81983_Auto_Edited.docx

Name of Journal: *World Journal of Clinical Cases*
Manuscript NO: 81983
Manuscript Type: ORIGINAL ARTICLE

Observational Study

Metformin effect on internal carotid artery blood flow assessed by area under the curve of carotid artery Doppler in women with polycystic ovarian syndrome

Metformin and internal carotid artery flow

Wisam Akram, Wassan Nori, Muna Abdul Ghani Zghair

Abstract

BACKGROUND

Insulin resistance (IR) was reported in most polycystic ovarian syndrome (PCOS) cases. Metformin, a biguanide drug, successfully reduced IR. Homeostatic Model Assessment for IR (HOMA-IR) and Doppler parameters assessed metformin's effectiveness.

AIM

To verify whether the area under the curve of the internal carotid artery (AUC-ICA) Doppler wave can be a useful marker for assessing IR among PCOS cases presented with menstrual irregularity, treated by metformin over six months.

METHODS

An observational cross-sectional study recruited 54 eligible PCOS women; anthropometrics; age, body mass index (BMI), menstrual cycle days, biochemical serum cholesterol, low and high-density lipoprotein, sex hormone-binding globulin, fasting blood glucose, and HOMA-IR, hormonal testosterone, luteinizing hormone over follicle-stimulating hormone ratio, and ultrasonic pulsatility index (PI) and resistance index (RI), carotid artery intima-media thickness (CIMT)and (AUC-ICA) parameters were initially recorded and repeated 3 and 6 mo later with metformin tab 500 mg; three times/day for six months. In addition, AUC-ICA was assessed by taking repeated systolic and diastolic wave height measurements.

RESULTS

Metformin caused a progressive reduction in BMI, menstrual cycle days, biochemical hormonal, and Doppler parameters (CIMT, PI, RI, and AUC-ICA). AUC-ICA correlated strongly to all PCOS parameters. AUC-ICA correlated inversely with treatment time (r= -0.98, $P<0.001$)and positively with HOMA-IR(r = 0.98, $P<0.0001$).Via the best subset regression model, the AUC-ICA had the highest predictive value for HOMA-IR.

CONCLUSION
AUC-ICA preceded PI, RI, and CIMT with a strong, meaningful correlation to all PCOS parameters, making it a reliable marker for the assessment of IR, especially during metformin therapy. Further studies are recommended for further application in practice.

Key Words: Carotid artery intima-media thickness; Insulin resistance; Internal carotid artery Doppler; Metformin; Polycystic ovarian syndrome.

Akram W, Nori W, Abdul Ghani Zghair M. Metformin effect on internal carotid artery blood flow assessed by area under the curve of carotid artery Doppler in women with polycystic ovarian syndrome. *World J Clin Cases* 2023; In press

Core Tip: Women with PCOS suffer from insulin resistance and an atherogenic state evidenced by increased carotid artery intima-media thickness (CIMT). Fortunately, this increase in CIMT is reversible with metformin therapy, an insulin-sensitizing drug. Moreover, treated cases had restored ovulatory cycles and exhibited reduced androgen levels. Herein we primarily aimed to examine whether the area under the curve (AUC) of the internal carotid artery (AUC-ICA) Doppler is related to insulin resistance among PCOS women presented with menstrual disturbances. Second, to examine if AUC-ICA can be a useful marker in assessing changes in insulin resistance among treated cases with metformin for follow-up.

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is still one of the most frequently challenging problems facing gynecologists worldwide. Despite much work conducted to understand its nature, its long-term complications from cardiovascular, infertility, and obesity-related problems are still major issues facing all affected women[1-3]. PCOS women are characterized by a state of life-long insulin resistance (IR) with permanently elevated serum insulin [4].

This hyperinsulinemia disturbed ovarian steroidogenesis (estrogens and progesterone) and disturbed pituitary secretion of gonadotropins, represented by chronically elevated serum luteinizing hormones (LH) and serum testosterone [5].

Elevated serum testosterone mainly affects lipid metabolism with an elevation of low-density lipoprotein (LDL) and serum cholesterol and a reduction of serum high-density lipoprotein (HDL) [6]. This disturbed lipid metabolism; leads to acute atherosclerotic changes affecting virtually every artery in the body but mostly in the medium-sized artery like the internal carotid artery, which can be scanned by B-mode ultrasound device. The atherogenic state is evidenced by increased carotid artery intima-media thickness (CIMT); fortunately, this increase in CIMT is usually reversible with the use of insulin-sensitizing drugs among young women below 35 years of age, which makes this reduction one of the most important prognostic variables for IR complications [7].

According to Bernoulli's rule, the increased CIMT per se is associated with a reduction in the arterial diameter, which consequently increases the artery's blood flow speed [8].

According to this rule, the narrower the artery lumen is the more blood speed per unit area in its section(inverse relationship). Modern Doppler devices allow arterial blood speed to be measured and graphed on paper strips directly from scanned arteries. With ultrasound waves beamed at 60 degrees, we can measure the difference in phase shift of the ultrasound wave [9].

The most commonly used Doppler indices to assess arterial blood flow are pulsatility and resistant index (PI and RI), respectively [10].

The PI is an ultrasonic blood flow parameter calculated from the highest, lowest, and mean Doppler frequency shifts during a given cardiac cycle. As for the RI, it estimates the resistance in a pulsatile vascular tree [11].

However, a new parameter can be easily conducted with current Doppler devices: measuring the area under the curve (AUC) of one complete heartbeat-associated blood flow graph in an artery represented by a systolic and diastolic wave.

Multiple readings of the heights of a systolic and diastolic wave of a single Doppler wave measure AUC under one Doppler wave. In physical terms, measuring AUC means measuring the amount of blood passing per unit area of the artery cross-section area [12]. For that, the speed of blood flow should increase while the amount of blood passed per unit sectional area of the internal carotid artery should reduce or remain the same according to the resistance distal to the vessel [12].

Metformin is an insulin sensitizer used for type 2 diabetes. Since many PCOS women are IR, metformin administration proved its efficacy in restoring ovulatory cycles and reducing androgen levels. This biguanide inhibits hepatic glycogenesis, increases insulin sensitivity in the periphery, increases glucose uptake, and decreases insulin secretion [1] .

Earlier studies in the field have shown reduced atherogenic indicators by insulin sensitizers like metformin and inositol for 3-6 mo, including dyslipidemia, IR, and improved endothelial function and coronary flow. Furthermore, there was a reduction in CIMT among treated women [13]. The aim of the study is to verify whether the AUC of internal carotid artery (AUC-ICA) Doppler is related to insulin resistance among women with PCOS presented with menstrual disturbances. Second, to examine if AUC-ICA can be a useful marker for the assessment of insulin resistance among women treated with metformin for follow-up.

MATERIALS AND METHODS

The current study was a cross-sectional study conducted in AL Yarmouk Teaching hospital between April 2019 till December 2021. The ethical committee of Mustansiriyah university approved the study dated February/21/2019 (IRB No. 115). Participants were briefed about the study's aim and methodology; all gave their consent before enrollment, and the Helsinki declaration was followed.

From the outpatients' clinic, unmarried women with PCOS presented with menstrual cycle abnormality and/or hirsutism, the age range of 18-35 years, and a body mass index (BMI) range of 18 to and 30; were invited to participate in the study. During this period, all patients have been prescribed a metformin tab. (Merck Santé/France) 500 mg TID times /day.

The diagnosis of PCOS was made based on Rotterdam criteria, where 2 out of 3 criteria confirm PCOS diagnosis [14].

(1) oligomenorrhea is defined as < than six cycles/ 12 mo, or amenorrhea is defined as a complete absence of the menstrual cycle(more than 90 days)[15]. (2) Clinical hyperandrogenism, with or without acne. (3) Ultrasonic feature of polycystic ovaries[16].

Exclusion criteria

Women with hypertension, diabetes mellitus, and thyroid diseases.

Drug intake; insulin sensitizers, lipid-lowering medicines, anti-androgenic therapies, oral contraceptives, and steroids.

Participants with a BMI of more than 30.

Those with missing data were also excluded

54 participants satisfied our criteria, patients in this study were all subjected to meticulous clinical examination, and all had an initial pelvic ultrasound scan to confirm the appearance of the PCOS ovaries. For each participant, four sets of data were collected; demographic criteria, biochemical and hormonal data, and biophysical data. These data were collected at the initial visit, 3 mo, and 6 mo later, and the patient was supplied with a data collection sheet for the dates of further scheduled visits. During this period, all patients have been prescribed a metformin tab. (Merck Santé/France) 500 mg TID times /day. At the end of the study, a total of 54 women with full data of biophysical, biochemical, and hormonal data were assessed at 0, 3, and 6 mo; all were described in the study flowchart **Figure 1.**

Initial patients' uptake :

It was based on the clinical criteria of menstrual cycle (MC) abnormality(oligomenorrhea or amenorrhea). Patients' age was recorded, and only body mass index BMI was calculated in the outpatient clinic according to the formula: Weight in kg/square meter of height. After exclusion, eligible cases were planned to be further investigated for hormonal, biochemical, and biophysical criteria.

Biochemical and hormonal assays:

On the second day of the menstrual cycle and after one night's fast, participants in the study were initially sent to the Teaching labs in Yarmouk Hospital for the following biochemical tests: high-density lipoprotein (HDL), low-density lipoprotein(LDL), serum cholesterol, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), fasting blood glucose (FBS), and sex hormone-binding globulin (SHBG). In addition to the hormones: follicle-stimulating hormone(FSH), luteinizing hormone(LH), and serum testosterone. The HOMA-IR tested insulin sensitivity based on the formula:

HOMA-IR=fasting insulin (micro U/L) x fasting glucose (nmol/L)/22.5 [17].

All patients were given subsequent appointments based on the initial visit to repeat all the above investigations 3 and 6 mo later while on metformin therapy, in addition to recording the days of the MC.

Biophysical data uptake: On the same day of biochemical data uptake, patients were sent for a Doppler assessment of the internal carotid artery.

Examination technique

In the radiology unit, an ultrasound machine TOSHIBA, Logic p5 with a linear array probe, and a frequency range of 5-10 MHZ were used. To measure carotid media intima thickness (CIMT), a special software computer option was used to adjust angle measurements for CIMT with a two–dimensional 2D grayscale maneuver. The assessment was made for both the right and left internal carotid artery (ICA), and the mean of both readings was taken.

Carotid intima-media thickness (CIMT) was defined as the distance between the lumen intima to the adventitia media layer line of interference on the far wall in the longitudinal axis [18]. In order to decrease intra- and inter-observer variability for CIMT measurements, all readings were made by the same radiologist in our department after a period of practice to master the technique.

As for blood flow parameters, pulsatility index (PI), and resistance index (RI), a Doppler study of the ICA was performed, and measurements were made to PI and RI.

The patient required no special preparation, and the examination was held while the patient lay in a supine position with their head turned to the other side and did not last more than ten minutes. As mentioned above, patients were provided with scheduled visits for further re-scan 3 and 6 mo later.

Measurement of Area Under Curve for Doppler wave:

To explain how we calculated the area under the curve (AUC), we will give an example. A sample of ICA Doppler is shown in Figure 2. In this picture, we measured the different heights of the Doppler wave (demarcated by dots in **Figure 2 A**)as it went up and down with a facility supplied by the ultrasound device. Depending on the width of the wave, these measurements averaged between 8 and 10; see the horizontal orange line in **Figure 2 A).** The measurement of the heights represents the speed of blood in the systolic and diastolic velocities. The calculated heights were put in an Excel table to analyze later with simple, free software called GRAPH, which can be downloaded from:

https://www.padowan.dk/download/ [19].

In Figure **2 B,** a graphical simulation of the internal Carotid Artery Doppler wave in Graph software is shown, with the different heights (demarcated in red dots) used to measure the systolic and diastolic blood flow for the calculation of AUC.

The area under the curve of the internal carotid artery Doppler (AUC-ICA) was calculated according to the following formula:

AUC = ∫ Blood velocity measured at systolic and diastolic velocity for a single Doppler wave [11].

AUC physically means the amount of blood passed per unit area of the internal carotid artery per single heartbeat. It was measured in unit 3. Following the initial measurement of AUC-ICA, a re-assessment was made 3 and 6 mo later. All data with associated biochemical and biophysical data were stored in an excel sheet for further data analysis at the end of the study.

Figure 2. A and B

Sample size calculation:

The sample size was calculated according to the following equation for a cross-sectional study with quantitative variables [20] :

Sample size= $(Z1-\alpha/2)$ 2 SD2/d2

$Z1-\alpha/2$ = is standard normal variate = 1.96

SD= standard deviation of the variable taken from already published studies.

d= absolute error or precision level as an operator decides.

Sample size= (1.96)2 (0.35)2 / (0.1)2 = (3.84*0.1225)/ 0.01= 43 patients.

So the sample size is 43 patients, and our study involved 54 patients.

Statistical analysis

Continuous data were expressed as mean and standard deviation. Data normality was checked with the Shapiro-Wilk test, and the data were normally distributed. One-way ANOVA test was used to assess the statistical data differences at the initial visit, at 3 mo, and 6 mo later for all the above biochemical, hormonal, and biophysical study variables. Linear regression was used to evaluate the decline of the AUC-ICA within 6 mo of metformin treatment with the calculation of the correlation coefficient and associated P-value. In addition, further linear regression was constructed between AUC as the main dependent variable *vs* all significant biochemical, hormonal and biophysical variables taken in this study with the calculation of the correlation coefficient and associated value to assess the effect of metformin treatment on those correlations for the six months treatment. AUC-ICA was assessed with freely downloadable software

GRAPH and further checked with MedCalc and NCSS software. P-values less than 0.05 were considered significant.

RESULTS

Fifty-four young unmarried PCOS women were collected with full hormonal, biochemical, and biophysical profiles at the initial visit, 3 mo, and 6 mo after starting the metformin tablet 500 mg/TID day. Regarding the anthropometric criteria, the mean age of the participants was (24.81±3.49) years. The days of the MC showed a significant decrease (P<0.034) from (57.6±5.8) in the initial visit to (43±56) and (31.97 ±4.9) days in the second and 3rd visits, respectively. Likewise, BMI showed a significant reduction (P < 0.04) from 28.22±0.75 in the initial visit to 25.88±0.64 and 23.81±0.74 Kg/m^2, respectively.

The main demographic criteria of those women are given at the three sampling and scanning times expressed as mean and standard deviation were described in **Table 1**., while the three columns were compared with one way ANOVA test. The results highlight a progressive increase in serum HDL and SHBG throughout the treatment period over 6 mo. Fasting blood glucose showed a trend decrease; however, it fails to have a statistical value. On the other hand, a significant reduction was found in serum cholesterol, LDL, HOMA- IR, testosterone, LH/FSH ratio, PI, RI, and CIMT. As for AUC-ICA, it showed a progressive decrease with the treatment period.

In order to shed more light on the trend of AUC-ICA correlation with various study parameters, a linear regression was constructed in **Table 2.**

All biochemical; cholesterol, HDL, LDL, SHBG, and HOMA_IR; the hormonal testosterone, and LH/FSH_Ratio; and ultrasonic parameters, RI, and CIMT used in PCOS women evaluation were correlated strongly to AUC-ICA, P <0.05.

A highly significant negative correlation exists between AUC-ICA Doppler *vs* HOMA-IR. An inverse correlation was confirmed between the six months' time (24 wk) of metformin therapy *vs* AUC-ICA with r=-0.99 and P-value less than 0.001, which was shown in **Figure 3 (A)** and highlighted by a real-time Doppler scan in **Figure 3 (B and**

C), where the wave peak decreased after treatment from 80 to 60 and accordingly; the AUC-ICA was reduced.

To assess the strength of association between HOMA-IR as the primary dependent variable *vs* the predictive biophysical profiles related to the ICA, namely PI, RI, CIMT, and AUC-ICA Doppler; the best subset regression model was constructed with a calculation of Mallow's coefficient described in Table 3. The lowest values are shown on the AUC-ICA Doppler, which means it has the highest predictive value for HOMA-IR. While RI has the highest Mallow's coefficient value, which means it has the lowest predictive value. Both CIMT and PI lie in between the two.

Table 1.

Table 2

Figure 3 (A,B, and C)

Table 3

DISCUSSION

Our results showed that metformin therapy for six months caused a progressive improvement in BMI, menstrual cycle days, metabolic markers, hormonal parameters, and Doppler parameters (PI, RI, and CIMT). AUC-ICA exhibits a meaningful correlation to all PCOS parameters. Furthermore, it showed a progressive reduction throughout the treatment period. AUC-ICA correlated inversely with treatment time ($r = -0.98$, $P<0.001$) and positively with HOMA-IR($r = 0.98$, $P<0.0001$).Via the best subset regression model, the AUC-ICA had the highest predictive value for HOMA-IR.

Women with PCOS present with multiple anthropometric, metabolic, and hormonal abnormalities successfully reversed by metformin therapy; our results were in accordance with published studies [21].

The reduced BMI in our result was in line with a recently published meta-analysis study. Their result discussed that metformin as a monotherapy or in combination with other drugs can improve all anthropometric parameters (weight, waist-to-hip ratio, and BMI)

among PCOS women. This was made irrespective of the dose and the duration of metformin use[22].

Abdalla meta-analysis declared a meaningful reduction of serum testosterone with metformin, $P < 0.0001$ with moderate grade evidence, our result was in good agreement with their results [23].

The role of IR in hyperandrogenemia is not well understood. Some authors suggested that hyperinsulinemia plays a dual role in triggering hyperandrogenemia, first *via* direct stimulation of ovarian androgens thanks to the insulin receptors on the theca cells, second *via* indirect stimulation of LH secretion and suppression of SHBG production by the liver with a net increase of free androgen levels[24].

Metformin's beneficial effects on PCOS include; antihyperglycemic and reduction of IR by increasing the peripheral uptake of glucose in addition to its indirect effect on insulin levels. Our data showed a progressive reduction of FBS and HOMA-IR with the treatment, as other studies pointed out [20]. It has an anti-androgenic effect *via* reducing CYP17 cytochrome activity involved in androgens production, not to mention increasing SHBG, which consequently reduces free androgens[20].

The favorable effect of metformin in cardiovascular disease (CVD) protection has more than one way. First, it protects endothelial integrity, which is a key player in the triggering and progression of CVD, consequently reducing future CVD risk. Second, metformin may inhibit hepatic de novo lipogenesis paths to lower plasma cholesterol levels and improves atherogenic milieu, although the exact mechanism is still unknown. Third, metformin has anti-inflammatory and anti-oxidative effects; both are accredited as an etiological factor in PCOS pathogenesis. Indirect action of metformin; *via* reducing IR and androgen, both were proposed to act independently and synergistically in the progression of atherogenic dyslipidemia and CVD risk among PCOS women[22-25].

Regarding the menstrual cycle, Yilmaz *et al* studied menstrual irregularities and hirsutism in women treated with two insulin-sensitizing medications, Rosiglitazone and metformin. Their data showed an improvement in cycle regularity and hirsutism score; however, they advised Rosiglitazone over metformin for greater patient acceptance and hirsutism improvement. In line with their result, our data showed significant improvement in MC days and regularity [26].

Androgens excess tends to associate with hyperinsulinemia and IR. This alliance seems to worsen menstrual cycle abnormality. Several studies showed that many women with metformin therapy have ovulated and had a pregnancy. In contrast, patients with higher levels of serum testosterone were more likely to be infertile [27,28].

There was a debate on which contributes more to improving MC by metformin therapy, reduced IR, reduced androgen, or reduced BMI caused by metformin. Ezeh *et al* results highlighted that menstrual cycle abnormality correlated positively with IR severity and not with hyperandrogenemia with adjustment of IR confounders, including BMI. In fact, amenorrheic PCOS women had the worst IR. Our results showed an improved IR and menstrual cycle pattern with metformin use, which suggests a clinical implication for daily practice; tracking down MC changes is easy and is free of charge, and it can reflect an improvement in the IR that underlies PCOS syndrome [29]. Prior studies demonstrated that MC abnormalities among adolescents would not impact future reproductive performance [30]. However, that was not the case for older women (> 30 years) who presented with oligomenorrheic and hirsute; they had lower reproductive performance than their age-matched controls [31].

Insulin resistance lies at the heart of PCOS pathogenesis and severity and is a prognostic marker for response to treatment [32]. IR is universally assessed by HOMA-IR, calculated from the fasting serum insulin levels and blood sugar. Nevertheless, the assessment of HOMA-IR is costy and time-consuming, and this has pushed many researchers to find alternatives to assess insulin resistance [33,34].

Since 2010 many papers have reported that women with PCOS have universally increased intima-media thickness IMT in all medium-sized arteries like the carotid and ovarian artery [35]. Since then, many researchers have declared an excellent correlation between CIMT and HOMA-IR, and the current study results are in good agreement with the aforementioned studies[36].

Blood flow parameters were used to monitor HOMA-IR among PCOS cases during metformin use. In this study, both PI and RI had a progressive reduction, consistent with results obtained by Kaya *et al* [37]. Their study highlighted the beneficial role of adding metformin to combined contraceptive pills among PCOS women compared to those treated with combined contraceptive pills alone. CIMT and flow-mediated dilatation (FMD) was improved with the metformin group. The author attributes this to the effect of metformin on endothelial integrity, which is responsible for nitric oxide release, reducing oxidative stress, and correction of altered cellular signaling pathways [27,37,38].

The foundation of this study is a simple physical fact. Bernoulli's rule states that fluid velocity has an inverse correlation to the diameter of a vessel [8]. The increased ICA-IMT will cause the passing of blood to be faster. Since the area under the curve physically means the amount of blood passed per one sectional area in the vessel wall, consequently, AUC might represent a sensitive marker to HOMA-IR [11].

Scientists have discussed that measuring insulin sensitivity through surrogate markers of insulin sensitivity (HOMA-IR and QUICKI) is no longer enough and raised the necessity for more acute ways [40]. Although IMT and FMD were investigated in PCOS, we believe that estimating the change of blood speed mirrored by AUC is more accurate, as described in earlier work [37-40] .

Indeed, the strong correlations of AUC-ICA with all biochemical, hormonal, and Doppler parameters (PI, RI, and CIMT) support our hypothesis; furthermore, the progressive reduction of AUC-ICA represents the initial positive predictive ability of AUC-ICA as a possible novel marker for predicting IR. The best subset regression added more strength to our result, which confirmed; that AUC-ICA had the highest predictive value; it preceded PI, RI, and CIMT. The parameters mentioned above are already validated in IR, and thus AUC-ICA use needs no external validation.

Study Limitations: The treatment period is relatively short, so we cannot be sure of the future implications of metformin treatment in the long run. The study type is another limitation, as in any cross-sectional study [41], the exact cause-and-effect link cannot be determined because the IR and AUC-ICA were simultaneously measured. Intra- and inter-observer variability for AUC-ICA measurements is another limitation. Finally, the COVID-19 pandemic has seriously affected the duration of the study due to the repeated lockdown conducted in Iraq at that time[42].

Study Strengths AUC is a novel marker proposed by the current study, calculated by serial readings of Doppler wave height using freely downloadable software from the web, namely GRAPH software. It was easily calculated, free of extra charge, as it can be integrated into pelvic scan sessions. Its strong association with HOMA-IR and the duration of the treatment added to its cost make it superior to HOMA-IR in terms of cost-benefit analysis. For that, AUC-ICA is recommended as a reliable predictive marker for IR, follow-up, and prognostic value, especially during metformin therapy. Further studies are warranted for AUC-ICA application in clinical practice.

CONCLUSION

Measurement of the area under the curve of ICA is a promising marker for assessing insulin resistance in polycystic ovarian syndrome cases during the metformin therapy period. AUC-ICA showed strong significant correlations to PCOS parameters and had a superior cost-benefit analysis over HOMA-IR. Further studies are recommended to explore future applications in practice.

ARTICLE HIGHLIGHTS

Research background

Insulin resistance IR is implicated in many aspects of polycystic ovarian syndrome (PCOS) pathogenesis. Metformin effectively decreased IR. Improved IR was evaluated via Homeostatic Model Assessment for IR (HOMA-IR) and Doppler parameters;

mainly carotid artery intima-media thickness(ICA-IMT). The area under the curve of the internal carotid artery (AUC-ICA) Doppler wave was examined as a helpful marker for determining IR among PCOS cases presented with menstrual irregularity; treated by metformin over six months.

Research motivation

Much research has shown that surrogate measures of insulin sensitivity are no longer sufficient for evaluating insulin sensitivity, which has increased the need for new direct methods. Demonstrating changes in blood flow mirrored by AUC appeared to be more dependable; as indicated in earlier work, ICA-IMT was already examined in PCOS.

Research objectives

The initial goal is to ascertain if insulin resistance is related to the AUC of internal carotid artery (AUC-ICA) Doppler in PCOS-affected women with menstrual irregularities. The second goal is to analyze the reliability of AUC-ICA as a helpful marker for monitoring inulin resistance in women who have received metformin treatment.

Research methods

The study enrolled 54 PCOS women in a cross-sectional study. *Anthropometric* data included patient age, body mass index (BMI), menstrual cycle days, *biochemical parameters:* serum cholesterol, low and high-density lipoprotein, sex hormone-binding globulin, fasting blood glucose, and HOMA-IR, *hormonal parameters:* testosterone, luteinizing hormone over follicle-stimulating hormone ratio, and *ultrasonic parameters*: (CIMT, PI, RI, and AUC-ICA). Measurements of the systolic and diastolic wave height were repeated in order to evaluate the AUC-ICA following metformin tab—500 mg; three times/day for six months.

Metformin caused a progressive reduction in BMI, menstrual cycle days, biochemical hormonal, and Doppler parameters (CIMT, PI, RI, and AUC-ICA). AUC-ICA correlated strongly to all PCOS parameters. AUC-ICA correlated inversely with treatment time (r= -0.98, $P<0.001$)and positively with HOMA-IR(r = 0.98, $P<0.0001$).Via the best subset regression model, the AUC-ICA had the highest predictive value for HOMA-IR.

Research results

BMI, menstrual cycle days, biochemical hormonal, and Doppler markers(CIMT, PI, RI, and AUC-ICA were all gradually reduced by metformin treatment). All PCOS indicators and AUC-ICA had significant correlations. AUC-ICA had a negative correlation (r=-0.98, P0.001) with treatment time and a positive correlation (r = 0.98, P0.0001) with HOMA-IR. The AUC-ICA demonstrated the best subset regression model's maximum predictive value for HOMA-IR.

Research conclusions

AUC-ICA was a reliable marker for the assessment of IR, especially during metformin medication. AUC-ICA preceded PI, RI, and CIMT and showed a high, meaningful correlation to other PCOS markers. For further use in practice, more research is suggested.

Research perspectives

The area under the curve of the internal carotid artery had a significant correlation with HOMA-IR and the length of metformin therapy, not to mention it has a superior cost-benefit analysis over HOMA-IR. AUC-ICA is a reliable indicator of IR, follow-up, and prognostic value, particularly while using metformin

81983_Auto_Edited.docx

ORIGINALITY REPORT

3%

SIMILARITY INDEX

PRIMARY SOURCES

1	Hind Hadi Majeed, Maher Abbood Mukheef, Hiba Sattar Jabbar. "Comparing the ICSI outcome between different causes of subfertility and estimate the role of IL-1β in predicting ICSI outcome.", The Journal of Medical Investigation, 2022 Crossref	39 words — 1%
2	Alaa Ibrahim Ali, Wassan Nori. "Correlation of Serum Visfatin Level in Non-obese Women with Polycystic Ovary Syndrome and Matched Control", Reproductive Sciences, 2022 Crossref	29 words — 1%
3	worldwidescience.org Internet	24 words — < 1%
4	Alperen Degirmenci, Emine Kara, Beyza Unalan Degirmenci, Mutlu Ozcan. "Evaluation the Effect of Different Antioxidants Applied After Bleaching on Teeth Color Stability", Brazilian Dental Science, 2020 Crossref	19 words — < 1%
5	particleandfibretoxicology.biomedcentral.com Internet	16 words — < 1%
6	M. Kupreeva, A. Diane, R. Lehner, R. Watts, M. Ghosh, S. Proctor, D. Vine. "Effect of metformin and flutamide on insulin, lipogenic and androgen-estrogen	15 words — < 1%

signaling, and cardiometabolic risk in a PCOS-prone metabolic syndrome rodent model", American Journal of Physiology-Endocrinology and Metabolism, 2019
Crossref

7 Perez-Cruzado, David, Gonzalez-Sanchez, Manuel, Cuesta-Vargas, Antonio. "Parameterization and reliability of single-leg balance test assessed with inertial sensors in stroke survivors: A cross-sectional study", 'Springer Science and Business Media LLC', 2014 — 12 words — < 1%
Internet

8 www.hindawi.com — 12 words — < 1%
Internet

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	< 12 WORDS
EXCLUDE BIBLIOGRAPHY	OFF	EXCLUDE MATCHES	< 12 WORDS