Effect of thyroid dysfunction on hemoglobin A1c in polycystic ovary patients during ovulation induction trials.

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Summary:

Background: Polycystic ovary syndrome (PCOS) is one of the most common female endocrine disorders leading to infertility. Majority of women with PCOS have insulin resistance and elevated hemoglobin A1c.The presence of thyroid dysfunction may affect the levels of HbA1c and the results of ovulation induction programs.

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Objectives: To evaluate the level of serum hemoglobin A1c according to the type of thyroid dysfunction in polycystic ovary patients during ovarian stimulation trials.

Patients and Methods: Eighty three polycystic ovary patients were enrolled in this study, attending the infertility clinic in Al-Yarmouk Teaching Hospital, in the period between November 2012 and May 2013. After thorough history and examination blood samples were withdrawn for the estimation of LH, FSH, testosterone, prolactin, TSH, T3, T4 and A1C in day 2 or 3 of the menstrual cycle, Progesterone was determined in day 21 of the cycle. Ultrasound was done also at cycle day 3 for antral follicles measurements. After diagnosing PCOS the patients were divided into 3 groups, euthyroid group (control), hypothyroid and hyperthyroid groups. Ovulation induction treatment was given and ultrasound was done at the day of hCG injection.

Results: There was no significant difference between control and patients groups regarding age (26.31 ± 5.04 Vs 27.17 ± 5.76) and BMI (31.7 ± 5.69Vs 29.25 ± 6.28).HbA1c level was significantly different between the control and patients group with a significant positive correlation between HbA1c and TSH. In clomiphene citrate treated groups, Hb A1c level, the number of antral follicles and the size of follicles at day of hCG injection were not significantly different between the patients and control groups.

Conclusions: HbA1c level is significantly affected by thyroid dysfunction in PCOS patients as it is higher in the Hypothyroid group and lower in the Hyperthyroid group. Using Clomiphene citrate in PCOS does not significantly increase the mean size of follicles after ovarian stimulation in patients with thyroid dysfunction from that in Euthyroid ones.

Key word: Polycystic ovary syndrome, thyroid dysfunction, hemoglobin A1c, ovulation induction.

Introduction:

Polycystic Ovary Syndrome (PCOS) is a common hormonal disorder that affects approximately 5 million reproductive-aged women in the United States. Women with PCOS have difficulty becoming pregnant (i.e., are infertile) due to hormonal imbalances that cause or result from altered development of ovarian follicles (1). Women with PCOS have altered metabolism of estrogen and androgenic hormones such as testosterone, androstenedione and dehydroepiandrosterone sulfate (DHEAS) and the vast majority of them have severe insulin resistance (2). Doctors very often misdiagnose Polycystic Ovarian Syndrome because the symptoms vary so widely and one might not display all the symptoms. In fact, 8 out of every 10 women with PCOS could have insulin resistance, resulting in higher-than-normal insulin levels that can act on the ovaries by increasing male hormones. The end result is that a PCOS sufferer can stop ovulating, gain weight, develop skin conditions like acne and skin tags, and grow abnormal facial and body hair and sometimes thyroid complications (3). In addition, obesity amplifies the conversion of androgen to estrogen, decreases sex hormone binding globulin (SHBG) and increases insulin levels (4). Also insulin drives ovarian androgen production by binding to insulin-like growth factor (IGF) receptors and thereby augmenting theca cell androgen production (5). Thyroid hormones have profound effects on reproduction and pregnancy. Thyroid dysfunction is implicated in a broad spectrum of reproductive disorders, ranging from abnormal sexual development to menstrual irregularities and infertility (6). Glycated hemoglobin (HbA1c) is a test that measures the amount of glycated hemoglobin in the blood. It's important to remember that HbA1c only reflects glucose concentrations over 4 to 8 weeks if there is a

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normal hemoglobin concentration and normal red blood cell survival (7).

The HbA1c blood test or glycosylated hemoglobin is used as a general indicator of average blood sugar levels present in plasma over about 3 months. It does not indicate whether a person is insulin resistant or not, whether they have high blood sugar or low blood sugar at times, only what the long term average blood sugar level is (8).

Patients and methods:

Eighty three polycystic ovary patients were enrolled in this study, attending the infertility clinic in Al-Yarmouk Teaching Hospital, in the period between November 2012 and May 2013. All are classified according to their thyroid hormone and TSH levels into Euthyroid patient as control group, Hypothyroid and Hyperthyroid patients as patients group. The age range of included women was between 16 and 43 years (mean 26.73 ± 5.394).Thorough history was obtained from the patients including age, duration and type of infertility, the present fertility problem, regularity of menstruation, history of previous diseases and occupation of both partners. Past history was taken regarding pervious medications (e.g contraceptive pills, thyroid hormone treatment, antithyroid drugs and metformin), in addition to the past surgical history (e,g wedge resection, laparoscopy ,thyroid surgery). Physical examination was done including, general examination, signs of hirsutisim and thyroid examination, weight and height were measured too using appropriate scales. Evaluation of tubal patency or any uterine malformation by sending the patients for hystrosalpingiography test.

Patients included in this study are polycytic ovary diagnosed patients, excluding patients with anemia, diabetes (by doing glucose tolerance test), and renal disease. In addition to that patients taking contraceptive pills or treatment for thyroid problem at least 3 months before starting the study were excluded too. Body mass index was calculated after measuring hight (meters), weight (kilograms), using the equation: BMI= Weight / (Height) ^{2}, (9). Patients were subjected to basal investigations including hemoglobin percentage, packed cell volume (PCV), thyroid function test (T3, T4, and TSH), testosterone and serum prolactin. For the measurement of LH, FSH, blood samples were taken during the early follicular phase (cycle day 3) of menstrual cycle, and for progesterone measurements (detection of ovulation) it was done on day 21 of the cycle. Vaginal ultrasound (US) was done to evaluate size and number of antral follicles in cycle day 2 or 3 of the cycle. After diagnosing PCOS patients, blood samples were collected for the measurement of HbA1c (Stanbio kit, using spectrophotometer, the cutoff point was 6.2%).Then the patients were divided into 3 groups according to the thyroid function test into euthyroid(control) group ,hypothyroid and hyperthyroid women as a patients group and were sent to the endocrinologist in the outpatient clinic to evaluate their urgent need for the treatment. Clomiphene citrate (Clomid 50 mg , Aventis, France) was given to all women (control and patients groups) according to their age and history. Serial ultrasounds were done for the evaluation of the follicular size, which if reached 18mm, human chorionic gonadotropin was given to the patient, and ultrasound was done at the same day.

Statistical methods: All statistical analyses were performed using (SPSS version 17). Statistical significance between mean values was attributed to two-tailed $P < 0.05$. The results are expressed as Mean ± SD (27). Significant relationships between HbA1c and other parameters were evaluated by the Spearman correlation coefficient test.

Results:

Measuring the age and the BMI in patients and control groups reveals that there was no significant difference in age and BMI between Euthyroid (the control) and the patients group as shown in table (1).

Table (1): Comparison of age and BMI between Euthyroid (control) and patients groups.

	Euthyroid (control) (n= 42)	Patients group (hypothyriod and hyperthyroid) (n= 41)	P
Age (years)	26.31 ± 5.04	27.17 ± 5.76	0.47 (N.S)
BMI (Kg/m^2)	31.7 ± 5.69	29.25 ± 6.28	0.07 (N.S)

***P<0.05**

HbA1c differs significantly between the three groups being higher in the hypothyroid group and lower in the hyperthyroid group. Post hoc test shows significant difference of HbA1c level between the patients and Euthyroid groups as demonstrated in table (2).

Table (2): Comparison of HbA1c between the Euthyroid and patients group

	Euthyroi-d (Control) (n=42)	Patients group		P
		Hypothyro-id (n=25)	Hyperthyroid (n=16)	
Hb-A1c %	6.6 ± 0.88	7.27 ± 0.74	5.52 ± 0.93	0.0001 *

***P<0.05**

Regarding TSH level in all studied groups it is found that it is correlated positively and significantly with HbA1c levels, i.e when there is increase in TSH there is increase significant increase in HbA1c levels as shown in figure (1).

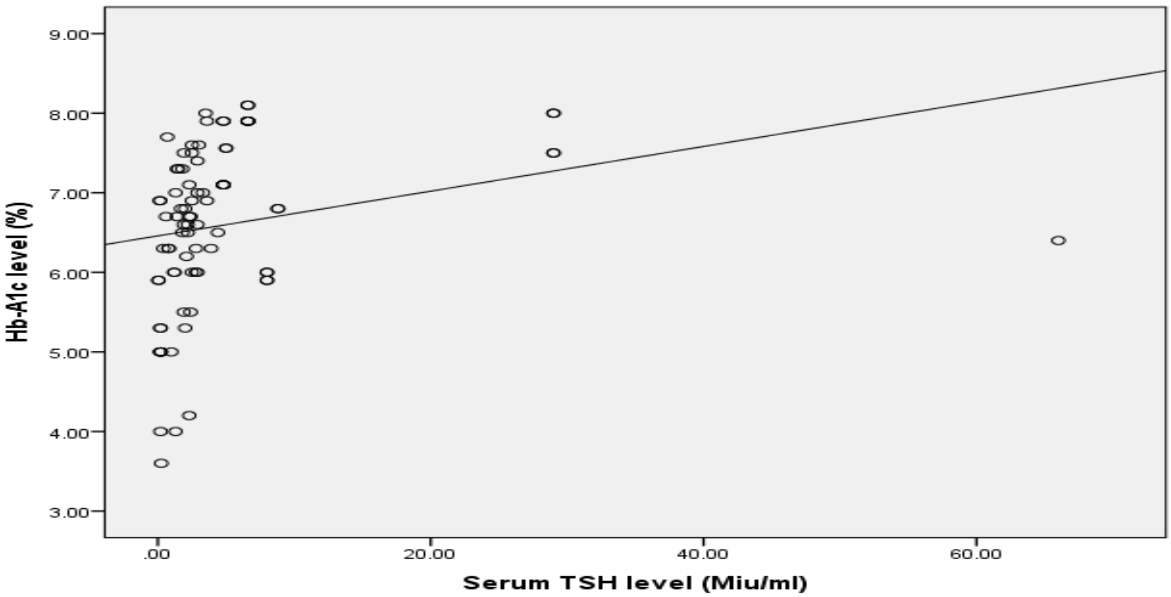

Figure (7): Correlation between HbA1c and TSH in all women.

The level of HbA1c was compared between Control and Patients group in Clomid treated women and there was no significant difference between them, also there was no significant difference in mean size of follicles after stimulation at day of hCG injection as demonstrated in table(3).

Table (3): Comparison of HbA1c, number of antral follicles and Mean size of follicles between control and patients group in Clomid treated women.

	Control (n= 28)	Patients(n= 39)	P
HbA1c %	6.38 ± 0.92	6.54 ± 1.2	0.53 (N.S)
Number of Antral follicles	7.60 ± 2.12	7.28 ± 2.58	0.57 (N.S)
Mean size of follicles at day of hCG injection (mm)	17.8 ± 3.7	17.09 ± 1.5	0.34 (N.S)

Discussion:

Polycystic ovary patients have been studied for age and BMI and it was obvious that there was no significant difference in age between Euthyroid (the control) and the patients group (Hypothyroid, Hyperthyroid) as shown in table (1). Laura and her coworkers found that age was independent predictor of thyroid stimulating hormone (TSH) and it would enable clinicians to better classify patients within their subpopulation-specific TSH reference range (10). Patricia on the other hand found that the prevalence of thyroid disease increases with age. In fact hypothyroidism is the most common thyroid disorder in the adult population and is more common in older women while Graves' disease affects primarily younger adults (11). Diez and his coworkers had obtained the same results and they found that there was some relation between age and thyroid disease (12). Body mass index (BMI) show also no significant difference between Euthyroid (the control) and the patients group (Hypothyroid, Hyperthyroid). This might be due to the narrow range of difference in the thyroid function which agrees with the work of Schuff et al in 2011 who demonstrated that minor differences in thyroid function might have a small effect on metabolic function (13), because T_3 regulates energy metabolism and thermogenesis and plays a critical role in glucose and lipid metabolism, food intake, and the oxidation of fatty acids (14). Polycystic Ovary Syndrome (PCOS) because in PCOS, the estrogen was dominant and extra estrogen caused an increase in the amount of circulating thyroid binding globulin (THG), Which "soaks up" freely circulating thyroid hormone, turned it from "free" thyroid hormone into "bound" thyroid hormone. This shift from "free" to "bound" hormone contributed to weight gain (15), because bound hormone increased the lipogenic effect of thyroid hormone and decrease the lipolytic effect so in Hypothyroidism, there was decreased fat synthesis and degradation, increased body fat and elevated lipids while in Hyperthyroidism there was increased fat synthesis and degradation, resulted in decreased lipids. Measuring HbA1c level in patients (Hypothyroid, Hyperthyroid) and control group (Euthyroid) demonstrated that it was significantly higher in the hypothyroid group and lower in the hyperthyroid group in comparison with control group as shown in table (2). This goes with the study of Takashima et al in 2007 who found also that patients with Hypothyroidism and subclclinical

Hypothyroidism have higher glycol-hemoglobin A1c levels compared with Euthyroid patients (16). Handisurya and his team also found that HbA1C levels were significantly higher in patients with overt hypothyroidism compared with control subjects (17). Other study documented that insulin sensitivity was lower in the Hypothyroid group than in the Euthyroid group, whereas acute insulin response to glucose was higher (18), this was explained by other study which stated that hypothyroidism often results in hypoproliferative erythropoiesis and decrease in reticulocyte count which leads to the increase in HbA1c level, as the changes in HbA1c level was negatively correlated with the changes in reticulocyte count because the number of reticulocytes is compared to the total number of red blood cells (RBCs) and is reported as a percentage of reticulocytes: Reticulocyte (%) = [Number of Reticulocytes / Number of total Red Blood Cells] X 100, (19) and any conditions that affect erythrocyte turnover or survival lead to falsely high or low HbA1c levels (20). On the other hand Mohan et al found that in hyperthyroid patients, HbA1c was significantly higher than in the control (Euthyroid) group (21), since hyperthyroidism is typically associated with worsening glycemic control and an increased insulin requirements and increased hepatic gluconeogenesis, rapid gastrointestinal glucose absorption, and probably increased insulin resistance (11). However other studies found that there was no significant difference in HbA1c between the types of thyroid dysfunction patients (12). Regarding TSH level in all studied groups it is found that it is correlated positively and significantly with HbA1c levels, i.e when there is an increase in TSH level, there is significant increase in HbA1c levels as shown in figure (1), which may be explained by the decrease in metabolic processes in hypothyroid patients and the change in reticulocyte count that affects the amount the Hb A1c level. This result agrees with the result found by Mee et al in 2010 who found that A1c level was significantly higher in patients with overt hypothyroidism (i.e high TSH level) compared with control subjects. HbA_{1C} levels were decreased by thyroid hormone replacement, which increases serum erythropoietin, reticulocyte count, and mean corpuscular hemoglobin (MCH), and as mentioned the change in Hb A1c level was significantly correlated with the change in reticulocyte count or MCH (22). Jennie et al in 2004 found that impaired blood sugar metabolism in PCOS patients leads to elevated testosterone levels that affect conversion of thyroid hormones T4 into T3 and production of thyroid binding globulin (TGB). Excess of T3 causes the cells develop resistance to the thyroid hormone. The women experience hypothyroid symptoms because T3 could not get into the cells (23). Regarding the clomid treated group, it was obvious that there was no significant difference between the patients and the control Euthyroid groups in terms of Hb A1c, antral follicles number and size of the follicles at day of hCG injection. Although the presence of thyroid problem may worsen the response of the ovary to Clomid in PCOS patients as Hypothyroidism is commonly associated with ovulatory dysfunction due to numerous interactions of thyroid hormones with the female reproductive system (24), but the results of this study shows no significant difference in the response from the Euthyroid patients which may be attributed to the early diagnosis of the patients. Cecconi et al in 1999 suggested that an adequate circulating level of thyroid hormone is one of the factors responsible for successful induction of ovulation by clomiphene citrate, since thyroid hormone synergizes with follicle-stimulating hormone (FSH) to exert stimulatory effects on granulosa cell differentiation and function, suggesting that it plays a physiological role in amplifying FSH-mediated differentiation of granulosa cells. The adequate differentiation of these cells, followed by normal follicle development, is indispensable for ovulation and subsequent corpus luteum formation (25). Other studies showed that insulin resistance in Hypothyroid and Euthyroid patients was comparable, insulin-stimulated rates of glucose transport were decreased due to impaired translocation of GLUT4 glucose transporters on the plasma membrane; so patients with the Hypothyroidisim and subclinical Hypothyroidism have higher plasma insulin than the Euthyroid patients (26), which affect negatively the maturation of the follicles in the ovaries.

Authors' contribution:

Hiba Salih participated in the collection of data and shared in processing of them with Hanan Luay who suggested the subject of the research and its aims. Abdulaali facilitated the collection of patients in the outpatient clinic.

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