insulin resistance and body composition in overweight and obese women with and without Polycystic ovary syndrome. *J Endocrinol Invest* 2011; 34: 84-89 [PMID: 2113-2121 DOI: 10.1007/humrep/den211]

Tfayli H, Ulrich JW, Lee S, Sutton-Tyrrell K, Arslanian S. Drosophila/ethinyl estradiol vs rosiglitazone treatment in overweight adolescents with Polycystic ovary syndrome: comparison of metabolic, hormonal, and cardiovascular risk factors. *J Clin Endocrinol Metab* 2011; 96: 1311-1319 [PMID: 21325466 DOI: 10.1210/jc.2010-2547]

Vital-Reyes VS, Carrillo-Martinez CR, Hinojosa-Cruz JC, Martinez-Basilia A, Lopez-Alarcon M. Insulin resistance frequency in women's with Polycystic ovary syndrome using hyperinsulinemic-euglycemic clamp. *Ginecol Obstet Mex* 2014; 82: 785-790 [PMID: 25829692]

Husley R, Mends S, Zbzeznayakov E, Reddy S, Chan J. Body mass index, waist circumference and waist/hip ratio as predictors of cardiovascular risk— a review of the literature. *Eur J Clin Nutr* 2010; 64: 16-22 [PMID: 19654593 DOI: 10.1038/ejcn.2009.68]

Koning de L, Merchant AT, Pogue J, Anand SS. Waist circumference and waist-to-hip ratio as predictors of cardiovascular events: meta-regression analysis of prospective studies. *Eur Heart J* 2007; 28: 850-856 [PMID: 17403720 DOI: 10.1093/eurheartj/ehn026]

Vazquez G, Duval S, Jacobs DR Jr, Silvestonien K. Comparison of body mass index, waist circumference, and waist/hip ratio in predicting incident diabetes: a meta-analysis. *Epidemiol Rev* 2007; 29: 115-128 [PMID: 17404056 DOI: 10.1093/epirev/mxm008]

Chouraki V, Wagner A, Ferrières J, Kee F, Bingham A, Haas B, Ruidavets JB, Evans A, Ducimetière P, Amouyel P, Dallongeville J. Smoking habits, waist circumference and coronary artery disease risk relationship: the PRIME study. *Eur
Lee JS, Aoki K, Kawakubo K, Gunji A. A study on indices of body fat distribution for screening for obesity. *Sangyo Eiseigaku Zasshi* 1995; 37: 9-18 [PMID: 7780864 DOI: 10.1539/sangyoisei.37.9]

Ashwell M, Gibson S. Waist to height ratio is a simple and effective obesity screening tool for cardiovascular risk factors: Analysis of data from the British National Diet And Nutrition Survey of adults aged 19-64 years. *Obes Facts* 2009; 2: 97-103 [PMID: 20054212 DOI: 10.1159/000203636]

Sohngwi E, Kengne AP, Echouffo-Tchegui JB, Choukem S, Sobngwi-Tambekou J, Balti EV, Pearce MS, Siaha V, Mamdjomak AS, Effe V, Lontchi-Yimagou E, Donfack OT, Atogho-Tiedeu B, Boudou P, Gautier JF, Mbanya JC. Fasting insulin sensitivity indices are not better than routine clinical variables at predicting insulin sensitivity among Black Africans: a clamp study in sub-Saharan Africans. *BMC Endocr Disord* 2014; 14: 65 [PMID: 25106496 DOI: 10.1186/1472-6823-14-65]

Keys A, Fidanza F, Karvonen MJ, Kimura N, Taylor HL. Indices of relative weight and obesity. *J Chronic Dis* 1972; 25: 329-343 [PMID: 4650929 DOI: 10.1016/0021-9681(72)90027-6]

Hartz AJ, Rupley DC Jr, Kalkhoff RD, Rimm AA. Relationship of obesity to diabetes: influence of obesity level and body fat distribution. *Prev Med* 1983; 12: 351-357 [PMID: 6878197 DOI: 10.1016/0091-7435(83)90244-X]

Skarftors ET, Selinus KL, Lithell HO. Risk factors for developing non-insulin dependent diabetes: a 10 year follow up of men in Uppsala. *BMJ* 1991; 303: 755-760 [PMID: 1929296 DOI: 10.1136/bmj.303.6805.755]

Cassano PA, Rosner B, Vokonas PS, Weiss ST. Obesity and body fat distribution in relation to the incidence of non-insulin-dependent diabetes mellitus. A prospective cohort study of men in the normative aging study. *Am J Epidemiol* 1992; 136: 1474-1486 [PMID: 12882277 DOI: 10.1093/oxfordjournals.aje.a116468]

Colditz GA, Willett WC, Stampfer MJ, Manson JE, Hennekens CH, Arky RA, Speizer FE. Weight as a risk factor for clinical diabetes in women. *Am J Epidemiol* 1990; 132: 501-513 [PMID: 2389754 DOI: 10.1093/oxfordjournals.aje.a115686]

Ohlson LO, Larsson B, Svärdssudd K, Welin L, Eriksson H, Wilhelmsen L, Björntorp P, Tibblin G. The influence of body fat distribution on the incidence of diabetes mellitus. 13.5 years of follow-up of the participants in the study of men born in 1913. *Diabetes* 1985; 34: 1055-1058 [PMID: 4043554 DOI: 10.2337/diabetes.34.10.1055]

Swendsen PF, Madsbad S, Nilas L. The insulin-resistant phenotype of Polycystic ovary syndrome. *Fertil Steril* 2010; 94: 1052-1058 [PMID: 19580964 DOI: 10.1016/j.fertnstert.2009.04.008]

Sirota I, Stein DE, Vega M, Keltz MD. Insulin Resistance and β-cell Function Calculated by Homeostasis Model Assessment in Lean, Overweight, and Obese Women with Polycystic ovary syndrome. *J Reprod Med* 2016; 61: 3-10 [PMID: 26995881]

Karabulut A, Yaylali GF, Demirkent S, Sevkot O, Acun A. Evaluation of body fat distribution in PCOS and its association with carotid atherosclerosis and insulin resistance. *Gynecol Endocrinol* 2012; 28: 111-114 [PMID: 21770828 DOI: 10.3109/09513590.2011.589929]

Amisi CA, Ciccozzi M, Pozzilli P. Wrist circumference: A new marker for insulin resistance in African women with Polycystic ovary syndrome. *World J Diabetes* 2020; 11: 42-51 [PMID: 32604035 DOI: 10.4237/wjd.v11.i2.42]

De Vries JP, van Staveren WA, Lakens D, Rouillon C, de Vroome SE. Waist circumference: A new marker for insulin resistance in PCOS and its association with carotid atherosclerosis and insulin resistance. *World J Diabetes* 2012; 3: 100-104 [PMID: 22981845 DOI: 10.4237/wjd.v3.i2.100]

Ashwell M, Gibson S. Waist to height ratio is a better screening tool than waist circumference and BMI for adult cardiometabolic risk factors: systematic review and meta-analysis. *Obes Rev* 2012; 13: 275-286 [PMID: 22106927 DOI: 10.1111/j.1467-789X.2011.00952.x]

Lee JS, Kawakubo K. A useful index highly correlated with coronary risk factors for community based obesity screening. *Nihon Koshu Eisei Zasshi* 1999; 46: 89-102 [PMID: 10331294]

Ashwell M, Gunn P, Gibson S. Waist-to-height ratio is a better screening tool than waist circumference and BMI for adult cardiometabolic risk factors: systematic review and meta-analysis. *Obes Rev* 2012; 13: 275-286 [PMID: 22106927 DOI: 10.1111/j.1467-789X.2011.00952.x]

Correà MM, Thumé E, De Oliveira ER, Tomasi E. Performance of the waist-to-height ratio in identifying obesity and predicting non-communicable diseases in the elderly population: A systematic literature review. *Arch Gerontol Geriatr* 2016; 65: 174-182 [PMID: 27061665 DOI: 10.1016/j.archger.2016.03.021]
56. Moges B, Amare B, Fantahun B, Kassu A. High prevalence of overweight, obesity, and hypertension with increased risk of cardiovascular disorders among adults in northwest Ethiopia: a cross sectional study. *BMC Cardiovasc Disord* 2014; 14: 155 [PMID: 25373922 DOI: 10.1186/1471-2261-14-155]

57. Hsieh SD, Muto T. The superiority of waist-to-height ratio as an anthropometric index to evaluate clustering of coronary risk factors among non-obese men and women. *Prev Med* 2005; 40: 216-220 [PMID: 15533532 DOI: 10.1016/j.ypmed.2004.05.025]

58. Huang X, Wang Q, Liu T, Pei T, Liu D, Zhu H, Huang W. Body fat indices as effective predictors of insulin resistance in obese/non-obese Polycystic ovary syndrome women in the Southwest of China. *Endocrine* 2019; 65: 81-85 [PMID: 30924083 DOI: 10.1007/s12020-019-01912-1]

59. Lee CM, Huxley RR, Wildman RP, Woodward M. Indices of abdominal obesity are better discriminators of cardiovascular risk factors than BMI: a meta-analysis. *J Clin Epidemiol* 2008; 61: 646-653 [PMID: 18359190 DOI: 10.1016/j.jclinepi.2007.08.012]

60. Costa EC, Soares EM, Lemos TM, Maranhão TM, Azevedo GD. [Central obesity index and cardiovascular risk factors in Polycystic ovary syndrome ]. *Arg Bras Cardiol* 2010; 94: 633-638 [PMID: 20428724 DOI: 10.1590/S0066-782X2010000500029]

61. Gateva AT, Kamenov ZA. Markers of visceral obesity and cardiovascular risk in patients with polycystic ovarian syndrome. *Eur J Obstet Gynecol Reprod Biol* 2012; 164: 161-166 [PMID: 22727921 DOI: 10.1016/j.ejogrb.2012.05.037]

62. Bhattacharya K, Sengupta P, Dutta S, Chaudhuri P, Das Mukhopadhyay L, Syamal AK. Waist-to-height ratio and BMI as predictive markers for insulin resistance in women with PCOS in Kolkata, India. *Endocrine* 2021; 72: 86-95 [PMID: 33400176 DOI: 10.1007/s12020-020-02555-3]

63. Capizzi M, Leto G, Petrone A, Zampetti S, Papa RE, Osmani M, Spoletini M, Lenzi A, Osborn J, Mastantuono M, Vania A, Bazzetti R. Wrist circumference as a critical marker of insulin resistance in overweight obese children and adolescents. *Circulation* 2011; 123: 1757-1762 [PMID: 21482965 DOI: 10.1161/CIRCULATIONAHA.110.012898]

64. Karsenty G, Ferron M. The contribution of bone to whole-organism physiology. *Nature* 2012; 481: 314-320 [PMID: 22528610 DOI: 10.1038/nature10763]

65. Confavreux CB, Levine RL, Karsenty G. A paradigm of integrative physiology, the crosstalk between bone and energy metabolisms. *Mol Cell Endocrinol* 2009; 310: 21-29 [PMID: 19376193 DOI: 10.1016/j.mce.2009.04.004]

66. Veldhuis-Vlug AG, Fliers E, Bisschop PH. Bone as a regulator of glucose metabolism. *Neth J Med* 2013; 71: 396-400 [PMID: 24127499]

67. Im JA, Yu BP, Jeon JY, Kim SH. Relationship between osteocalcin and glucose metabolism in postmenopausal women. *Clin Chim Acta* 2008; 386: 66-69 [PMID: 18657532 DOI: 10.1016/j.cca.2008.07.001]

68. Schwetz V, Pieber T, Obermayer-Pietsch B. The endocrine role of the skeleton: background and clinical evidence. *Eur J Endocrinol* 2012; 166: 959-967 [PMID: 22436399 DOI: 10.1530/EJ-12-0030]

69. Stolk RP, Van Daele PL, Pols HA Burger H, Hofman A, Kirchenha’ger JC, Lamberts SW, Grobbee DE. Hyperinsulinemia and bone mineral density in an elderly population: the Rotterdam Study. *Bone* 1996; 18: 545-549 [DOI: 10.1016/0365-3515(96)00079-8]

70. Kinjo M, Setoguchi S, Solomon DH. Bone mineral density in adults with the metabolic syndrome: analysis in a population-based U.S. sample. *J Clin Endocrinol Metab* 2007; 92: 4161-4164 [PMID: 17785365 DOI: 10.1210/jc.2007-0575]

71. Jahangiri Noudesh Y, Hadaegh F, Vatankhah N, Momennan AA, Saadat N, Khalidi D, Azizi F. Wrist circumference as a novel predictor of diabetes and prediabetes: results of cross-sectional and 8.8-year follow-up studies. *J Clin Endocrinol Metab* 2013; 98: 777-784 [PMID: 23341488 DOI: 10.1210/jc.2012-2416]

72. Derakhshan A, Tohid M, Hajebririm MA, Saadat N, Azizi F, Hadaegh F. Sex-specific incidence rates and risk factors of insulin resistance and β-cell function: a decade follow-up in a Middle Eastern population. *Diabet Med* 2017; 34: 245-252 [PMID: 26996519 DOI: 10.1111/dme.13117]

73. Amini A, Soltanian N, Iraj B, Askari G, Elneyamine S, Ghias M, Hajar H, Zahed A, Amini M. Association of wrist circumference with cardio metabolic risk factors. *J Pak Med Assoc* 2012; 62: S34-S36 [PMID: 22768455]

74. Ramezankhani A, Pournik O, Shahrabi J, Azizi F, Hadaegh F. An application of association rule mining to extract risk pattern for type 2 diabetes using tehran lipid and glucose study database. *Int J Endocrinol Metab* 2015; 13: e25389 [PMID: 25926550 DOI: 10.5812/ijem.25389]

75. Esmaeilzadeh S, Delavar MA, Amini M, Khafris S, Pasha NG. Polycystic ovary syndrome in Iranian adolescents. *Int J Adolesc Med Health* 2014; 26: 559-565 [PMID: 24447981 DOI: 10.1515/ijamh-2013-0335]

76. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2011; 34 Suppl 1: S62-S69 [PMID: 21936268 DOI: 10.2337/dc11-S062]

77. Asante A, Omurtug K, Stewart EA, Coddington CC. Screening for Insulin Resistance in Polycystic ovary syndrome: Views of Physician Members of the American Society for Reproductive Medicine. *J Reprod Med* 2015; 60: 371-377 [PMID: 26392060]

78. Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. Consensus on women’s health aspects of Polycystic ovary syndrome (PCOS). *Hum Reprod* 2012; 27: 14-24 [PMID: 22147920 DOI: 10.1093/humrep/det396]

79. Nagasaka S, Iwashita S, Saito T. Comment on glucose-to-insulin ratio as a measure of insulin sensitivity in women with PCOS. Polycystic ovary syndrome. *J Clin Endocrinol Metab* 1999; 84: 383 [PMID: 9920114 DOI: 10.1210/jcem.84.1.5427-3]

80. Vugun P, Saenger P, Dimartino-Nardi J. Fasting glucose insulin ratio: a useful measure of insulin resistance in girls with premature adrenarche. *J Clin Endocrinol Metab* 2001; 86: 4618-4621 [PMID: 11600513 DOI: 10.1210/jcem.86.10.7956]

81. Popovska-Dimova Z, Krsstevska B. The frequency of insulin resistance calculated upon the basis of a fasting glucose to insulin ratio and characteristics of insulin resistant women with Polycystic ovary syndrome. *Prilozi* 2006; 27: 87-95 [PMID: 16985482]

82. Legro RS, Castracane VD, Kauffman RP. Detecting insulin resistance in Polycystic ovary syndrome: purposes and
pitfalls. *Obstet Gynecol Surv* 2004; 59: 141-154 [PMID: 14752302 DOI: 10.1097/01.OGX.0000109523.25076.E2]

83 Legro RS, Finegood D, Dunia F. A fasting glucose to insulin ratio is a useful measure of insulin sensitivity in women with Polycystic ovary syndrome. *J Clin Endocrinol Metab* 1998; 83: 2694-2698 [PMID: 9709933 DOI: 10.1210/jcem.83.8.2694A]

84 Quon MJ. Limitations of the fasting glucose to insulin ratio as an index of insulin sensitivity. *J Clin Endocrinol Metab* 2001; 86: 4615-4617 [PMID: 11600512 DOI: 10.1210/jcem.86.10.7952]

85 McAuley KA, Williams SM, Mann JJ, Walker RJ, Lewis-Barned NJ, Temple LA, Duncan AW. Diagnosing insulin resistance in the general population. *Diabetes Care* 2001; 24: 460-464 [PMID: 11289468 DOI: 10.2337/diacare.24.3.460]

86 Laakso M. How good is a marker insulin level for insulin resistance? *Am J Epidemiol* 1993; 137: 959-965 [PMID: 8317453 DOI: 10.1093/oxfordjournals.ajec.117666]

87 Johnson JL, Duick DS, Chui MA, Aldaasouqi SA. Identifying prediabetes using fasting insulin levels. *Endocr Pract* 2010; 16: 47-52 [PMID: 19789156 DOI: 10.4158/EP09031.OR]

88 Consensus Development Conference on Insulin Resistance. 5-6 November 1997. American Diabetes Association. *Diabetes Care* 1998; 21: 310-314 [PMID: 9540000 DOI: 10.2337/diacare.21.2.310]

89 Wang F, Han L, Hu D. Fasting insulin, insulin resistance and risk of hypertension in the general population: A meta-analysis. *Clin Chim Acta* 2017; 464: 57-63 [PMID: 27836689 DOI: 10.1016/j.cca.2016.11.009]

90 Ciampelli M, Leoni F, Cucinelli F, Mancuso S, Panunzi S, De Gaetano A, Lanzone A. Assessment of insulin sensitivity from measurements in the fasting state and during an oral glucose tolerance test in Polycystic ovary syndrome and menopausal patients. *J Clin Endocrinol Metab* 2005; 90: 1398-1406 [PMID: 15596699 DOI: 10.1210/jcem.2004-0410]

91 Luenger F, Wildt L, Seeger B. Accurate screening for insulin resistance in PCOS women using fasting insulin concentrations. *Gynecol Endocrinol* 2013; 29: 541-544 [PMID: 23464983 DOI: 10.3109/09513590.2013.774362]

92 Bergman RN, Ider YZ, Bowden CR, Cobelli C. Quantitative estimation of insulin sensitivity. *Am J Physiol* 1979; 236: E667-E677 [PMID: 443421 DOI: 10.1152/ajpendo.1979.236.6.E667]

93 Bergman RN, Prager R, Voland A, Olefsky JM. Equivalence of the insulin sensitivity index in man derived by the minimal model method and the euglycemic glucose clamp. *J Clin Invest* 1987, 83: 790-800 [PMID: 3546379 DOI: 10.1172/JCI112886]

94 Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; 28: 412-419 [PMID: 3898825 DOI: 10.1007/BF00280883]

95 Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care* 2004; 27: 1487-1495 [PMID: 15161807 DOI: 10.2337/diacare.27.6.1487]

96 Bonora E, Targher G, Alberiche M, Bonadonna RC, Saggiani F, Zenere MB, Monauni T, Muggeo M. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. *Diabetes Care* 2000; 23: 57-63 [PMID: 10857969 DOI: 10.2337/diacare.23.1.57]

97 Hosker JP, Matthews DR, Rudenski AS, Burnett MA, Darling P, Bown EG, Turner RC. Continuous infusion of glucose with model assessment: measurement of insulin resistance and beta-cell function in man. *Diabetologia* 1985; 28: 401-411 [PMID: 3899824 DOI: 10.1007/BF0280882]

98 De Ugartete CM, Bartolucci AA, Aziz R. Prevalence of insulin resistance in the Polycystic ovary syndrome using the homeostasis model assessment. *Fertil Steril* 2005; 83: 1454-1460 [PMID: 15866584 DOI: 10.1016/j.fertnstert.2004.11.070]

99 Cebeci F, Onsman N, Mert C. Insulin resistance in women with hirsutism. *Arch Med Sci* 2012; 8: 342-346 [PMID: 22662009 DOI: 10.5114/ams.2012.28563]

100 Lankarani M, Valizadeh N, Heshrmat R, Peiman M, Sohravand F. Evaluation of insulin resistance and metabolic profiles in patients with Polycystic ovary syndrome. *Gynecol Endocrinol* 2009; 25: 504-507 [PMID: 19499403 DOI: 10.1080/09513590.2009.9927083]

101 Wei HJ, Young R, Kuo IL, Liaw CM, Chiang HS, Yeh CY. Prevalence of insulin resistance and determination of risk factors for glucose intolerance in Polycystic ovary syndrome: a cross-sectional study of Chinese infertility patients. *Fertil Steril* 2009; 91: 1864-1868 [PMID: 18565519 DOI: 10.1016/j.fertnstert.2008.02.168]

102 Levy JC, Matthews DR, Hermans MP. Correct homeostasis model assessment (HOMA) modeling uses the computer program. *Diabetes Care* 1998; 21: 2191-2192 [PMID: 9839117 DOI: 10.2337/diacare.21.12.2191]

103 Fukushima M, Taniguchi A, Sakai M, Doi K, Nagata I, Nagasaka S, Tokuyama K, Nakai Y. Assessment of insulin sensitivity from a single sample. *Diabetes Care* 2000; 23: 1434-1435 [PMID: 10977049 DOI: 10.2337/diacare.23.9.1434]

104 Oktar K, Iwashahi H, Kozawa J, Okauchi Y, Funahashi T, Imagawa T, Shimomura I. Homeostasis model assessment of insulin resistance for evaluating insulin sensitivity in patients with type 2 diabetes on insulin therapy. *Endocr J* 2013; 60: 283-290 [PMID: 23149658 DOI: 10.1507/endocrj.EJ12-0320]

105 Zheng X, Chen Y, Ma D, Zhang M, Huang Y, Tong M, Yan B, Lin S, Yan X, Liu C. Correlation Between Daily Energy Intake from Fat with Insulin Resistance in Patients with Polycystic ovary syndrome. *Diabetes Metab Syndr Obes* 2021; 14: 2953-2957 [PMID: 35319128 DOI: 10.2147/DMSO.S287936]

106 Yilmaz M, Bukan N, Ersoy R, Karaqoc A, Yetkin I, Ayyaz G, Cakir N, Arslan M. Glucose intolerance, insulin resistance and cardiovascular risk factors in first degree relatives of women with Polycystic ovary syndrome. *Hum Reprod* 2005; 20: 2144-2140 [PMID: 15890734 DOI: 10.1093/humrep/dei070]

107 Duncan MH, Singh BM, Wise PH, Carter G, Alghabband-Zadeh J. A simple measure of insulin resistance. *Lancet* 1995; 346: 120-112 [DOI: 10.1016/S0140-6736(95)92143-5]

108 Jakubowska J, Bohdanowicz-Pawlak A, Milewicz A. The effect of rosiglitazone on plasma adiponectin and resistin levels in obese PCO woman-patientinal report. *Prezg Lek* 2007; 64: 70-73 [PMID: 17892035]

109 Dravetka I, Lazarova I, Kraus V. Obesity is the major factor determining an insulin sensitivity and androgen production levels in women with anovulatory cycles. *Bratisl Lek Listy* 2003; 104: 393-399 [PMID: 15053311]

110 Katz A, Namibi SS, Mather K, Baron AD, Pollmann DA, Sullivan G, Quon MJ. Quantitative insulin sensitivity check
Amisi CA. Markers of insulin resistance in PCOS

index: a simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab 2000; 85: 2402-2410 [PMID: 10902785 DOI: 10.1210/jcem.85.7.6661]

111 Chen H, Sullivan G, Quon MJ. Assessing the predictive accuracy of QUICKI as a surrogate index for insulin sensitivity using a calibration model. Diabetes 2005; 54: 1914-1925 [PMID: 15983190 DOI: 10.2337/diabetes.54.7.1914]

112 Otten J, Ahren B, Olsson T. Surrogate measures of insulin sensitivity vs the hyperinsulinemic-euglycemic clamp: a meta-analysis. Diabetologia 2014; 57: 1781-1788 [PMID: 24891021]

113 Borali A, Livingstone C, Ferns GA. The biochemical assessment of insulin resistance. Ann Clin Biochem 2007; 44: 324-342 [PMID: 17594780 DOI: 10.1255/0004563031233125779]

114 Perseghin G, Caumo A, Caloni M, Testolin G, Luzi L. Incorporation of the fasting plasma FFA concentration into QUICKI improves its association with insulin sensitivity in nonobese individuals. J Clin Endocrinol Metab 2001; 86: 4776-4781 [PMID: 11660540 DOI: 10.1210/jcem.86.10.7902]

115 Hanley AJ, Williams K, Gonzalez C, D’Agostino RB Jr, Wagenknecht LE, Stern MP, Haffner SM, San Antonio Heart Study; Mexico City Diabetes Study; Insulin Resistance Atherosclerosis Study. Prediction of type 2 diabetes using simple measures of insulin resistance: combined results from the San Antonio Heart Study, the Mexico City Diabetes Study, and the Insulin Resistance Atherosclerosis Study. Diabetes 2003; 52: 463-469 [PMID: 12540622 DOI: 10.2337/diabetes.52.2.463]

116 Cenk Sayin N, Gucier F, Balkanli-Kaplan P, Ali Yuce M, Yardim T. Insulin resistance and lipid profile in women with polycystic appearing ovaries: implications with regard to Polycystic ovary syndrome. Gynecol Endocrinol 2003; 17: 387-396 [PMID: 14710586 DOI: 10.1080/09513590312331290278]

117 de Paula Martins W, Santana LF, Nasri CO, Ferriani FA, de SA MF, Dos Reis RM. Agreement among insulin sensitivity indexes on the diagnosis of insulin resistance in Polycystic ovary syndrome and ovulatory women. Eur J Obstet Gynecol Reprod Biol 2007; 133: 203-207 [PMID: 17207902 DOI: 10.1016/j.ejogrb.2006.10.038]

118 Chen X, Yang D, Li L, Feng S, Wang L. Abnormal glucose tolerance in Chinese women with Polycystic ovary syndrome. Hum Reprod 2006; 21: 2027-2032 [PMID: 16684838 DOI: 10.1093/humrep/del142]

119 Tosi F, Bonora E, Moghetti P. Insulin resistance in a large cohort of women with Polycystic ovary syndrome : a comparison between euglycaemic-hyperinsulinemic clamp and surrogate indexes. Hum Reprod 2017; 32: 2515-2521 [PMID: 29040529 DOI: 10.1093/humrep/dex308]

120 Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic clamp. Diabetes Care 1999; 22: 1462-1470 [PMID: 10480510 DOI: 10.2373/diabetes.22.9.1462]

121 Stumvoll M, Mitrauk A, Pimenta W, Jenssen T, Yki-Järvinen H, Van Haeften T, Renn W, Gerich J. Use of the oral glucose tolerance test to assess insulin release and insulin sensitivity. Diabetes Care 2000; 23: 295-301 [PMID: 10868854 DOI: 10.2337/diabetes.33.3.295]

122 Gutt M, Davis CL, Spitzer SB, Llubre MM, Kumar M, Czarnecki EM, Schneiderman N, Sklyer JS, Marks JB. Validation of the insulin sensitivity index (ISI(0,120)): comparison with other measures. Diabetes Res Clin Pract 2000; 47: 177-187 [PMID: 10741566 DOI: 10.1016/S0168-8227(99)00116-3]

123 Rizzo M, Tyndall EK, Frontoni S, Jacoangeli F, Sarlo F, Panebianco F, Mistorni A, Di Renzo L, Calafiore R, Luca G, De Lorenzo A. Rapid and easy assessment of insulin resistance contributes to early detection of Polycystic ovary syndrome. J Endocrinol Invest 2013; 36: 527-530 [PMID: 23612476 DOI: 10.3257/jo.8947]

124 Lewandowski KC, Skowrońska-Jóźwiak E, Łukasiak K, Gałuszko K, Dukowicz A, Cedro M, Lewiński A. How much insulin resistance in Polycystic ovary syndrome? Arch Med Sci 2019; 15: 613-618 [PMID: 31110526 DOI: 10.5114/aoms.2019.826672]

125 Tao MF, Zhu JP, Zhou J, Lu W, Qin W, Teng YC, Jia WP. Insulin release and daily glucose change in Polycystic ovary syndrome women with normal glucose tolerance. Zhonghua Yi Xue Za Zhi 2009; 89: 659-663 [PMID: 19593075]

126 Song DK, Hong YS, Sung YA, Lee H. Insulin resistance according to β-cell function in women with Polycystic ovary syndrome and normal glucose tolerance. PLoS One 2017; 12: e01718120 [PMID: 28542421 DOI: 10.1371/journal.pone.0178120]

127 Avignon A, Boegner C, Mariano-Goulart D, Colette C, Monnier L. Assessment of insulin sensitivity from plasma insulin and glucose in the fasting and post oral glucose load state. Int J Obes Relat Metab Disord 1999; 23: 512-517 [PMID: 10375055 DOI: 10.1038/sj.ijo.0800664]

128 Goedecke JH, Dave JA, Faulenbach MV, Utschneider KM, Lambert EV, West S, Collins M, Olsson T, Walker BR, Seckl JR, Kahn SE, Levitt NS. Insulin response in relation to insulin sensitivity: an appropriate beta-cell response in black African women. Diabetes Care 2009; 32: 860-865 [PMID: 19196884 DOI: 10.2337/dc09-1216]

129 Hudecova M, Holte J, Olovsson M, Larsson A, Berne C, Poroma IS. Diabetes and impaired glucose tolerance in patients with Polycystic ovary syndrome --a long term follow-up. Hum Reprod 2011; 26: 1462-1468 [PMID: 21427116 DOI: 10.1093/humrep/der065]

130 Vrbikova J, Bendlova B, Vankova M, Dvorakova K, Grimmichova T, Vondra K, Pacini G. Beta cell function and insulin sensitivity in women with Polycystic ovary syndrome : influence of the family history of type 2 diabetes mellitus. Gynecol Endocrinol 2009; 25: 597-602 [PMID: 19572227 DOI: 10.1080/09513590902972133]

131 Tao T, Wu P, Wang Y, Liu W. Comparison of glycemic control and β-cell function in new onset T2DM patients with PCOS of metformin and saxagliptin monotherapy or combination treatment. BMJ Endocr Disord 2018; 18: 14 [PMID: 29482528 DOI: 10.1186/s12992-018-0243-5]

132 Adeniji AA, Essah PA, Nestler JE, Cheung KL. Metabolic Effects of a Commonly Used Combined Hormonal Oral Contraceptive in Women With and Without Polycystic ovary syndrome. J Womens Health (Larchmt) 2016; 25: 638-645 [PMID: 26871978 DOI: 10.1089/jwh.2015.5418]

133 Morciano A, Romani F, Sagnella F, Scarinci E, Palla C, Moro F, Tropea A, Pollici C, Della Casa S, Guido M, Lanzone A, Apa R. Assessment of insulin resistance in lean women with Polycystic ovary syndrome. Fertil Steril 2014; 102: 250-256.e3 [PMID: 24825420 DOI: 10.1016/j.fertnstert.2014.04.004]

134 Legro RS, Kunselman AR, Danai F. Prevalence and predictors of dyslipidemia in women with Polycystic ovary syndrome. Am J Med 2001; 111: 607-613 [PMID: 11755503 DOI: 10.1016/S0002-9343(01)00948-2]
135 Wild RA, Rizzo M, Clifton S, Carmina E. Lipid levels in Polycystic ovary syndrome: systematic review and meta-analysis. Fertil Steril 2011; 95: 1073-9.e1 [PMID: 21247558 DOI: 10.1016/j.fertnstert.2010.12.027]

136 Wild RA. Dyslipidemia in PCOS. Steroids 2012; 77: 295-299 [PMID: 22197663 DOI: 10.1016/j.steroids.2011.12.002]

137 Robinson HD, Henderson AD, Gelding SV, Kiddy D, Nithiyathanthan R, Bush A, Richardson W, Johnston DG, Franks S. Dyslipidaemia is associated with insulin resistance in women with polycystic ovaries. Clin Endocrinol (Oxf) 1996; 44: 277-284 [PMID: 8729522 DOI: 10.1111/j.1365-2265.1996.674495.x]

138 González-Chávez A, Simental-Mendía LE, Elizondo-Argeuta S. Elevated triglycerides/HDL-cholesterol ratio associated with insulin resistance. Cir Cir 2011; 79: 126-131 [PMID: 21631973]

139 Xiang SK, Hua F, Tang Y, Jiang XH, Zhuang Q, Qian FJ. Relationship between Serum Lipoprotein Ratios and Insulin Resistance in Polycystic ovary syndrome. Int J Endocrinol 2012; 2012: 173281 [PMID: 22792101 DOI: 10.1155/2012/173281]

140 Ghaffarzad A, Amani R, Mehrzad Sadaghiani M, Darabi M, Cheraghi A. Correlation of Serum Lipoprotein Ratios with Insulin Resistance in Infertile Women with Polycystic Ovarian Syndrome: A Case Control Study. Int J Fertil Steril 2016; 10: 29-35 [PMID: 27123197 DOI: 10.22074/ijfs.2016.4765]

141 Tangvarasittichai S, Poonshp, Tangvarasittichai O. Association of serum lipoprotein ratios with insulin resistance in type 2 diabetes mellitus. Indian J Med Res 2010; 131: 641-648 [PMID: 20516555]

142 Brehm A, Pfeifer G, Pacini G, Vierhapper H, Roden M. Relationship between serum lipoprotein ratios and insulin resistance in obesity. Clin Chem 2004; 50: 2316-2322 [PMID: 15459091 DOI: 10.1373/clinchem.2004.037556]

143 Castelli WP, Garrison RJ, Wilson PW, Abbott RD, Kannel WB. Incidence of coronary heart disease and lipoprotein cholesterol levels. The Framingham Study. JAMA 1986; 256: 2835-2838 [PMID: 3773200 DOI: 10.1001/jama.256.20.2835]

144 Kinosian B, Glick H, Garland G. Cholesterol and coronary heart disease: predicting risks by levels and ratios. Ann Intern Med 1994; 121: 641-647 [PMID: 7944071 DOI: 10.1373/0003-4816-121-9-199410100-00002]

145 Gazzano JM, Hennekens CH, O'Donnell CJ, Breslow JL, Buring JE. Fasting triglycerides, high-density lipoprotein, and risk of myocardial infarction. Circulation 1997; 96: 2520-2525 [PMID: 9355888 DOI: 10.1161/01.CIR.96.8.2520]

146 Phelan N, O'Connor A, Kaye-Tun T, Correa N, Boran G, Roche HM, Gibney J. Lipoprotein subclass patterns in women with Polycystic ovary syndrome (PCOS) compared with equally insulin-resistant women without PCOS. J Clin Endocrinol Metab 2010; 95: 3933-3939 [PMID: 20519354 DOI: 10.1210/jc.2009-2444]

147 McLaughlin T, Abbassi F, Cheal K, Chu J, Lamendola C, Reaven G. Use of metabolic markers to identify overweight individuals who are insulin resistant. Ann Intern Med 2003; 139: 802-809 [PMID: 14623617 DOI: 10.7326/0003-4819-139-10-200311180-00007]

148 Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK. Cardiovascular risk factors in confirmed prediabetic individuals. Does the clock for coronary heart disease start ticking before the onset of clinical diabetes? JAMA 1990; 263: 2893-2898 [PMID: 2338751 DOI: 10.1001/jama.1990.03440200403040]

149 Roa Barrios M, Arata-Bellabarba G, Valeri L, Velázquez-Maldonado E. Relationship between the triglyceride/high-density lipoprotein-cholesterol ratio, insulin resistance index and cardiometabolic risk factors in women with Polycystic ovary syndrome. J Endocrinol Investig 2009, 56: 59-65 [PMID: 19627713 DOI: 10.1007/s15755-009(209)70553-4]

150 Yu SS, Castillo DC, Courville AB, Sumner AE. The triglyceride paradox in people of African descent. Metab Syndr Relat Disord 2012; 10: 77-82 [PMID: 22242930 DOI: 10.1089/met.2011.0108]

151 Garg A, Helderman JH, Koffler M, Ayuso R, Rosenstock J, Raskin P. Relationship between lipoprotein levels and in vivo insulin action in normal young white men. Metabolism 1988;37:982-7. [PMID: 3361105]

152 Jeppesen J, Facchin SF, Reaven GM. Individuals with high total cholesterol/HDL cholesterol ratios are insulin resistant. J Intern Med 1998; 243: 293-298 [PMID: 9627143 DOI: 10.1046/j.1365-2796.1998.00301.x]

153 Wieser V, Moschen AR, Tilg H. Inflammation, cytokines and insulin resistance: a clinical perspective. Arch Immunol Ther Exp (Warsz) 2013; 61: 119-125 [PMID: 23307037 DOI: 10.1007/s00005-012-0210-1]

154 Escobar-Morreale HF, Luque-Ramírez M, González F. Circulating inflammatory markers in Polycystic ovary syndrome: a systematic review and meta-analyses. Fertil Steril 2011; 95: 1048-58.e1 [PMID: 21168133 DOI: 10.1016/j.fertnstert.2010.11.036]

155 Yudkin JS, Kumari M, Humphries SE, Mohamed-Ali V. Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link? Atherosclerosis 2000; 148: 209-214 [PMID: 10657556 DOI: 10.1016/S0021-9150(99)00463-3]

156 Kelly CC, Lyall H, Petrie JR, Gould GW, Connell JM, Sattar N. Low grade chronic inflammation in women with polycystic ovarian syndrome. J Clin Endocrinol Metab 2001; 86: 2453-2455 [PMID: 11397838 DOI: 10.1210/jcem.86.6.7580]

157 Peng Z, Sun Y, Lv X, Zhang H, Liu C, Dai S. Interleukin-6 Levels in Women with Polycystic ovary syndrome : A Systematic Review and Meta-Analysis. PLoS One 2016; 11: e0148531 [PMID: 26849355 DOI: 10.1371/journal.pone.0148531]

158 Bahecchi M, Tuzcu A, Canoroc N, Tuzun Y, Kidir V, Aslan C. Serum C-reactive protein (CRP) levels and insulin resistance in obese women with polycystic ovary syndrome, and effect of bicalutamide on hirsutism, CRP levels and insulin resistance. Horm Res 2004; 62: 283-287 [PMID: 15542929 DOI: 10.1159/000081973]

159 Pasceri V, Willerson JT, Yeh ET. Direct proinflammatory effect of C-reactive protein on human endothelial cells. Circulation 2000; 102: 2165-2168 [PMID: 11056086 DOI: 10.1161/01.CIR.102.18.2165]

160 Meng YX, Ford ES, Li C, Quarshie A, Al-Mahmoud AM, Giles W, Gibbons GH, Strayhorn G. Association of C-reactive protein with surrogate measures of insulin resistance among nondiabetic US from National Health and Nutrition Examination Survey 1999-2002. Clin Chem 2007; 53: 2152-2159 [PMID: 17951292 DOI: 10.1373/clinchem.2007.088930]

161 Handberg A, Levin K, Hajlund K, Beck-Nielsen H. Identification of the oxidized low-density lipoprotein scavenger receptor CD36 in plasma: a novel marker of insulin resistance. Circulation 2006; 114: 1169-1176 [PMID: 16952981 DOI: 10.1161/CIRCULATIONAHA.106.626135]
Amisi CA. Markers of insulin resistance in PCOS

Glintborg D, Hjulund K, Andersen M, Henriksen JE, Beck-Nielsen H, Handberg A. Soluble CD36 and risk markers of insulin resistance and atherosclerosis are elevated in Polycystic ovary syndrome and significantly reduced during pioglitazone treatment. Diabetes Care 2008; 31: 328-334 [PMID: 18000176 DOI: 10.2373/dcd07-1424]

Muscati A, Antonelli S, Bianchi G, Cavrini G, Dappporto S, Ligabue A, Ludovico C, Magalotti D, Poggiopollini G, Zoli M, Pianoro Study Group. Serum C3 is a stronger inflammatory marker of insulin resistance than C-reactive protein, leukocyte count, and erythrocyte sedimentation rate: comparison study in an elderly population. Diabetes Care 2007; 30: 2362-2368 [PMID: 17595349 DOI: 10.2373/dcd07-0637]

Germainario R, Sniderman AD, Manuel S, LeFevre SP, Baldo A, Cianflone K. Coordinate regulation of triacylglycerol synthesis and glucose transport by acylation-stimulating protein. Metabolism 1993; 42: 574-580 [PMID: 8492712 DOI: 10.1016/0026-0495(93)90215-A]

Yang S, Li Q, Song Y, Tian B, Cheng Q, Qing H, Zhong L, Xia W. Serum complement C3 has a stronger association with insulin resistance than high-sensitivity C-reactive protein in women with Polycystic ovary syndrome. Fertil Steril 2011; 95: 1749-1753 [PMID: 21316661 DOI: 10.1016/j.fertnstert.2011.01.136]

Lewis RD, Narayanaswamy AK, Farewell D, Rees DA. Complement activation in Polycystic ovary syndrome occurs in the postprandial and fasted state and is influenced by obesity and insulin sensitivity. Clin Endocrinol (Oxf) 2021; 94: 74-84 [PMID: 32652642 DOI: 10.1111/cen.14322]

Dehdatishahghirat S, Mehdizadehkashi A, Arbabi A, Pishgharoudsari M, Chaichian S. Assessment of C-reactive Protein and C3 as Inflammatory Markers of Insulin Resistance in Women with Polycystic ovary syndrome: A Case-Control Study. J Reprod Infertil 2013; 14: 197-201 [PMID: 24551574]

Fumeron F, Péan F, Driss F, Balkau B, Tichet J, Marre M, Grandchamp B. Insulin Resistance Syndrome (DESIIR) Study Group. Ferritin and transferrin are both predictive of the onset of hyperglycemia in men and women over 3 years: the data from an epidemiological study on the Insulin Resistance Syndrome (DESIIR) study. Diabetes Care 2006; 29: 2090-2094 [PMID: 16936188 DOI: 10.2373/dcd06-0092]

Ko PC, Huang SY, Hsieh CH, Hsu MI, Hsu CS. Serum ferritin levels and Polycystic ovary syndrome in obese and nonobese women. Taiwan J Obstet Gynecol 2015; 54: 403-407 [PMID: 26834059 DOI: 10.1016/j.jtcv.2014.06.005]

Luque-Ramírez M, Alvarez-Blasco F, Botella-Carretero JI, Sánchez R, San Millán JL, Escober-Morreale HF. Increased iron stores of obese women with Polycystic ovary syndrome are a consequence of insulin resistance and hyperinsulinemia and are not a result of reduced menstrual losses. Diabetes Care 2007; 30: 2309-2313 [PMID: 17536071 DOI: 10.2337/dc07-0642]

Adamska A, Lebkowska A, Krentowska A, Adamski M, Kowalska I. The Association Between Serum Ferritin Concentration and Visseral Adiposity Estimated by Whole-Body DXA Scan in Women With Polycystic ovary syndrome. Front Endocrinol (Lausanne) 2019; 10: 873 [PMID: 31969861 DOI: 10.3389/fendo.2019.00873]

Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, Tataranni PA. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab 2001; 86: 1930-1935 [PMID: 11344187 DOI: 10.1210/jcem.86.5.7463]

Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, Hotta K, Shimomura I, Nakamura T, Miyaoka K, Kuriyama H, Nishida M, Yamashita S, Okubo K, Matsubara K, Muraguchi M, Ohmoto Y, Funahashi T, Matsuzawa Y. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun 1999; 257: 79-83 [PMID: 10092513 DOI: 10.1006/bbrc.1999.2525]

Matsubara M, Maruoka S, Katayose S. Decreased plasma adiponectin concentrations in women with dyslipidemia. J Clin Endocrinol Metab 2002; 87: 2764-2769 [PMID: 12050247 DOI: 10.1210/jcem.87.6.8550]

Trujillo ME, Scherer PE. Adiponectin—journey from an adipocyte secretory protein to biomarker of the metabolic syndrome. J Intern Med 2005; 257: 167-175 [PMID: 15666875 DOI: 10.1111/j.1365-2796.2004.01426.x]

Hara K, Horikoshi M, Yamauchi T, Yago H, Miyazaki O, Ebinuma H, Imai Y, Nagai R, Kadowaki T. Measurement of the high-molecular weight form of adiponectin in plasma is useful for the detection of insulin resistance and metabolic syndrome. Diabetes Care 2006; 29: 1357-1362 [PMID: 16732021 DOI: 10.2373/dcd05-1801]

Xu A, Chan KW, Hoo RL, Wang Y, Tan KC, Zhang J, Chen B, Lam MC, Tse C, Cooper GJ, Lam KS. Testosterone selectively reduces the high molecular weight form of adiponectin by inhibiting its secretion from adipocytes. J Biol Chem 2005; 280: 18073-18080 [PMID: 15760892 DOI: 10.1074/jbc.M414231200]

Pajvani UB, Hawkins M, Combs TP, Rajala MW, Doebber T, Berger JP, Wagner J; Wu M, Knoops A, Xiang AH, Utzschneider KM, Kahn SE, Olefsky JM, Buchanan TA, Scherer PE. Complex distribution, not absolute amount of insulin resistance and atherosclerosis are elevated in Polycystic ovary syndrome and significantly reduced during pioglitazone treatment in a randomized placebo-controlled study in Polycystic ovary syndrome. Clin Endocrinol (Oxf) 2008; 68: 165-174 [PMID: 17803698 DOI: 10.1111/j.1365-2265.2007.03015.x]

Niafar M, Nader ND. Adiponectin as serum biomarker of insulin resistance in patients with polycystic ovarian syndrome. Gynecol Endocrinol 2015; 31: 473-476 [PMID: 25884891 DOI: 10.1080/09513590.2015.1008445]

Zinman B, Hanley AJ, Harris SB, Kwan J, Fantus IG. Circulating tumor necrosis factor-alpha concentrations in a native Canadian population with high rates of type 2 diabetes mellitus. J Clin Endocrinol Metab 1999; 84: 272-278 [PMID: 9920095 DOI: 10.1210/jcem.84.1.5405]

Tarkun I, Cetinarslan B, Türemen E, Cantürk Z, Biyikli M. Association between Circulating Tumor Necrosis Factor-
Alpha, Interleukin-6, and Insulin Resistance in Normal-Weight Women with Polycystic ovary syndrome. *Metab Syndr Relat Disord* 2006; 4: 122-128 [PMID: 18370758 DOI: 10.1089/met.2006.4.122]

Thathapudi S, Kordati V, Erakakkambattu J, Katragadda A, Addeppally U, Hasan Q. Tumor necrosis factor-alpha and polycystic ovary syndrome: a clinical, biochemical, and molecular genetic study. *Genet Test Mol Biomarkers* 2014; 18: 605-609 [PMID: 25083576 DOI: 10.1089/gtmb.2014.0152]

Terranova PF, Rice VM. Review: cytokine involvement in ovarian processes. *Am J Reprod Immunol* 1997; 37: 50-63 [PMID: 9138453 DOI: 10.1111/j.1600-0997.1997.tb00192.x]

Anonymous. Summary of revisions for the 2010 Clinical Practice Recommendations. *Diabetes Care* 2010; 33 Suppl 1: S3 [PMID: 20042773 DOI: 10.2337/dc10-5003]

Kim JJ, Choi YM, Cho YM, Jung HS, Chae SJ, Hwang KR, Hwang SS, Ku SY, Kim SH, Kim JG, Moon SY. Prevalence of elevated glycated hemoglobin in women with Polycystic ovary syndrome. *Hum Reprod* 2012; 27: 1439-1444 [PMID: 22357766 DOI: 10.1093/humrep/deo39]

Hurd WW, Abdel-Rahman MY, Ismaii SA, Abdellah MA, Schnotzer CL, Sood A. Comparison of diabetes mellitus and insulin resistance screening methods for women with Polycystic ovary syndrome. *Fertil Steril* 2011; 96: 1043-1047 [PMID: 21813121 DOI: 10.1016/j.fertnstert.2011.07.002]

Lerchbaum E, Schwetz V, Giuliani A, Obermayer-Pietsch B. Assessment of glucose metabolism in Polycystic ovary syndrome: HbA1c or fasting glucose compared with the oral glucose tolerance test as a screening method. *Hum Reprod* 2013; 28: 2537-2544 [PMID: 23756702 DOI: 10.1093/humrep/det255]

Zhen Y, Yang P, Dong R, Wu Y, Sang Y, Du X, Wang Y, Song Q, Yu L, Rao X. Effect of HbA1c detection on the diagnostic screening for glucose metabolic disorders in Polycystic ovary syndrome. *Clin Exp Obstet Gynecol* 2014; 41: 58-61 [PMID: 24707685]

Celic C, Abali R, Bastu E, Tasdemir N, Tasekim UG, Gul A. Assessment of impaired glucose tolerance prevalence with hemoglobin A1c and oral glucose tolerance test in 252 Turkish women with Polycystic ovary syndrome : a prospective, controlled study. *Hum Reprod* 2013; 28: 1062-1068 [PMID: 23335611 DOI: 10.1093/humrep/det002]

Osei K, Rhinesmith S, Guillard T, Schuster D. Is glycosylated hemoglobin A1c a surrogate for metabolic syndrome in non-diabetic, first-degree relatives of African-American patients with type 2 diabetes? *J Clin Endocrinol Metab* 2003; 88: 4596-4601 [PMID: 14557429 DOI: 10.1210/jc.2003-03066]

de Medeiros SF, Yamamoto MM, Bueno HB, Belizario D, Barbosa JS. Prevalence of elevated glycated hemoglobin concentrations in the Polycystic ovary syndrome : anthropometrical and metabolic relationship in amazonian women. *J Clin Med Res* 2014; 6: 278-286 [PMID: 24883154 DOI: 10.14740/jocmr1829a]

Nakamura MT. Another obese gene function. *Nature* 1995; 374: 124 [PMID: 7787681 DOI: 10.1038/374124a0]

Zhang Y, Poonen R, Maffe H, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. *Nature* 1994; 372: 425-432 [PMID: 7984236 DOI: 10.1038/372425a0]

Rizk NM, Sharief E. Leptin as well as Free Leptin Receptor Is Associated with Polycystic ovary syndrome in Young Women. *Int J Endocrinol* 2015; 2015: 927805 [DOI: 10.1155/2015/927805]

Morris DL, Rui L. Recent advances in understanding leptin signaling and leptin resistance. *Am J Physiol Endocrinol Metab* 2009; 297: E1247-E1259 [DOI: 19724019 DOI: 10.1152/ajpendo.00274.2009]

Budak E, Fernández Sánchez M, Bellver J, Cerveró A, Simón C, Pellicer A. Interactions of the hormones leptin, ghrelin, adiponectin, resistin, and PYY3-36 with the reproductive system. *Fertil Steril* 2006; 85: 1563-1581 [PMID: 16759918 DOI: 10.1016/j.fertnstert.2006.09.065]

Wang TN, Chang WT, Chiu YW, Lee CY, Lin KD, Cheng YY, Su YJ, Chung HF, Huang MC. Relationships between changes in leptin and insulin resistance levels in obese individuals following weight loss. *Kaohsiung J Med Sci* 2013; 29: 436-443 [PMID: 23966234 DOI: 10.1016/j.kjms.2012.08.041]

Pehlivanov B, Mitkow M. Serum leptin levels correlate with clinical and biochemical indices of insulin resistance in women with Polycystic ovary syndrome. *Eur J Contracept Reprod Health Care* 2009; 14: 153-159 [PMID: 19340711 DOI: 10.1002/ejcr.2005.09.065]

Yildizhan R, Ilihan GA, Yildizhan B, Kolusari A, Adali E, Bugdayci G. Serum retinol-binding protein 4, leptin, and plasma asymmetric dimethylarginine levels in obese and nonobese young women with Polycystic ovary syndrome. *Fertil Steril* 2011; 96: 246-250 [PMID: 21600576 DOI: 10.1016/j.fertnstert.2011.04.073]

Vicennati V, Giambineri A, Calzoni F, Casimirri F, Macor C, Vettor R, Pasquali R. Serum leptin levels in obese women with Polycystic ovary syndrome is correlated with body weight and fat distribution but not with androgen and insulin levels. *Metabolism* 1998; 47: 988-992 [PMID: 9711997 DOI: 10.1006/metm.1997.0356-0]

Nasrat H, Patra SK, Goswами B, Jain A, Raghunandani C. Study of Association of Leptin and Insulin Resistance Markers in Patients of PCOS. *Indian J Clin Biochem* 2016; 31: 104-107 [PMID: 26855496 DOI: 10.1007/s12291-015-0499-8]

Gennarelli G, Holte J, Wide L, Berne C, Lithell H. Is there a role for leptin in the endocrine and metabolic aberrations of Polycystic ovary syndrome? *Hum Reprod* 1998; 13: 535-541 [PMID: 9572406 DOI: 10.1093/humrep/13.3.535]

Carmina E, Buchieri S, Mansueto P, Rini G, Ferin M, Lobo RA. Circulating levels of adipose products and differences in fat distribution in the ovulatory and anovulatory phenotypes of Polycystic ovary syndrome. *Fertil Steril* 2009; 91: 1332-1335 [PMID: 18455165 DOI: 10.1016/j.fertnstert.2008.03.007]

Swendsen PF, Christiansen M, Hedley PL, Nilsa L, Pedersen SB, Madshad S. Adipose expression of adipocytokines in women with Polycystic ovary syndrome. *Fertil Steril* 2012; 98: 235-241 [PMID: 22607892 DOI: 10.1016/j.fertnstert.2012.03.056]

Wang Q, Guo T, Tao Y, Wang Q, Song Y, Huang W. Association between serum adipocyte factor level and insulin resistance in polycystic ovarian syndrome. *Gynecol Endocrinol* 2011; 27: 931-934 [PMID: 21495802 DOI: 10.3109/09513590.2011.665957]

Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, Patel HR, Ahima RS, Lazar MA. The hormone resistin links obesity to diabetes. *Nature* 2001; 409: 307-312 [PMID: 11201732 DOI: 10.1038/35051000]

Kim KH, Lee K, Moon YS, Sul HS. A cysteine-rich adipose tissue-specific secretory factor inhibits adipocyte

Amisi CA. Markers of insulin resistance in PCOS

Chen X, Jia X, Qiao J, Guan Y, Kang J. Adipokines in reproductive function: a link between obesity and Polycystic ovary syndrome. J Mol Endocrinol 2013; 50: R21-R37 [PMID: 23335807 DOI: 10.1530/JME-12-0247]

Lee JH, Chan JL, Yiannakouris N, Kontogianni M, Estrada E, Seip R, Orlova C, Mantzoros CS. Circulating resistin levels are not associated with obesity or insulin resistance in humans and are not regulated by fasting or leptin administration: cross-sectional and interventional studies in normal, insulin-resistant, and diabetic subjects. J Clin Endocrinol Metab 2003; 88: 4848-4856 [PMID: 14557464 DOI: 10.1210/jc.2003-030519]

Vozarova de Courtine B, Degaswa-Yamachi M, Considine RV, Tataranni PA. High serum resistin is associated with an increase in adiposity but not a worsening of insulin resistance in Pima Indians. Diabetes 2004; 53: 1279-1284 [PMID: 15111497 DOI: 10.2337/diabetes.53.5.1279]

Silva JV, Kerske M, Skrha J, Sucharda P, Nyomha BL, Murphy LJ. Plasma resistin, adiponectin and leptin levels in lean and obese subjects: correlations with insulin resistance. Eur J Endocrinol 2003; 149: 331-335 [PMID: 14514348 DOI: 10.1530/eje.0.1490331]

Osawa H, Tabara Y, Kawamoto R, Ohashi J, Ochi M, Onuma H, Nishida W, Yamada K, Nakura J, Kohara K, Miki T, Makino H. Plasma resistin, associated with single nucleotide polymorphism –420, is correlated with insulin resistance, lower HDL cholesterol, and high-sensitivity C-reactive protein in the Japanese population. Diabetes Care 2007; 30: 1501-1506 [PMID: 17384338 DOI: 10.2337/dc06-1936]

Munir U, Yen HW, Barthü T, Tarkowski R, Aziz R, Magoffin DA, Jakimiuk AJ. Resistin stimulation of 17alpha-hydroxylase activity in ovarian theca cells in vitro: relevance to Polycystic ovary syndrome. J Clin Endocrinol Metab 2005; 90: 4852-4857 [PMID: 15886251 DOI: 10.1210/jc.2004-2152]

Escobar-Morreale HF, Villuendas G, Botella-Carretero JI, Alvarez-Blasco F, Sanchón R, Luque-Ramírez M, San Millán JL. Adiponectin and resistin in PCOS: a clinical, biochemical and molecular genetic study. Hum Reprod 2006; 21: 2257-2265 [PMID: 16675483 DOI: 10.1093/humrep/del146]

Seow KM, Juan CC, Hsu YP, Ho LT, Wang YY, Hwang JW. Serum and follicular resistin levels in women with polycystic ovarian syndrome during IVF-stimulated cycles. Hum Reprod 2005; 20: 117-121 [PMID: 15513972 DOI: 10.1093/humrep/deh589]

Tan BK, Heufling D, Chen J, Farhatullah S, Adya R, Keay SD, Kennedy CR, Lehnert H, Randeva HS. Metformin decreases the adipokine vaspin in overweight women with Polycystic ovary syndrome concomitant with improvement in insulin sensitivity and a decrease in insulin resistance. Diabetes 2008; 57: 1501-1507 [PMID: 18375437 DOI: 10.2337/db08-0127]

Dogan K, Helvacioğlu C, Baghaki S, Ekim M. Comparison of body mass index and metabolic parameters with serum vaspin levels in women with Polycystic ovary syndrome. Diabetes Metab Syndr 2020; 14: 137-139 [PMID: 32087564 DOI: 10.1016/j.dsx.2020.01.008]

Franik G, Plinta R, Madej P, Owczarek A, Bozentowicz-Wikarek M, Chudek J, Skrzypele-Plinta V, Olszanecka-Glinianowicz M. Circulating vaspin levels and nutritional status and insulin resistance in Polycystic ovary syndrome. Ginekol Pol 2020; 91: 251-255 [PMID: 32495305 DOI: 10.5603/GP.2020.0056]

Lee DK, Cheng R, Nguyen T, Fan T, Kariyawasam AP, Liu Y, Osmond DH, George SR, O'Dowd BF. Characterization of adipokine, the ligand for the APJ receptor. J Neurochem 2000; 74: 34-41 [PMID: 10617103 DOI: 10.1046/j.1471-4159.2000.0740034.x]

Altinkaya ŞO, Nergiz S, Küçük M, Yüksel H. Apelin levels in relation with hormonal and metabolic profile in patients with Polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol 2014; 176: 168-172 [PMID: 24642195 DOI: 10.1016/j.ejogrb.2014.02.023]

Cekmez Y, Pirgon O, Canpolat FE, Aydinöz S, Metin Ipcioglu O, Karademir F. Evaluation of new adipocytokines and insulin resistance in adolescents with Polycystic ovary syndrome. Eur Cytokine Netw 2011; 22: 32-37 [PMID: 21441410 DOI: 10.1684/ecn.2011.0279]

Gören K, Sağsöz N, Noyan Y, Yücel A, Çağlayan O, Bostancı MS. Plasma apelin levels in patients with Polycystic ovary syndrome. J Turk Ger Gynecol Assoc 2012; 13: 27-31 [PMID: 26247671 DOI: 10.5152/jjgga.2011.74]

Olszanecka-Glinianowicz M, Madej P, Nylec M, Owczarek A, Szanecki W, Skalba P, Chudek J. Circulating apelin level in relation to nutritional status in Polycystic ovary syndrome and its association with metabolic and hormonal disturbances. Clin Endocrinol (Oxf) 2013; 79: 238-242 [PMID: 23199261 DOI: 10.1111/cen.12120]

Liu Q, Jiang J, Shi Y, Mo Z, Li M. Apelin/Apelin receptor: A new therapeutic target in Polycystic ovary syndrome. Life Sci 2020; 260: 118310 [PMID: 32835696 DOI: 10.1016/j.lfs.2020.118310]

Sun X, Wu X, Zhou Y, Yu X, Zhang W. Evaluation of Apelin and Insulin Resistance in Patients with PCOS and Therapeutic Effect of Drosiprene-Ethinylestradiol Plus Metformin. Med Sci Monit 2015; 21: 2547-2552 [PMID: 26314870 DOI: 10.12659/MSM.894926]

Karbek B, Özbek M, Karakose M, Topaloglu O, Bozkurt NC, Cakır E, Aslan MS, Delibas T. Copeptin, a surrogate marker for arginine vasopressin, is associated with cardiovascular risk in patients with Polycystic ovary syndrome. J Ovarian Res 2014; 7: 31 [PMID: 24628831 DOI: 10.1186/1757-2215-7-31]

Taskın MI, Bulbul E, Adali E, Hismiogulları AA, Inceboz U. Circulating levels of obestatin and copeptin in obese and nonobese women with Polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol 2015; 189: 19-23 [PMID: 25837320 DOI: 10.1016/j.ejogrb.2015.03.006]

Salem U, Khaleghi M, Morgenthaler NG, Bergmann A, Struck J, Mosley TH Jr, Kullo IJ. Plasma carboxy-terminal provasopressin (copeptin): a novel marker of insulin resistance and metabolic syndrome. J Clin Endocrinol Metab 2009; 94: 2558-2564 [PMID: 19366852 DOI: 10.1210/jc.2008-2278]

Boström P, Wu J, Jedrzychowski MP, Korde A, Ye L, Lo JC, Raszbach KA, Boström EA, Choi JH, Long JZ, Kajimura S, Zingaretti MC, Vind BF, Tu H, Cinti S, Höjlland K, Gygi SP, Spiegelman BM. A PGC1α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature 2012; 481: 463-468 [PMID: 22237023 DOI: 10.1038/nature10777]

Li M, Yang M, Zhou X, Fang X, Hu W, Zhu W, Wang C, Liu D, Li S, Liu H, Yang G, Li L. Elevated circulating levels of...
Amisi CA. Markers of insulin resistance in PCOS

irisin and the effect of metformin treatment in women with Polycystic ovary syndrome. *J Clin Endocrinol Metab* 2015; **100**: 1485-1493 [PMID: 25675380 DOI: 10.1210/jc.2014-2544]

234 Li H, Xu X, Wang X, Liao X, Li L, Yang G, Gao L. Free androgen index and Irisin in Polycystic ovary syndrome. *J Endocrinol Invest* 2016; **39**: 549-556 [PMID: 26584566 DOI: 10.1007/s40618-015-0403-7]

235 Yang M, Liu R, Li S, Luo Y, Zhang Y, Zhang L, Liu D, Wang Y, Xiong Z, Boden G, Chen S, Li L, Yang G. Zinc-a2-glycoprotein is associated with insulin resistance in humans and is regulated by hyperglycemia, hyperinsulinemia, or liraglutide administration: cross-sectional and interventional studies in normal subjects, insulin-resistant subjects, and subjects with newly diagnosed diabetes. *Diabetes Care* 2013; **36**: 1074-1082 [PMID: 23275352 DOI: 10.2337/dc12-0940]

236 Lai Y, Chen J, Li L, Yin J, He J, Yang M, Jia Y, Liu D, Liu H, Liao Y, Yang G. Circulating zinc-a2-glycoprotein levels and Insulin Resistance in Polycystic ovary syndrome. *Sci Rep* 2016; **6**: 25934 [PMID: 27180914 DOI: 10.1038/srep25934]

237 Pearson HM, Henson J, Sargeant JA, Davies MJ, Khunti K, Suzuki T, Bowden-Davies KA, Cuthbertson DJ, Yates TE. Zinc-alpha2-glycoprotein, dysglycaemia and insulin resistance: a systematic review and meta-analysis. *Rev Endocr Metab Disord* 2020; **21**: 569-575 [PMID: 32377863 DOI: 10.1007/s11154-020-09553-w]

238 Zheng S, Liu E, Zhang Y, Long T, Liu X, Gong Y, Mai T, Shen H, Chen H, Lin R, Zheng Y, Xie Y, Wang F. Circulating zinc-a2-glycoprotein is reduced in women with Polycystic ovary syndrome , but can be increased by exenatide or metformin treatment. *Endocr J* 2019; **66**: 555-562 [PMID: 30918134 DOI: 10.1507/endocrj.EJ18-0153]

239 Sampson M, Kong C, Patel A, Unwin R, Jacobs HS. Ambulatory blood pressure profiles and plasminogen activator inhibitor (PAI-1) activity in lean women with and without the Polycystic ovary syndrome. *Clin Endocrinol (Oxf)* 1996; **45**: 623-629 [PMID: 8977761 DOI: 10.1046/j.1365-2265.1996.00863.x]

240 Orio F, Jr, Palomba S, Cascella T, Tauchmanová L, Nardo LG, Di Biase S, Labella D, Russo T, Savastano S, Tolino A, Zullo F, Colao A, Lombardi G. Is plasminogen activator inhibitor-1 a cardiovascular risk factor in young women with Polycystic ovary syndrome? *Reprod Biomed Online* 2004; **9**: 505-510 [DOI: 10.1016/S1472-6483(10)61634-3]

241 Tarkan I, Cantürk Z, Arslan BC, Türemen E, Tarkan P. The plasminogen activator system in young and lean women with Polycystic ovary syndrome. *Endocr J* 2004; **51**: 467-472 [PMID: 15516780 DOI: 10.1507/endocrj.51.467]

242 Cassar S, Teede HJ, Harrison CL, Joham AE, Moran LJ, Stepto NK. Biomarkers and insulin sensitivity in women with Polycystic ovary syndrome : Characteristics and predictive capacity. *Clin Endocrinol (Oxf)* 2015; **83**: 50-58 [PMID: 25262763 DOI: 10.1111/cen.12619]
