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Effect of Thyroid Hormone Abnormalities on Hemoglobin A1c in Hemodialysis Patients Taking Erythropoietin

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ABSTRACT

Background: Hemoglobin A1c (HbA1c) is a widely used test for glycemic control. It is done for chronic kidney disease (CKD) patients. Renal disease is accompanied by thyroid abnormalities, which affect HbA1c, especially in those taking erythropoiesis-stimulating agents (ESAs). We aimed to find the effect of thyroid dysfunction on HbA1c in hemodialysis patients taking ESAs and those who do not.

Materials and Method: Fifty six patients were included in this study, which was done between September 2017 and June 2018, in Baghdad Teaching Hospital. Thyroid stimulating hormone, free T3, free T4 and HbA1c measurements were done. The patients were divided into 2 groups; those who took ESAs and those who did not, then they were subdivided into those with hypothyroidism and hyperthyroidism according to the Body mass index (BMI).

Results: Comparing HbA1c levels in hemodialysis patients taking ESAs and those who did not, showed no significant difference (5.79 ± 1.91 vs. 6.19 ± 1.64, P=0.09). The difference was also not significant in both hypothyroid and hyperthyroid patients in both high and low BMI patients. The only significant difference in HbA1c was between hyperthyroid and hypothyroid patients in those not taking ESAs, and having low BMI (4.97 ± 1.36 and 7.51 ± 0.87 respectively, P=0.02).

Conclusion: There is no significant influence of thyroid hormone changes on HbA1c levels in hemodialysis patients taking and not taking ESAs.

Keywords: *Hemoglobin A1c, Chronic kidney disease, Thyroid dysfunction, Hemodialysis, Erythropoiesis-stimulating agents.*

Introduction

Chronic kidney disease (CKD) is a universal problem causing great burden on the health system.[1] It is a prevalent state that influence more than fifty million people worldwide.[2] A lot of endocrinological deviations followed it, although pathogenesis is not settled yet.[3] Thyroid hormones (THs) are mandatory for kidney development and for preserving water and electrolyte homeostasis. The kidney is responsible for THs metabolism and excretion.[4] In CKD, level of thyroid hormones is usually aberrant.[3] Different changes occur in the thyroid gland, these involve decreased thyroid hormone levels in the circulation, changed metabolism of peripheral hormone, reduced attaching to carrier proteins, potential decrease in hormone content in tissues, and a rise in iodine storing in the thyroid gland. Iodine excretion in urine decreases in CKD, which increasing inorganic iodine in the presence of iodine in the thyroid gland, which then makes the gland larger.[5]

Although the occurrence rate of hyperthyroidism is nearly the same in end stage renal disease (ESRD) patients and normal individuals, hypothyroidism is noticed in 3.4% of ESRD patients and 0.6% of normal individuals. This increased occurrence of hypothyroidism in ESRD

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illustrates that searching for thyroid abnormal function, must be taken into account in assessing ESRD patients.[5]

Thyroid hormones encourage erythrocyte formation, and hypothyroidism generally leads to hypoproliferative erythropoiesis. Moreover, thyroid hormones stimulate albumin metabolism, and its destruction is decreased in hypothyroidism. The cases which influence erythrocyte production cause incorrect increase or decrease in HbA1c.[6, 7]

HbA1c is made up by the permanent attachment of glucose to hemoglobin across the lifetime of the red blood cells,[8] and it constitutes about 60% to 80% of the glycated hemoglobin. In a hyperglycemic state, beta-chain of the hemoglobin increases glycation, making the assessment of HbA1c beneficial.[9]

The American Diabetes Association (ADA) suggested the measurement of HbA1c for diagnosing diabetes and pre-diabetic state. It is the most approved method for evaluating chronic glycemia in diabetic patients.[10] Low HbA1c levels, which are not because of lack of proper nutrition or anemia, were related to better survival in hemodialysis patients.[8] An updated study found that HbA1c levels may show an underestimated glycemic control results in diabetic patients on hemodialysis.[11]

Although some studies reported that erythropoietin intake might influence HbA1c in hemodialysis patients, this condition is not proved in people with CKD not on hemodialysis schedule.[12]

We aimed to find the effect of thyroid dysfunction on HbA1c in hemodialysis patients taking erythropoiesis-stimulating agents (ESAs) and those who do not.

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Materials and Method

Fifty six participants were included in this prospective study during the period between September 2017 and June 2018. They were thirty four females aged 36.82 ± 14.46 years and twenty two males aged 47.39 ± 14.17 years. The data were collected from the dialysis unit of Baghdad Teaching Hospital.

The patients enrolled were those with ESRD on regular hemodialysis, some of them were taking ESAs for at least four months.

Exclusion criteria: Diabetic patients, patients having hemoglobinopathy, and patients taking treatment for thyroid dysfunction.

The research was in accordance with the ethical standards of Helsinki Declaration of 1975, as revised in 2000. Informed consents were taken from the participants.

Demographic data, height, weight, smoking condition, and medications history were recorded.

The body mass index (BMI) was measured, a patient with BMI of ≥ 25 was considered obese, and a patient with BMI of <25 was considered non obese.[13]

Blood (ten ml) was withdrawn, 5 ml was sent for HbA1c measurement and 5 ml was centrifuged and the serum was frozen then analyzed for free T3, free T4 and TSH.

HbA1 was analyzed within 24 hours of collection (refrigerated when not measured directly) by an automated high-performance liquid chromatography analyzer (ion-exchange chromatography) (HLC-723 G7; Tosoh Corporation, Tokyo, Japan or the Menarini HA-8160 A1C analyser). Free T3 (FT3) and free T4 (FT4) were determined by fluorimmunnoassay method and TSH by immunoradiometric assay (IRMA).

All patients were on hemodialysis for 4 hours/3 times a week. The participants were divided into two groups, those who were on ESAs treatment (number=27) and those who were not (number=29), then they were subdivided into high BMI patients (number=30), and low BMI patients (number=26) and into hypothyroid (number=31) and hyperthyroid (number=25) patients.

All participants taking ESAs had hemoglobin ≤10.5 g/dl and were considered iron, vitamin B12, and folate replete before starting the treatment. Patients were considered iron replete after a serum ferritin level of >200 µg/l or have taken intravenous iron at least 6 weeks before ESAs treatment. Darbepoetin α (Aranesp) was given at 750 nanograms/kg (or 60 U/kg as intravenous bolus injection after each dialysis session) every two weeks and continued during study duration. ESAs dose was adjusted every month till reaching hemoglobin value of 10.5–12 g/dl.

Measurement of HbA1c in those taking ESAs was done after at least 4 months of the treatment.

The guidelines of the 2005 National Kidney Foundation Kidney Disease Outcomes Quality Initiative

did not obviously confirm a target HbA1c level for diabetic and ESRD patients, but levels of 6-7% was accepted.[14] The ADA considered HbA1c levels <5.7% as normal, 5.7- 6.4% as the pre-diabetic level and ≥6.5% as the diabetic level.[15]

Statistical Analysis: Statistical analysis was done by SPSS 20.0. Values were in mean ± standard deviation and using Independent samples T test where appropriate. A *P* value less than 0.05 was considered significant.

Results

There were no significant differences between males and females regarding age and BMI (Table 1).

Table 1: Age and BMI of hemodialysis patients

	Males (number = 22)	Females (number = 34)	P
Age (years)	47.39 ± 14.17	36.82 ± 14.46	0.13
BMI (Kg/m^2)	26.14 ± 8.81	26.72 ± 10.30	0.08

BMI = Body mass index

Regarding HbA1c level, it was non-significantly higher in patients who did not take ESAs (Table 2).

Table 2: HbA1c in patients taking ESAs and patients not taking ESAs.

	Patients taking ESAs (number = 27)	Patients not taking ESAs (number = 29)	P
HbA_1c (%)	5.79 ± 1.91	6.19 ± 1.64	0.09

ESAs= Erythropoiesis-stimulating agents

Table 3 shows the differences in HbA_1c level between hyperthyroid patients taking and not taking ESAs with high and low BMI, HbA_1c is higher in patients not taking ESAs in both groups of patients with high and low BMI, but these differences are not statistically significant. Patients with hypothyroidism who were taking ESAs had less HbA_1c levels than those not taking ESAs in both high and low BMI groups, but the difference was also not significant (Table 3).

Table 3: HbA_1c in hypothyroid and hyperthyroid patients in those taking ESAs and those who were not in both high BMI and low BMI groups

	High BMI patients (number = 30)			Low BMI patients (number = 26)		
	Patients taking ESAs (number = 8)	**Patients not taking ESAs (number = 9)**	**P**	**Patients taking ESAs (number = 7)**	**Patients not taking ESAs (number = 7)**	**P**
HbA_1c (%) in hypothyroid patients (number = 31)	5.93 ± 2.03	8.14 ± 1.06	0.18	5.91 ± 2.48	7.51 ± 0.87	0.17
	Patients taking ESAs (number = 6)	**Patients not taking ESAs (number = 7)**	**P**	**Patients taking ESAs (number = 6)**	**Patients not taking ESAs (number = 6)**	**P**
HbA1c (%) in hyperthyroid patients (number = 25)	6.32 ± 2.40	7.34 ± 1.84	0.12	4.8 ± 0.25	4.97 ± 1.36	0.15

ESAs= Erythropoiesis-stimulating agents; BMI= Body mass index

No significant differences were found in HbA_1c between hyperthyroid and hypothyroid patients taking ESAs or not with high BMI although it was slightly higher in hypothyroid patients not taking ESAs, Table 4.

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Table 4: The differences of HbA_1c between hypothyroid and hyperthyroid high BMI patients in those taking ESAs and those who were not

	Patients with high BMI not taking ESAs (number =1 6)			Patients with high BMI taking ESAs (number = 14)		
	Hyperthyroid (number = 7)	Hypothyroid (number = 9)	P	Hyperthyroid (number = 6)	Hypothyroid (number = 8)	P
HbA1c (%)	7.34 ± 1.84	8.14 ± 1.06	0.27	6.32 ± 2.40	5.93 ± 2.03	0.19

ESAs= Erythropoiesis-stimulating agents; BMI= Body mass index

A statistically significant difference was shown in HbA_1c in participants not taking ESAs with low BMI between hypothyroid and hyperthyroid patients being higher in hypothyroid group (P=0.02) whereas this difference was not significant in patients taking ESAs (Table 5).

Table 5: The difference of HbA_1c between hypothyroid and hyperthyroid low BMI patients in those taking ESAs and those who were not

	Patients with low BMI not taking ESAs (number = 13)			Patients with low BMI taking ESAs (number = 13)		
	Hyperthyroid (number = 6)	Hypothyroid (number = 7)	P	Hyperthyroid (number = 6)	Hypothyroid (number = 7)	P
HbA1c (%)	4.97 ± 1.36	7.51 ± 0.87	0.02	4.8 ± 0.25	5.91 ± 2.48	0.09

ESAs = Erythropoiesis-stimulating agents; BMI = Body mass index

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Discussion

HbA1c may be influenced by the severity of kidney malfunction.[2] This study found that HbA1c level is lower in patients taking ESAs than those who did not, however the difference was not significant.

In hemodialysis patients, blood loss during treatment and multiple blood tests cause reduction of erythrocytes survival. Shortened red blood cell survival, the transfusion of blood and erythropoietin also decrease HbA1c.[11] This agrees with Ng et al, [8] who found a reduction of HbA1c in patients treated with ESAs and iron therapy. The decrease of the HbA1c after ESAs or iron has been thought to be due to the production of new erythrocytes, leading to disturbance of young to old cells percentage, in addition to a change in red-cell glycation rates.[8] Nakao and team mentioned a decrease in HbA1c in non-diabetic patients with CKD on hemodialysis after ESAs treatment. This reduction was higher compared with our results, which could be explained by the fact that iron therapy when given at the same time, most likely stimulated HbA1c lowering action.[16]

Blood sugar binds with the hemoglobin to pinpoint a level for HbA1c. But, HbA1c results are only correct when erythrocytes have normal lifespan. Patients on dialysis have shorter red cell survival; which reduces the needed time for sugar to bind with hemoglobin, and resulting in lower HbA1c levels.[17] It was shown that hemodialysis patients treated with erythropoietin have a transient reduction in HbA1c.[12]

No significant differences were found in HbA1c between hyperthyroid patients taking ESAs and those who were not whether they have high or low BMI, although the level is higher in patients not taking ESAs. The same results were obtained in hypothyroid patients. HbA1c was higher in those with high BMI, this was in accordance with other researchers.[18,19] However, Iso et al,[20] and Koga et al,[21] found no association between BMI and HbA1c.

Hypothyroidism and hyperthyroidism, cause changes in kidney function, and reticulocyte production. HbA1c was non-significantly different between hyperthyroid and hypothyroid patients in high BMI group whether in those taking ESAs or not. But the difference was significant between hyperthyroid and hypothyroid patients in the group of low BMI and was not taking ESAs, where it was higher in hypothyroid patients. This agrees with Kim and co-workers who

found that HbA1c is spuriously high in non-diabetic patients with overt hypothyroidism.[6] HbA1c was higher in hypothyroid patients than control subjects, and its levels were reduced by thyroid hormone treatment. THs potentiate erythrocyte formation, and hypothyroidism mostly causes hypoproliferative erythropoiesis,[22] THs replacement increases erythropoietin, reticulocyte count, and mean corpuscular hemoglobin (MCH). The change in HbA1c value has a significant negative correlation with the change in reticulocyte count or MCH. All the above suggests that thyroid hormone treatment is accompanied by a reduction of HbA1c.[6,23] Whereas, Ford and team reported a significant increase in HbA1c in the hyperthyroid group due to alterations of glycemic regulation in most hyperthyroid patients.[24]

The limitation is a relatively small sample size as it was hard to find patients with thyroid problems especially hyperthyroid ones who have renal problems.

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Conclusion

There is no significant difference in HbA1c level between hemodialysis patients who were taking ESAs and those who were not, in the hyperthyroid and hypothyroid patients having high and low BMI although it was lower in the treatment groups. The only significant difference in HbA1c was found between hyperthyroid and hypothyroid patients who were not taking ESAs and with low BMI being higher in the hypothyroid group.

Conflict of Interest: None.

Source of Funding: None.

Ethical Clearance: All experimental protocols were approved by the College of Medicine, University of Baghdad, Iraq, and all experiments were carried out in accordance with approved guidelines.

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