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Research Article

Exploring on the Hyperinsulinism Management in Women with Polycystic Ovary Syndrome

Sebastião Freitas de Medeiros[1, 2, *], MárciaMarlyWinck Yamamoto[2], JamillyAparecida Vicente Jacomeli[2], José Maria Soares Junior[3], Gustavo Arantes Rosa Maciel[3], Edmund Chada Baracat[3]

[1]Department of Gynecology and Obstetrics, Federal University of Mato-Grosso, Cuiabá, Brazil

[2]Tropical Institute of Reproductive Medicine, Cuiabá, Brazil

[3]Department of Gynecology and Obstetrics, University of São Paulo, São Paulo, Brazil

Abstract

This comprehensive review focuses on the relevance of hyperinsulinemia in women with polycystic ovary syndrome (PCOS). It highlights the most robust scientific evidence on the management of this condition within the context of PCOS. A systematic search of studies published in English language was conducted using Google Scholar, PubMed, and Cochrane databases. Keywords used alone or combined with "PCOS" included: hyperinsulinemia, incretin hormones, and dipeptidyl peptidase-4. The search strategy was complemented by manual review of references from selected articles. Glucagon-like peptide-1 receptor agonist and glucagon-dependent insulin tropic polypeptide provide various metabolic beneficial effects in addition to the weight loss. Dipeptidyl peptidase-4 inhibitors, expressed by various cells, prevent GLP-1 degradation and decreases insulin signaling in different cells, particularly in hepatocytes, and adipocytes. Regarding the management of hyperinsulinemia, the review suggests that incretin hormone agonist and dipeptidyl peptidase-4 inhibitors may represent favorable therapeutic options for addressing insulin resistance in women with PCOS, particularly those with obesity. However, this review does not explore dietary interventions and physical activity as primary strategies for managing dysglycemia in this population.

Keywords

Polycystic Ovary Syndrome, Hyperinsulinism, Incretin Hormone, Dipeptylpeptidase

1. Introduction

In adults, PCOS has been defined by the presence of oligoanovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovary morphology (PCOM) and/or ovarian volume >10cm^3 [1]. In adolescents, despite the use of ultrasound has not been recommended, nevertheless the recommendation is based only on opinion of specialists as practical points, not in scientific evidences [2]. For that reason the results must be considered with certain reserve. The prevalence of polycystic ovary syndrome (PCOS) ranges from 3% to 11% in adolescents and from 5% to 20% in adults, according to diagnostic criteria and population studied [3, 4]. Although

*Correspondence: Sebastião Freitas de Medeiros (de.medeiros@terra.com.br)

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PCOS was recently renamed to polyendocrine metabolic ovarian syndrome (PMOS), in this review, the PCOS abbreviation will be maintained without affecting the review's conclusions. [5]. The most prevalent characteristic of PCOS is increased ovarian androgen production, found in over 75% of patients, and increased adrenal androgens can be found in about 20% - 30% [6]. Regarding androgens, either from adrenal or ovarian sources, there have been attempts to translate basic knowledge into clinical practice [6]. It is already clear that the biochemical hyperandrogenism increases the risk of central obesity, dysfunctional and hypertropic adipocytes, dyslipidemia, impaired fasting glucose (IFG), glucose intolerance (GI), low-grade chronic inflammation, and hyperinsulinemia [7]. Additionally, hyperinsulinemia may stimulate the ovarian synthesis of androstenedione and testosterone [7-9].

Considering the leading role of the hyperandrogenism in the development of comorbidities, such as central obesity and hyperinsulism, in women with PCOS, the clinical management needs to be based on different phenotypes of PCOS since individual characteristics must tailor the finest treatment choice [10]. It must be highlighted however that some procedures are applied to all PCOS phenotypes [11]. Insulin regulates plasma glucose homeostasis and acts indifferent tissues such as ovarian cells, liver, skeletal muscle, and adipose tissue. Insulin resistance, common in PCOS, determines various metabolic dysfunctions linked to an increased risk of cardiovascular disease (CVD) [12]. As dysglicemia can be present in 50%- 70% of women with PCOS, the present review is focused in the pharmacological management of hyperinsulinism/ hyperinsulinemia in these patients.

2. Definition of Hyperinsulinemia/Insulin Resistance in Women with PCOS

Hyperinsulinemia may be either a cause or a consequence of hyperandrogenemia [9, 13, 14]. As mentioned before, hyperinsulinemia itself may induce an increase in androgen levels [8, 9]. On the other side, hyperandrogenism may promote central obesity, dysfunctional adipocytes, impaired fasting glucose (IFG), glucose intolerance (GI) and insulin resistance (IR) with elevated circulating insulin levels [9, 13]. Increased levels of insulin in women with PCOS vary with the phenotype and are reported in over 65% of patients [15]. Insulin inhibits liver synthesis of sex hormone binding globulin (SHBG) and insulin- like growth fator-1 (IGF-1) and a decrease in SHBG results in increased free testosterone levels, a predictive marker of insulin resistance [16, 17].

Table 1. *Recommended cut-offs and ranges commonly used for diagnosing insulin resistance/hy.*

Parameter	Cut offs	Ranges	References
SHBG(nmol/l)	20	20-37	Chen et al, 2021 Jayagopal et al, 2003 Nadaraja et al, 2018
Baseline insulin (pmol/l)	85	68-105	McAuley et al, 2001 Lewandowsky et al, 2019 Lee et al, 2003
HOMA-IR	2.2	1.8-3.8	De Medeiros et al, 2017 Lewandowsky et al, 2019 Gayoso-Diz et al, 2013 Abdesselan et al, 2021
Quicki	0.357	0.310-0.360	Martins et al, 2007 Kartz et al, 2000 Park et al, 2021

SHBG=sex hormone binding globulin
HOMAR-IR=homeostatic model assessment of insulin resistance.
Quicki=quantitative insulin sensitivity check index

Clinically, the presence of hyperinsulinemia is identified by the presence of acanthosis nigricans (AN) in about 30%- 68%

of patients [18, 19] and skin tags in nearly 16% [20]. The laboratorial diagnosis of hyperinsulinemia might be performed with baseline levels of insulin over 12.2 μUI/ml (85 pmol/l) [21, 22]. Moreover, different published cut-offs for hyperinsulinemia (IR) are shown in Table 1 [21-32]. IR in adipose tissue and skeletal muscle may be diagnosed using the Homeostatic Model Assessment-IR (HOMA-IR), the Quantitative Insulin Sensitivity Check Index (QUICKI test) or many other biochemical and validated anthropometric biomarkers [26, 33].

2.1. Highlights on Treatment of Hyperinsulinemia/Insulin Resistance in PCOS

Any treatment for insulin resistance and/or hyperinsulinemia in women with PCOS should be prescribed only after a precise diagnosis of this condition. Initially, lifestyle and diet could be prescribed to nearly all women with PCOS. Various new drugs have been demonstrated to be an adequate treatment for women with PCOS with IR (Figure 1). The present review will be limited to the use of glucagon-like peptide-1 receptor agonists (GLP-1RAs), glucose-dependent insulinotropic polypeptide (GIP), and dipeptidyl peptidase-4 (DPP-4) inhibitors (Table 1), particularly recommended in obese PCOS [34, 35]. Incretins are the gut secreted hormones GIP and GLP-1[34, 36]. The GLP-1 is synthesized by post-translational processing of glucagon in the epithelial L-cells of the intestine, particularly in the ileum and colon that are in contact with nutrients [37].

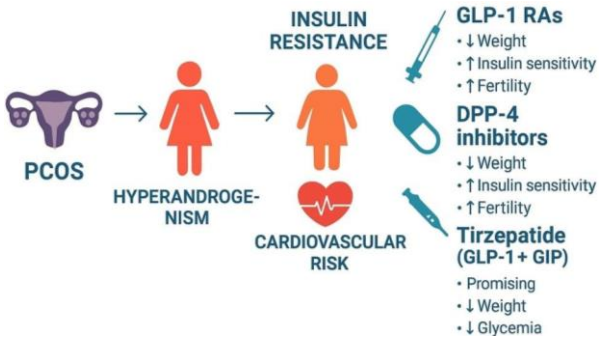

Figure 1. *Dipeptidyl peptidase-4 and incretins use in polycystic ovary syndrome.*

Table 1. *Current therapy approaches for management of hyperinsulinemia/ insulin resistance in obese women with PCOS.*

Glucagon-like peptídeo-1 receptor agonist (GLP-1 RA)
Exenatide
Liraglutide
Semaglutide
Dipeptidyl peptidase-4 (DDP-4) inhibitors
Sitagliptin
Alogliptin
Sexagliptin
GLP-1 RA and GIP synergic activities
Tirzepatide

2.2. Glucagon-Like Peptide-1 Receptor Agonist

The GLP-1 RAs, mimic incretin GLP-1 secreted by L-cells of distal intestine, bind to insulin receptors on pancreatic β-cells, stimulate insulin secretion, expand pancreatic β-cells through growth, differentiation and proliferation via activation of epidermal growth factor receptor [37]. Additionally, they reduce glucagon secretion and exhibit anti-inflammatory properties [37]. Nutrient ingestion, mainly glucose and fat are the primary physiological stimulus for L-cell to secret GLP-1, as soon as 15-30 min after ameal [37]. In clinical practice, GLP-1 RA, are adequate alternative to the use of metformin, it does not increase the risk of hypoglycemia and has shown significant improvement in insulin action, weight reduction, waist circumference reduction and reproductive function with increased pregnancy rates [38, 39]. Nowadays various studies indicate the effectively of GLP-1 RAs in the treatment of women with PCOS [34, 40-49].

Currently, a few types of GLP-1 RAs are approved for treatment of dysglycemia and insulin resistance in overweight or obese women with PCOS; particularly exenatide, liraglutide, dulaglutide and semaglutide. Furthermore, they can be associated with metformin or other oral hypoglycemic drugs [50]. In their action GLP-1 RAs suppress appetite (central anorexic effect) at hypothalamic level by increasing the electrical activity

in the pro-opiomelanocortin (POMC) neurons [43, 46], help to decrease central obesity by activated protein kinase (AMPK) in the centro medial hypothalamic nucleus, reducing body weight [50, 51], improve glycemic control by increasing insulin sensitivity in peripheral tissues and glucose uptake [49, 50], and decline the inflammation state by reducing macrophages secretion of proinflammatory cytokines [40, 49] (Figure 2). Moreover, GLP-1 RAs reduce glucagon secretion; reduce metabolic disorders associated fatty liver disease (MASLD) and visceral adipose tissue [40, 49]. After oral glucose tolerance test (OGTT) in women with PCOS it was observed increase in GIP and lower GLP-1 concentrations. GLP-1 is also reduced in impaired glucose tolerance (ITG), impaired fasting glucose (IFG) and dyslipidemic states [47]. In total, GLP-1RAS exhibit a cardio protective effect [48].

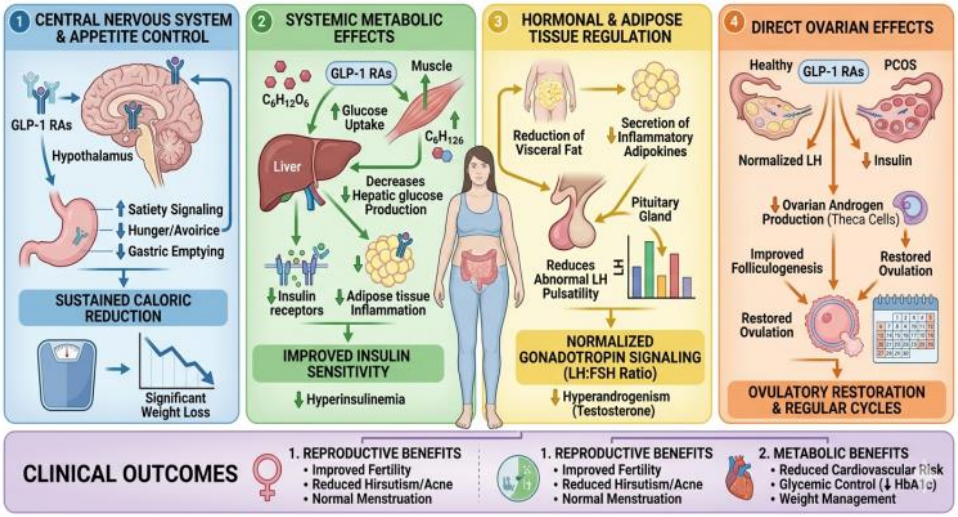

Figure 2. *Integrated pathways: GLP-1 RAs in the treatment of PCOS.*

The first GLP-1RA exenatide, approved for clinical use in 2005, has a short half-life of 2.4 hours and immediate effect [52]. For clinical use, it is available in two preparations: a short action formulation for subcutaneous (SC) administrations twice daily (BID) before meals and a long acting formulation given weekly, containing exenatide dispersed in microspheres to be released via biodegradation in three stages: 48 hours, 2 weeks, and approximately 7 weeks. With a dosevarying between 5 µg- 10µg, SC, (BID) in women with PCOS for 24 weeks, exenatide promoted weight loss, reduced fat mass, reduced body mass index (BMI) and waist circumference (WC) [53, 54]. Regarding weight loss it was shown to be superior to metformin [53, 54]. Additionally, it improved lipid profile, hepatocyte IR, glucose concentration, decreased glycated hemoglobin (HbA1C), decrease HOMA-IR, decrease C-reactive protein (CRP), and improved p- selectin and e-selectin accepted biomarkers of CVD [52-57]. Exenatide promotes benefic metabolic changes and diminishes the risk of CVD [58]. Adverse events related to exenatide are of low intensity and frequency, being common nausea, vomiting, diarrhea, nasopharingite and headache with respect to hormone levels, exenatide (10µg) increases SHBG (24%), decreases total testosterone level (17%), and increases the number of menstrual cycles. However, in other study, with 20 µg/day, exenatide did not modify the levels of total testosterone (T), androstenedione (A4), dehydroepiandrostenone (DHEA), and SHBG [53-57].

Liraglutide given once a day, at doses ranging from 0.6 mg to 1.8 mg, delays gastric emptying, controls appetite and reduces body weight [59-62]. In a study including women with PCOS, liraglutide, given at a daily dose of 1.8 mg, for 26 weeks, reduced body weight (5%), decreased liver fat mass (44%), decreased body fat mass (19%) and decreased visceral adipose tissue [45, 62]. Yet, in other study, also enrolling women with PCOS, liraglutide given for 6 months, promoted more than 5% loss in body weight, with total body loss of 4-6 kg [61]. Body weight loss of 5.2 kg to 9.1 kg, BMI loss of 1.9kg, WC decrease of 4.1 cm was also showed in PCOS [38, 60, 61]. Because some inconsistent results, it is currently recommended to increase liraglutide dose to 3 mg daily in overweight/obese women with PCOS [61]. Liraglutide, at doses of 1.2 to 3.0 mg daily has been shown to increase luteinizing hormone (LH), follicle-stimulating hormone (FSH), SHBG, and decrease total T, A4, and DHEAS [61]. Regarding menstrual cycles length the current results remain inconsistent [61].

In preclinical study, examining a DHEA induced PCOS female rats, dulaglutide was shown to decrease insulin with significant reduction in T and increased of SHBG levels, when compared with no treated rats. Additionally, the ovarian gene expressions of 3B-HSD, CYP (19α1), and STAR were decreased after three weeks of treatment [62, 63]. Recent studies have considered the effects of dulaglutide in women with PCOS [43, 62, 64]. Dulaglutide is a once weekly GLP-1 RA that may ameliorate adherence [65]. It is used at a weekly dose

of 1.5 mg by subcutaneous injection [65]. Combined with caloric-restricted diet (CRD) of 1.000-1.300 kcal day dulaglutide was recently used in overweight/obese adult women with PCOS [66]. This initial study did not show significant differences in menstrual cycles and anthropometric measures when compared with the use of CRD alone. However, during six months of treatment a 7% loss of weight took a shorten time [66].

Regarding metabolic biomarkers, dulaglutide associated with CRD significantly decreases fasting glucose and HbA1C levels without clear benefits in lipids, hormones, liver function biomarkers, and C-reactive protein (CRP). About body composition, no different was observed in visceral adipose tissue (VAT) with the addition of dulaglutide to CRD in women with PCOS [67]. No difference in lean body mass (LBM) was also observed. The decrease in systolic (SBP) and diastolic blood pressures (DBP) was similar between use isolated of CRD or of a combination of CRD with dulaglutide. With different intensities, adverse events have been reported in about 37% of users of dulaglutide; mainly gastrointestinal reactions such us nausea, vomiting, constipation, diarrhea, abdominal distension, dyspepsia, and loss of appetite. These adverse events tend to ameliorate after three/ four weeks of use [66, 67] and are particularly exacerbated at daily dose of 3.0 mg to 4.5 mg.

Semaglutide, approved by FDA in 2019, is a GLP-1 RA with a long half-life of 7-8 days, was recently used in overweight/obese women with PCOS in a weekly dose of 0.5 mg, subcutaneous [68]. It delays gastric emptying in up to four hours [68] and has shown the ability of more consistently reduction in body weight, either in diabetic obese subjects [69-74] or in women with PCOS [72]. The use of 1 mg per week also demonstrated to diminish body weight, BMI, WC, VAT, fasting insulin, and HDL-C [72, 73]. When given to women with PCOS, phenotype A, for three months, semaglutide demonstrated ability to decrease body weight over 10%, 7.6±3.0 kg, BMI (↓3.1±1.0kg/m^2) [74]. When its use was extended to 6 months, body weight loss reached up to 11.5 kg, therefore more than weight loss seen with the use of liraglutide [75].

It was also reported that some patients might lose less than 5% of body weight, particularly those more obese women and were considered unresponsive to semaglutide even when given for 6 months [74]. This observation result suggested the need to increase the doses to 1 mg to 5 mg/weekly [75]. Semaglutide was also reported to decrease fasting glucose, fasting insulin, HOMA-IR, triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C) levels [72-76]. The main reported adverse event of semaglutide was nausea, and to minimize adverse events the dose might gradually be increased from 0.2 to 1 mg every two weeks up to reach 1-2 mg [72, 73]. If necessary and well tolerated the dose may be till increased to 2mg-4mg/weekly [72]. Regarding hormone levels, semaglutide significantly increased SHBG, decreased both calculated and measured free T [72]. Additionally, an oral formulation of semaglutide may be soon introduced in the treatment of PCOS, using a dose of 7 mg once daily. In other conditions such as diabetes mellitus and obesity this oral presentation has been evaluated at doses varying between 30 to 50 mg/day [76]. Recently, when associated with metformin in women with type 2 diabetes metabolites (T2DM), cycle length and HOMA-IR were significantly decreased [76]. In animal model, semaglutide was shown to alleviate ovary inflammation in PCOS [73]. Regarding the effect on the bioavailability of the combined oral contraceptive, the current results remain inconsistent [77].

2.3. Dipeptidyl Peptidas-4 (DPP-4)

The enzyme DPP-4 (CD26), a glycoprotein protease expressed by various cells, prevents GLP-1 degradation, prolonging its half-life with increased blood levels [78]. DPP-4 protease decreases insulin signaling pathways in different cells, including hepatocytes, and adipocytes [79-81]. More recently, it was seen that its expression and activity appears to be higher in women with PCOS due to hyperandrogenism [82, 83]. Despite these observations at the present time the studies showed inconsistency [81, 83]. By reducing GLP-1 degradation, the use of DPP-4 inhibitors, increases the levels of incretions and can be an alternative treatment for insulin resistance/hyperinsulinemia in women with PCOS [82, 83].

In women with PCOS sitagliptin, a DPP-4 inhibitor, has been used at doses of 100-200 mg daily and adverse events such as abdominal pain, nausea, vomiting, diarrhea are not common [83]. The use of sitagliptin in women with PCOS have shown increased GLP-1 levels, increased growth hormone half-life, decreased blood glucose, enhanced insulin secretion, decreased total cholesterol, and decreased VAT in overweight/obese women with PCOS [82, 83]. Currently, there is no study with power and time enough regarding weight loss and insulin sensitivity in women with PCOS using DPP-4 receptor inhibitors [82, 83].

2.4. Glucagon- Dependent Insulin Tropic Polypeptide

GLP-1Randglucose-dependent insulinotropic polypeptide (GIP) synergic activities Tirzepatide, a synthetic peptide with 39 amino acids has a dual agonist effect for GLP-1 and gastric GIP receptors [84]. GIP was the first incretin hormone identified in humans [84] with potent insulinotropic action [84, 85]. Duodend and jejuna mucosas are the primary source of GIP by K-cells [85]. Currently, it was approved for treating obese T2DM patients [86-91]. Clinical trials in patients with T2DM have demonstrated that its use improves glycemic control and promotes weight loss [89, 90]. Terzepatide has a long half-life of about 5 days allowing it to be used once a week [91, 92]. In non-PCOS T2DM patients, when used at a dosage of 15mg/weekly for 26 to 40 weeks, tirzepatide was shown to decrease glycated hemoglobin (HbA1C), HOMA-IR, triglycerides (TG) levels and up to 15% of the body weight [93-95].

A reduction of 3% to 8% in weight has been reported by other studies [96]. Reported adverse events are vomiting, constipation, diarrhea, and abdominal pain. Additionally, it may interact with anti-platelet drugs and by affecting the absorption of oral contraceptives, it may diminish its effectively [97]. Because dysglycemia, obesity and metabolic syndrome are common microbiome in women with PCOS, tirzepatide has a potential utility in the treatment of this condition [97, 98] (Figure 3). Further, tirzepatide helps alter the gut microbiome which is beneficial to women with PCOS [97]. In a recent trial in women with PCOS, used in combination with metformin a reduction in body weight of about 8 kg in 90% of women was observed [91]. More recently, GLP-1 RAs isolated or combined with GIP has shown to be very effective in promoting weight loss and improve dysglycemia and dyslipidemia in women with PCOS [98-100].

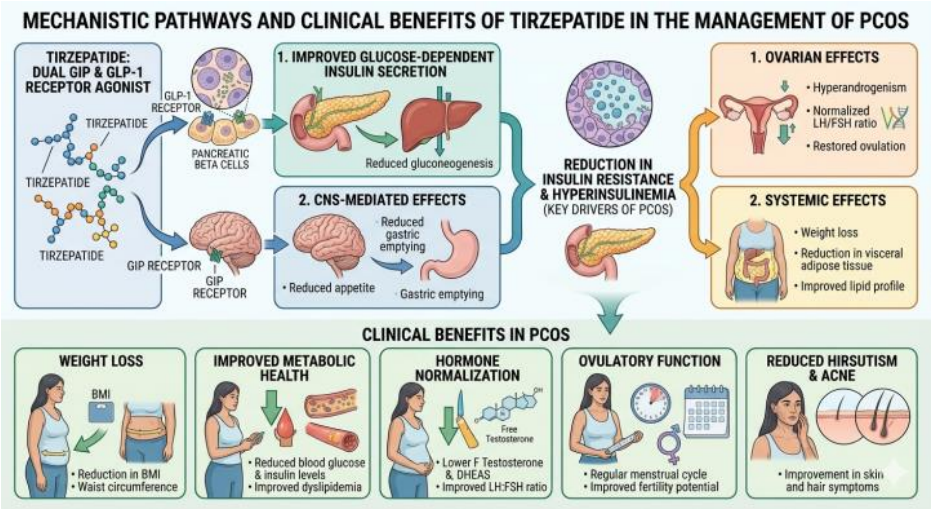

Figure 3. *Mechanistic Pathways and clinical benefits or Tirzepatide in the management of PCOS.*

3. Conclusions

Insulin resistance with hyperinsulinemia accompanied of obesity must be considered a crucial aspect for the development of CVD in women with PCOS. It is clearly established that physical activity and hypo caloric diet remain the first-line treatment to all PCOS phenotypes. When needed, various pharmacologic products are available to treat IR and hyperinsulinemia in this population. The use of GLP-1 RAs has demonstrated varying effectiveness in promoting weight loss, decrease in VAT over different time of treatment in women with PCOS. Considering the heterogeneity of PCOS phenotypes, it is needed to tailor an ideal management for individual patients. Women with PCOS and hyperinsulinism in their phenotype may be safety treated with agonists of incretin hormones and dipeptyl-peptidase-4.

Abbreviations

3 B-HSD	3-Beta-hydroxysteroid Dehydrogenase
A4	Androstenediona
AMPK	Activated Protein Kinase
AN	Acanthosis Nigricans
BID	Twice daily
BMI	Body Mass Index
CRD	Calorie-Restricted Diet
CRP	C- Reactive Protein
CVD	Cardiovascular Disease
CYP	Aromatase
DBP	Diastolic Blood Pressure
DHEA	Dehydroepiandrosterone
DHEAS	Dehydroepiandrosterone Sulfate
DPP-4	Dipeptidyl peptidase-4
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GI	Glucose Intolerance
GIP	Glucose-dependent Insulinotropic Polypeptide
GLP-1	Glucagon-Like Peptide-1
GPL-1 RA	Glucagon-Like Peptide-1 Receptor Agonist
HbA1C	Glycated Hemoglobin
HDL- C	High-Density Lipoprotein Cholesterol
HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
IFG	Impaired Fasting Glucose
IGF-1	Insulin-like Growth Factor-1
IR	Insulin Resistance
ITG	Impaired Tolerance Glucose
LH	Luteinizing Hormone
MASLD	Metabolic Dysfunction-Associated Steatotic Liver Disease
OGTT	Oral Glucose Tolerance Test

PMOS	Polyendocrine Ovarian Metabolic Syndrome
PCOM	Polycystic Ovary Morphology
PCOS	Polycystic Ovary Syndrome
QUICKI	Quantitative Insulin Sensitivity Check Index
SBP	Systolic Blood Pressure
SC	Subcutaneous
SHBG	Sex Hormone-Binding Globulin
StAR	Steroidogenic Acute Regularoy Protein
T	Total Testosterone
T2DM	Diabetes Mellitus Tipo 2
TG	Triglycerides
VAT	Visceral Adipose Tissue
WC	Waist Circumference

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Author Contributions

Sebastião Freitas de Medeiros: Supervision, Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing

MárciaMarlyWinck Yamamoto: Data curation, Methodology, Formal analysis, Writing – review & editing

JamillyAparecida Vicente Jacomeli: Data curation, methodology, writing – original draft.

José Maria Soares Junior: Formal analysis, Writing – review & editing

Gustavo Arantes Rosa Maciel: Formal analysis, Writing – review & editing

Edmund Chada Baracat: Supervision, Formal analysis, Writing – review & editing

Data Availability Statement

There search data are not publicly available on legal or ethical grounds. In addition, all data produced and analyzed during this study were included in this article. Further inquiries can be directed to the corresponding author.

Conflicts of Interest

The authors declare no conflicts of interest.

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