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CORRELATION BETWEEN GLYCATED HEMOGLOBIN LEVELS WITH POLYCYSTIC OVARY SYNDROME PHENOTYPES AND METABOLIC SYNDROME

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Abstract

Polycystic Ovary Syndrome (PCOS) is one of the endocrine disorders that causes oligo-anovulation, clinical and biochemical signs hyperandrogenism and ovarian-specific morphological signs on ultrasound examination are common in women of reproductive age. Conditions of insulin resistance and hyperandrogenism accompanied by hypertension and obesity can lead to dyslipidemia that can meet the diagnostic criteria for the metabolic syndrome. The American Diabetes Association approved the examination of glycated hemoglobin (HbA1c) levels as a routine screening for impaired glucose tolerance and hyperglycemic conditions. Examination of HbA1c levels using the method Point of Care Test. Several studies have shown a direct correlation between elevated HbA1c levels and complications of PCOS, providing evidence that HbA1c plays a potential role in PCOS. This study aims to determine the correlation between HbA1c levels with PCOS phenotype and metabolic syndrome. The study used an analytical study with a cross sectional analytic study design, the number of samples was 52 respondents. The sample was using selected consecutive sampling and then analyzed for HbA1c levels using POCT, PCOS phenotype, and metabolic syndrome for univariate and bivariate. The study with 52 respondents with PCOS patients, the results showed that the number of respondents with increased HbA1c levels was 17 (32.7%) respondents, most of the respondents with phenotype A were 30 (57.7%) respondents. The number of PCOS respondents with metabolic syndrome was 21 (40.4%) respondents. The results of statistical tests showed that correlation between the PCOS phenotype and HbA1c levels. The proportion of the incidence of metabolic syndrome was higher in respondents with phenotype A than phenotypes B, C, and D. The proportion of metabolic syndrome was higher in the category of elevated HbA1c levels compared to normal HbA1c levels, based on statistical tests there was a correlation between HbA1c levels and metabolic syndrome. Conclusion: There was an increase in HbA1c levels in PCOS patients in this study, which was 32.7% and most of the respondents were with phenotype A. Less than half of the respondents had metabolic syndrome. Statistically, there is a correlation between HbA1c levels and PCOS phenotype in PCOS patients and a correlation between HbA1c levels and metabolic syndrome in PCOS patients..

Keywords: PCOS phenotype, glycated hemoglobin, metabolic syndrome

Introduction

Polycystic Ovary Syndrome (PCOS) according to the Management Consensus Polycystic Ovary Syndrome is one of the endocrine disorders that causes oligo-anovulation, clinical and biochemical signs of hyperandrogenism and morphological signs specific to the ovaries on ultrasound examination.(Hestiantoro et al., 2016) (Rezaee et al., 2016) According to The International Evidence Based Guideline For The Assessment and Management of Polycystic Ovary Syndrome, PCOS is the most common chronic anovulatory disorder in women of reproductive age. The incidence of PCOS varies widely depending on the population and the diagnostic criteria (Hestiantoro et al., 2016) Most PCOS studies have looked at the age group between 18 and 45 years.(Wolf et al., 2018)

Insulin resistance causes compensatory hyperinsulinemia, which predisposes to a progressive decrease in pancreatic β-cell reserves, leading to hyperglycemia and glucose intolerance in type 2 diabetes mellitus (Hugh S. Taylor LP, 2020) Conditions of insulin resistance and hyperandrogenism are the most common hormonal disorders found in PCOS patients and contribute to the risks and complications such as reproductive disorders (irregular menstruation, oligo-ovulation or anovulation, infertility), metabolic disorders (dyslipidemia, type 2 diabetes mellitus, cardiovascular disease, metabolic syndromes) and psychological problems (depression, anxiety, low quality of life).(Hugh S. Taylor LP, 2020) (Tsikouras et al., 2015)

This condition of insulin resistance and hyperandrogenism accompanied by hypertension and obesity can lead to dyslipidemia that can meet the diagnostic criteria for the metabolic syndrome (Hugh S. Taylor LP, 2020) The American Diabetes Association (ADA) since 2010 has approved the use of the glycated hemoglobin (HbA1c) test as a routine screening for impaired glucose tolerance and hyperglycemic conditions (Numbi et al., 2019) Examination of HbA1c levels using the Point Of Care Test (POCT) method has several advantages such as the results can be obtained immediately at the same time when the patient visits the doctor so that it is more efficient in terms of time, effort and cost (Tuti, 2018) Several studies have demonstrated a direct correlation between elevated HbA1c levels and complications of PCOS, providing evidence that HbA1c levels plays a potential role in PCOS (Numbi et al., 2019)

Method

This research is an analytic study using a cross sectional analytic study design taking place from July 2020 to August 2021. The sample of this study used consecutive sampling, that every patient with PCOS at the Polyclinic of Dr. M. Djamil Padang Central Public Hospital and a private hospital in Padang City, General hospital of BMC Padang, private practice specialist obstetrics and gynecology were given information about the research (Information for Consent) which included the purpose of the study, the method of research, benefits, rights and obligations and risks as a sample. After the patient understands the information submitted, the patient who is willing to participate

in the study will sign an informed consent as a sign of agreement to be used as a research sample and there are witnesses from the sample family. The sample of this study with inclusion criteria, such as subjects with PCOS aged 18-45 years and exclusion criteria, such as patients taking metformin in the last 3 months and anemia with a total sample of 52 people.

The examination procedure in this study was to conduct an initial screening of all patients with PCOS that met the inclusion criteria and informed consent regarding the study, then an interview was conducted through anamnesis to assess the characteristics of PCOS (oligomenorrhea or amenorrhea); clinical examination like measurement of waist circumference, blood pressure, Ferriman- Gallwey score to assess hirsutism; ultrasound supporting examination to see the picture of the ovaries performed by a specialist in Reproductive Endocrinology and infertility or a specialist in obstetrics and gynecology who has fulfilled the competence in ultrasound examination, and then taking capillary blood samples to measure hemoglobin levels using a dr. Family brand hemoglobin measuring device, to measure HbA1c levels using the Biohermes brand device with POCT method and to measure fasting blood glucose using the Accu Chek brand. Analyzes of HbA1c levels from blood samples obtained with the Biohermes brand POCT, PCOS phenotype, and metabolic syndrome (obesity, hypertension, hyperglycemia) were then entered into the master table.

Categorical analysis data in this study was univariate in the form of categorical variables presented in the form of a frequency distribution (frequency and percentage), but the numerical variables were presented in the form of central tendency (mean, standard deviation, minimum and maximum) and bivariate analysis to assess the correlation between levels. HbA1c and PCOS phenotype (phenotype A, B, C, D) with PCOS using the chi- square statistical test or Fisher's test. Bivariate analysis to assess the correlation between HbA1c levels and metabolic syndrome in PCOS patients using the chi-square statistical test or Fisher's test. If the results of the analysis obtained a p value <0.05, then there is a significant relationship. Analysis data was carried out with a computer program.

Results

Research has been carried out on 52 respondents of PCOS patients at the Polyclinic of Dr. M. Djamil Padang Central Public Hospital and a private hospital in Padang City, General hospital of BMC Padang, a private practice for obstetrics and gynecology specialists. This study assessed correlation of HbA1c levels with PCOS phenotype and metabolic syndrome**.**

Table 1
Frequency Distribution of HbA1c Levels in PCOS Patients

HbA1c levels	f	%
Increased Normal	17	32,7
Total	35	67,3
	52	100

Based on Table 1, it can be concluded that the number of respondents with increased HbA1c levels is 17 (32.7%) respondents.

The frequency distribution of the PCOS phenotype of PCOS patients can be seen in Table 2 below:

Table 2
Frequency Distribution of PCOS Phenotypes in PCOS Patients

Phenotype	f	%
A	30	57,7
B	10	19,2
C	7	13,5
D	5	9,6

Based on Table 2 it can be concluded that most of the respondents with phenotype A was 30 respondents (57.7%) and the least with phenotype D was 5 respondents (9.6%).

The frequency distribution of metabolic syndrome in PCOS patients can be seen in Table 3 below:

Table 3
Frequency Distribution of Metabolic Syndrome in PCOS Patients

Metabolic Syndrome	f	%
Yes	21	40,4
No Total	31	59,6
	52	100

Based on Table 3, it can be concluded that the number of respondents with metabolic syndrome is 21 respondents (40.4%).

The correlation between HbA1c levels and the PCOS phenotype in PCOS patients can be seen in Table 4 below:

Table 4
Correlation of HbA1c Levels with PCOS Phenotype in PCOS Patients

Phenotype	HbA1c levels Mean ± SD	P value
A	6,41 ± 0,86	0,004
B	5,57 ± 0,43	
C	5,73 ± 0,64	
D	5,62 ± 0,51	

Based on Table 4, it is known that the highest mean HbA1c level in phenotype A Was 6.41 ± 0.86 and the lowest was in phenotype B, which was 5.57 ± 0.43. Based on the results of statistical tests this difference is significant. This shows that there is correlation between phenotype and HbA1c levels (p value <0.05).

The correlation between PCOS phenotype and metabolic syndrome in PCOS patients can be seen in Table 5 below:

Table 5
Correlation of PCOS Phenotype with Metabolic Syndrome

Phenotype	Metabolic Syndrome				Total		P value
	Yes		No				
	f	%	f	%	f	%	
A	15	50	15	50	30	100	0,41
B	3	30	7	70	10	100	
C	2	28,6	5	71,4	7	100	
D	1	20	4	80	5	100	
Total	21	40,4	31	59,6	52	100	

Based on Table 5, it can be concluded that the proportion of the incidence of metabolic syndrome was higher in respondents with phenotype A than phenotypes B, C, and D. Based on the results of statistical tests, this difference was not significant. This shows that there is no correlation between the phenotype PCOS and metabolic syndrome (p value >0.05).

Table 6
Correlation of HbA1c Levels with Metabolic Syndrome in PCOS Patients

HbA1c levels	**Metabolic Syndrome**				**Total**		**P value**
	Yes		No				
	f	%	f	%	f	%	
Increased	15	88,2	2	11,8	17	100	0,0001
Normal	6	17,1	29	82,9	35	100	
Total	21	40,4	31	59,6	52	100	

Based on Table 6, it is known that the proportion of metabolic syndrome was higher in the category of elevated HbA1c levels compared to normal HbA1c levels, based on statistical tests this difference was significant. This shows that there is correlation between HbA1c levels with metabolic syndrome with a p value =0.0001 (p value <0.05).

Discussion

From the research conducted, it was found that the average age of the respondents was 28.71 ± 3.53 years. Research conducted by Sumapraja et al in 2011, the highest frequency of PCOS incidence was in the age range of 26-30 years, which was 45.7% (Hestiantoro et al., 2016).

In this study, the frequency of PCOS criteria in the form of oligomenorrhea was 86.5%, hyperandrogenism with an FG score was 90.4% and polycystic ovarian morphology (PCO) on ultrasound examination was 80.8%. The results of this study,

based on the Consensus on PCOS complain of oligomenorrhea or amenorrhea.8 Ovarian hyperandrogenism conditions often occur in PCOS which explains all the main clinical features of PCOS including: hyperandrogenism, oligo-anovulation, and polycystic ovaries and conditions of LH and insulin hypersecretion will cause premature luteinization and cessation of the maturation process in ovarian follicles. The cessation of the ovarian follicle maturation process in its development will result in an increase in the number of follicles and produce polycystic ovarian morphology on ultrasound examination.(Hestiantoro et al., 2016) (Rosenfield & Ehrmann, 2016)

In this study, 52 samples of PCOS patients were obtained with 57.7% dominant phenotype A, phenotype B was 19.2%, phenotype C was 13.5% and phenotype D was 9.6%. This result is the same as the research conducted by Gluszak et al in 2011 which found that the prevalence of the most dominant phenotype A was 60.2%.10 Another study by Lizneva et al and Guatella showed that the A and B phenotypes were the most frequently found (Lizneva et al., 2016) (Guastella et al., 2010).

In this study, the PCOS sample was also seen for complications of metabolic syndrome using the NCEP ATP III criteria (3 out of 5 criteria, such as waist circumference > 35 inches, hypertension with systolic blood pressure 130 mmHg or diastolic blood pressure ≥ 85 mmHg or previous hypertension treatment, hyperglycemia with fasting blood glucose levels > 100 mg/dL or receiving therapy for high blood glucose) then obtained the results that 40,4% of the sample had metabolic syndrome and 59,6% of the sample did not have metabolic syndrome. Women with PCOS generally have insulin resistance and other risk factors for developing type 2 diabetes and cardiovascular disease. Insulin resistance causes hyperinsulinemia, which results in glucose intolerance in type 2 diabetes mellitus. Insulin resistance is an important factor in the pathophysiology of the metabolic syndrome. Metabolic syndrome is associated with disorders of glucose metabolism (insulin resistance, hyperinsulinemia, glucose intolerance, diabetes mellitus), central obesity, and risk factors for cardiovascular disease (hypertension, elevated triglycerides, decreased HDL cholesterol) (Hugh S. Taylor LP, 2020).

In this study, an increase in HbA1c levels (≥6.5%) in samples of PCOS patients was 32.7% and normal HbA1c levels were 67.3%. In this study, categorical analysis data test with Chi- square was perfomed to see the correlation between HbA1c levels and the PCOS phenotype, then the results showed that there was correlation between HbA1c levels and the PCOS phenotype with p value <0.05. The results of this study are supported by the ADA recommendation, HbA1c is the best diagnostic of dysglycemia in PCOS women, because its levels are influenced by excessive androgen production in PCOS (AE-PCOS). The results of this study also showed that patients with PCOS had a significant increase in HbA1C levels (5.799 ± 1.022; 4.96 ± 0.625, p = 0.001) when compared to the control group (Renuka et al., 2018).

This study also looked at the correlation between PCOS phenotype and metabolic syndrome, it was found that the highest prevalence of metabolic syndrome was found in phenotype A (13 out of 21 samples). The results of this study based on the

research conducted by Sobti S et al in 20017 where the highest prevalence of metabolic syndrome was found in phenotype A (23 of 41 samples).14 This study continued with an analytical test to see the correlation between each PCOS phenotype with the metabolic syndrome, the results showed that there was no correlation between the PCOS phenotype and metabolic syndrome conditions with p value >0.05. This is because the number of samples for each group of PCOS phenotypes is insufficient and other supporting examinations are needed such as total cholesterol, HDL, LDL to see the condition of dyslipidemia in the study sample. This study is not accordance with the study conducted by Sobti S et al in 20017 that there was a significant correlation between PCOS phenotype levels and metabolic syndrome parameters (waist circumference ≥ 80 cm, fasting blood sugar 100 mg/dl, HDL 50 mg/dl) with p value < 0.001. 14 Another study conducted by Gluszak et al showed that there was a correlation between PCOS phenotype and metabolic syndrome parameters (total cholesterol, LDL, HDL), where phenotype A had total cholesterol, LDL, HDL values compared to other PCOS phenotypes that show an intensification of dysregulation and an increased risk of cardiovascular and metabolic disease in women with the phenotype A PCOS (Gluszak et al., 2012)

In this study, it was seen whether there was a correlation between increased HbA1c levels with metabolic syndrome conditions in PCOS patients by using the Chi-square categorical data analysis test that the result was 15 (88.2%) respondents with elevated HbA1c levels had metabolic syndrome, while normal HbA1c levels was 6 (17.1%) had metabolic syndrome. The results of statistical tests showed that there was correlation between HbA1c levels with metabolic syndrome in PCOS patients with p value <0.05. The results of this study are supported by several studies, namely a study conducted by Holly et al., in 2013 supporting the examination of HbA1c as a marker of dysglycemia in PCOS patients with a sample of twenty-four participants with abnormal glucose tests where more patients were identified as having dysglycemia by HbA1c examination with 60% sensitivity and 69% specificity for diagnosing dysglycemia.15 Based on the ADA recommendations, HbA1c is the best diagnostic of dysglycemia in PCOS women, because its levels are influenced by excess androgen production in PCOS (AE-PCOS). The results of this study also showed that patients with PCOS had a significant increase in HbA1c levels (5.799 ± 1.022; 4.96 ± 0.625, p = 0.001) when compared to the control group.13 According to research by Marianne A and Dorte G in 2018, international guidelines support that HbA1c values >48 mmol/mol (≥6.5%) can be used as a reference for diagnosing type 2 diabetes in asymptomatic patients, while HbA1c levels are between 6 and 6. 4% (42-47 mmol/mol) should be followed by OGTT and an HbA1c level below 6% does not require further testing. HbA1c is required to assess the correlation between HbA1c and microvascular disease (Andersen & Glintborg, 2018).

Conclusion

In this study, it was concluded that there was an increase in HbA1c levels in PCOS patients in this study, namely 32.7% and normal levels of HbA1c 67.3%. Most of the respondents with phenotype A and the least with phenotype D. Respondents who have metabolic syndrome are less than half of the respondents. In statistical tests, in this study there was a correlation between HbA1c levels with PCOS phenotype in PCOS patients and there was a correlation between HbA1c levels with metabolic syndrome in PCOS patients. In this study, there was no correlation between the PCOS phenotype and the metabolic syndrome. Suggestions in this study for menstrual cycle data submitted by respondents might be better if obtained from the menstrual calendar which should be owned by each individual to reduce bias. There is a need for further research, it is better to carry out other supporting examinations such as total cholesterol, LDL, HDL levels to look for other criteria for the metabolic syndrome that were not examined in this study.

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