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COEXISTANCE OF DIABETES MELLITUS AND THYROID DISORDERS: A VIEW ON DYSFUNCTION OF THE ENDOCRINE SYSTEM

Adu Albert Asare[1], Daniel K. Sam[2], Adeyemi Adedayo M.[1], Makharynska O. S.[1]
[1] V. N. Karazin Kharkiv National University, Kharkiv, Ukraine
[2] Cape Coast Teaching Hospital, Ghana

Thyroid disorders in patients with diabetes mellitus were studied in 196 patients, divided into 4 main groups (hyperthyroidism in patients with diabetes, hypothyroidism in patients with diabetes, euthyroidism in patients with diabetes and diabetes patients without any thyroid pathology). It was found that diabetes and thyroid disorders have been shown mutually influence on each other and proved associations between both conditions. Compensation of thyroid function due to adequate therapy leads to controlled hyperglycemia, positive arterial hypertension disease mode and better diabetes mellitus outcome.

KEY WORDS: Diabetes Mellitus, thyroid dysfunction, comorbidities, arterial hypertension, complications

СПІВІСНУВАННЯ ЦУКРОВОГО ДІАБЕТУ І ЗАХВОРЮВАННЬ ЩИТОВИДНОЇ ЗАЛОЗИ: ПОГЛЯД НА ДИСФУНКЦІЮ ЕНДОКРИНОЇ СИСТЕМИ

Аду Альберт Асаре[1], Даниель К. Сем[2], Адейемі Адедайо М.[1], Махаринська О. С.[1]
[1] Харківський національний університет імені В. Н. Каразіна, м. Харків, Україна
[2] Кайп Коаст Тічін Хоспітал, Гана

Були вивчені особливості впливу порушень щитовидної залози у хворих на цукровий діабет у 196 пацієнтів, які були розділені на 4 основні групи (гіпертиреоз у хворих на цукровий діабет, гіпотиреоз у пацієнтів із цукровим діабетом, еутиреоз у пацієнтів із цукровим діабетом та пацієнти з діабетом без будь-якої патології щитовидної залози). Було встановлено, що цукровий діабет і розлади щитовидної залози взаємно впливають один на одного і підтверджено асоціацію між обома захворюваннями. Компенсація функції щитовидної залози за рахунок адекватної терапії призводить до контрольованої гіперглікемії, полегшеної течії артеріальної гіпертензії у таких хворих і зниження кількості негативних наслідків захворювання.

КЛЮЧОВІ СЛОВА: цукровий діабет, дисфункція щитовидної залози, супутні захворювання, артеріальна гіпертензія, ускладнення

СОСУЩЕСТВОВАНИЕ САХАРНОГО ДИАБЕТА И РАССТРОЙСТВ ЩИТОВИДНОЙ ЖЕЛЕЗЫ: ВЗГЛЯД НА ДИСФУНКЦИЮ ЭНДОКРИННОЙ СИСТЕМЫ

Аду Альберт Асаре[1], Даниэль К. Сэм[2], Адейеми Адедао М.[1], Махаринская Е. С.[1]
[1] Харьковский национальный университет им. В. Н. Каразина, Харьков, Украина
[2] Кейп-Кост Тичин госпиталь, Гана

Были изучены особенности влияния заболеваний щитовидной железы на пациентов с сахарным диабетом у 196 пациентов, разделенных на 4 основные группы (гипертиреоз у пациентов с диабетом, гипотиреоз у пациентов с диабетом, эутиреоз у пациентов с диабетом и больные с сахарным диабетом без какой-либо патологии щитовидной железы). Было показано, что диабет и заболевания щитовидной железы взаимно влияют друг на друга и подтверждена ассоциация между обоими состояниями. Компенсация функции щитовидной железы вследствие адекватной терапии приводит к контролируемой гипергликемии, более легкому течению артериальной гипертензии и уменьшению частоты тяжелых исходов заболевания.

КЛЮЧЕВЫЕ СЛОВА: сахарный диабет, дисфункция щитовидной железы, сопутствующие заболевания, артериальная гипертензия, осложнения

INTRODUCTION

Diabetes mellitus (DM) and thyroid dysfunction are two the most common endocrine disorders diagnosed and found in different ages and subgroups of patients worldwide. Both of them influence clinical course of each other. The total prevalence of DM is increasing day by day and World Health Organization is declared DM rate about 366 millions in 2030 in the world, affecting 4,4 % of all age groups [1]. Thyroid disorders can have a major impact on glucose control, and untreated thyroid disorders affect the management and clinical course of diabetes in patients.The frequency of thyroid dysfunction in diabetic patients is higher than in the general population: according to the American Diabetes Association's 2016 Standards of Medical Care in Diabetes autoimmune thyroid disease occurs in 17 to 30 percent of people with DM type 1. A recent studies data in 10 920 patients with DM showed that a mean frequency of thyroid disease is around 11 % [2]. The pathophysiological basis of this association rests on a complex interaction of common signaling pathways and, in the case of type 1 diabetes and autoimmune thyroid disease [1], as result of the impact of particular environmental factors on individuals with genetical susceptiblity, which leads to loss of self-tolerance and there by triggering disease or a linked genetic susceptibility for both thyroid disease and DM [3].

OBJECTIVE

The aim of the current study was to investigate the influence of thyroid gland dysfunction on patients with diabetes mellitus. Can present interactions between two endocrine diseases lead to increasing of the severity of the patient's health state and loss of hyperglycemia effective control?

MATERIALS AND METHODS

In our retrospective study were included 196 patients (65 men, 33 % and 134 women, 68 %) diagnosed with diabetes mellitus, treated in 13 Kharkiv city hospital, Ukraine, with or without thyroid disorders (36 patients with hypothyroidism, 6 patients with hyperthyroidism, 51 patient with euthyroidism and 106 patients with diabetes mellitus itself). All diagnoses were maiden and confirmed by 13 Kharkiv city hospital endocrinologist previously according to criterias of the main treatment protocols of the Health Ministry of Ukraine and WHO [4]. Patients were divided into 4 study groups: (1) DM in patients with hypofunction of thyroid gland (mean age 62 ± 2 years, 2 patients with DM 1 and 34 patients with DM 2 type); (2) diabetes in patients with hyperfunction of thyroid gland (mean age 71 ± 3 years, 0 patients with DM 1 and 6 patients with DM 2 type); (3) diabetes in patients with compensated function of thyroid gland (mean age 62 ± 2 years, 3 patients with DM 1 and 48 patients with DM 2 type) and (4) diabetes mellitus patients without dysfunction of thyroid gland (mean age 63 ± 1 years, 9 patients with DM 1 and 97 patients with DM 2 type). All groups were equal by gender, age, duration of DM and quantity of patients with diagnosis DM 1type and 2type inside of each group (see table 1). These parameters were analysed: levels of fasting blood glucose, HbA1c, creatinine, blood pressure, incidence of the main diabetes complications in all groups, appearance and severity of Arterial Hypertension (AH). Exclusion criterias were: patients with neoplasia and paraneoplastic syndrome, diffuse diseases of connective tissues, cardiomyopathy of any genesis, tuberculosis or other opportunistic infections, alcoholics or drug addicted patients, psychiatric disorders. Duration of DM was equal in all groups (7 ± 1 (1) vs 7 ± 3 (2) vs 8 ± 1 (3) vs 7 ± 1 (4) years relatively). Diagnosis Arterial Hypertension was present in 189 patients in the study (96 %) and all of them received antihypertensive treatment according to national guidelines and hypertension degree with 5 main antihypertensive drug classes. Diagnosis AH stage 1 was maden in 99 patient's cases (50 % of patients in the study, 14(1) vs 1(2) vs 27(3) vs 57(4) respectively), AH stage 2 in 11 patients in the study (6 % of patients in the study, 2(1) vs 0(2) vs 3(3) vs 6(4) respectively), AH stage 3 in 33 patients in the study (17 % of patients in the study, 10 (1) vs 6(2) vs 2(3) vs 15(4) respectively), see table 1.

Table 1

Study groups description (data has been presented as absolute count (percentage); age, systolic and diastolic pressures and duration of DM are represented as mean ± standard error of mean)

Demographic Variables		DM + Hypothyroidism 1 group (36 patients)	DM + Hyperthyroidism 2 group (6 patients)	DM + Euthyroidism 3 group (51 patients)	DM 4 group (106 patients)	P-value
Sex	Male	15 (42 %)	1 (17 %)	13 (25 %)	36 (34 %)	0.348
	Female	21 (58 %)	5 (83 %)	38 (75 %)	70 (66 %)	
Age		62 ± 2	71 ± 3	62 ± 2	63 ± 1	0.336
DM types	Type 1	2 (6 %)	0 (0.0)	3 (6 %)	9 (9 %)	0.796
	Type 2	34 (94 %)	6 (100 %)	48 (94 %)	97 (91 %)	
SAP		161 ± 6	148 ± 2	142 ± 2	146 ± 2	< 0.05
DAP		97 ± 4	83 ± 5	80 ± 1	86 ± 1	< 0.0001
Duration of DM (years)		7 ± 1	7 ± 3	8 ± 1	7 ± 1	0.836
Hypertension groups	Normal BP	0 (0.0)	0 (0.0)	1 (2 %)	6 (6 %)	2- 1,3,4 -< 0.05 1-4– 0.02 1-3 – 0.001
	Pre-hypertension	10 (27 %)	0 (0.0)	18 (35 %)	22 (20 %)	
	Stage 1	14 (39 %)	1 (17 %)	27 (53 %)	57 (54 %)	
	Stage 2	2 (5 %)	0 (0.0)	3 (6 %)	6 (6 %)	
	Stage 3	10 (29 %)	6 (83 %)	2 (4 %)	15 (14 %)	

The data is entered into Microsoft Excel database 2010. Statistic evaluation of the results was performed in Statistica program by parametric methods to estimate the mean (M) and standard error of mean and non-parametric Student's T-test. Study limitations: small groups of patients with thyroid disorders in combination with DM.

RESULTS AND DISCUSSION

Despite the fact that all groups were equal by the main parameters list, we noticed that the prevalence of combined DM – thyroid pathology in female patients was higher in each group (1–3 groups in our study). In scientific medical sources indicated that usual prevalence of DM-thyroid pathology combination is in two fold higher in woman subgroup that in men, which is corresponds to results in our study [2]. Levels of BP, both systolic and diastolic, in patients with hypothyroidism group (1), despite antihypertensive treatment prescribed for all patients, were statistically higher than in other groups. It can be explained by the fact that in patients with Hypothyroidism T3 hormone deficiency leads to peripheral vasoconstriction with increased arterial stiffness, which is an important determinant of arteriosclerosis and changes in arterial wall elasticity [5]. Also increasing of systolic and diastolic BP may stimulate changes inside of the arterial wall with further reducing of elasticity and increasing of the wall stiffness. In this group of patients (1) and also in patients with combination of Hyperthyroidism and DM (2group) quantity of patients with 3rd stage of Arterial Hypertension by WHO classification with the highest prevalence of AH complications were higher than in uncompromised function of thyroid gland groups (3, 4). This possibly can be explained by the main effects of thyroid hormones as increased β-adrenergic activity with heart rate and cardiac contractility increasing, increasing

of systolic and mean pulmonary artery pressures, cardiac output, diastolic relaxation, appearance of atrial arrhythmias and myocardial oxygen consumption. Also increased density of β-adrenergic receptors in the renal cortex usually results in increased plasma renin, angiotensin II, and serum angiotensin converting enzyme levels especially in DM patients with compromised function of kidneys, micro and macrovascular DM complications present [6].

Incidence of the main DM complications as stroke, myocardial infarction (MI), diabetic nephropathy (DN) and chronic heart failure (CHF) were investigated in our study. So stroke incidence were significantly higher in DM +Hyperthyroidism group (1) comparing with Hypothyroidism group patients (2), but there were no significant difference between (2) group and groups with uncompromised thyroid function despite prevalence of stroke incidence in 2nd group (83 % (2) vs 2 %(3) vs 3 % (4) respectively) (see table 2). Hyperthyroidism as well-known disorder associated with an increased risk of atrial fibrillation (AF) especially among 60 years or older patients and due to AF also with the high risk for cardioembolic events as a cause of stroke [7] in presence of compromised endothelial function, dyslipidemia, insulin resistance, microvasculopathy in DM patients may lead to increased incidence of stroke events especially ischemic one in patients with DM comparing with other groups.

Table 2

Levels of DM complications in study groups

Complications	1group (patients, %)	2 group (patients, %)	3 group (patients, %)	4 group (patients, %)	p
Stroke	2 (5 %)	5 (83 %)	1 (2 %)	3 (3 %)	1–2 groups – 0,0001
MI	2 (5 %)	0 (0.0)	2 (4 %)	2 (1.8 %)	> 0.05
Diabetic nephropathy	21 (58 %)	6 (100 %)	20 (39 %)	60 (57 %)	1–2 groups – 0,03 2–4 groups – 0,02
CHF	29 (80 %)	6 (100 %)	36 (70 %)	66 (62 %)	1–4 groups – 0,04 1–2 groups – 0,001 2–4 groups – 0,01 2–3 groups – 0,005

No significant difference was found in study groups in incidence of MI, which can be explained by small quantity of patients with thyroid pathology presented in the study. But if we talk about diabetic nephropathy, were found statistically significant prevalence of DN in hyperthyroidism group (2) patients comparing with hypothyroidism group (1) and patients with DM without thyroid pathology (4). Incidence of DN was higher in 2nd group too, comparing with euthyroidism group (3), but difference was not significantly higher (100 % vs 39 % respectively). Diabetic nephropathy is one of the most common microvascular complications of diabetes mellitus and several clinical studies show that thyroid dysfunction is related to renal disease, especially hypothyroidism. Thyroid dysfunction causes remarkable changes in renal blood flow, glomerular filtration rate, tubular secretory and absorptive capacity, electrolyte pumps, and kidney structure [8]. Recent studies suggest that hyperthyroidism results in increased filtration pressure because of intra-glomerular hypertension and hyperfiltration. Also it may lead to proteinuria appearance, one of the main factors of direct renal injury and hyperthyroidism-induced increased mitochondrial energy metabolism along with down-regulation of superoxide dismutase contributes to the increased free radical generation and consequent renal injury too [9]. But also this

result can be explained by limitation of our study – only a few patients in 2nd group. This fact despite equality of all groups by main parameters may influence the result.

Moreover, thyroid dysfunction can be counted as risk factor of CHF appearance. Untreated hyperthyroidism as hypothyroidism too has been reported as a common cause of CHF. Persistent subclinical thyroid dysfunction has recently been associated with the development of CHF in patients with and without underlying heart disease [6]. In our study CHF incidence were significantly higher in hyperthyroidism group (2) comparing with other 3 groups (100 % (2) vs 80 % (1) vs 70 % (3) vs 62 % (4) respectively). Otherwise, prevalence of CHF episodes in hypothyroidism group (1) was significantly higher too comparing with DM group without thyroid diseases present (4) (see table 2). In multiple studies has been demonstrated that the heart is particularly vulnerable to the reduction in local T_3 levels which is essential to preserve both cardiac morphology and performance in adult life [6]. Thyroid hormones also increase cardiac output by affecting stroke volume and hear rate, several important cardiac structural and functional proteins are transcriptionally regulated by T_3, thyroid hormone regulates the transcription of pacemaker-related genes and hyperpolarization-activated cyclic nucleotide-gated channels 3 and 4 and guanine nucleotide regulatory proteins. Furthermore, hyperthyroiddism is characterized by a high cardiac output state with a remarkable increase in heart rate and cardiac preload and a reduction in peripheral vascular resistance, resulting in a hyperdynamic circulation and increased risk of atrial arrhythmias and cardiac death [10]. Other studies proved that due to decreased αMHC expression and increased βMHC expression hypothyroidism causes cardiacatrophy and may lead to chamber dilatation and impaired myocardial blood flow [11]. All these factors make the heart vulnerable in case of thyroid disorders present especially in DM patients with high incidence of atherosclerosis and arterial hypertension, presence of microvasculopathy and DN.

Optimal hyperglycemia control is the key-task in treatment of DM that helps to avoid the appearance of the main complication of DM, make lesser severity of disease, reduce mortality and improve prognosis for the patient's life. In our study we found that fasting blood glucose levels were markedly raised in both thyroid disorders (10.18 ± 0.72 mmol/l in (1) and 16.25 ± 3.07 mmol/l in (2) vs 9.07 ± 0.35 mmol/l in (3) and 9.21 ± 0.39 mmol/l in (4)), but significantly higher these levels were only if comparing (2) group level with (3) and (4) groups of patients with uncompromised function of thyroid gland (p-0.02). Similar situation was in comparing of HbA1c group levels as marker of hyperglycemia control during last 3 month. We found that HbA1c levels were markedly raised in both thyroid disorders (7.73 ± 0.29 % in (1) and 7.48 ± 0.81 % in (2) group vs 6.89 ± 0.17 %in (3) and 6.95 ± 0.11 % in (4)), but significantly higher these levels were only if comparing (1) hypothyroidism group level with (3) and (4) groups of patients with uncompromised function of thyroid gland (p-0.01). Non-optimal hyperglycemia control in this patient's group and could be explained by increased insulin resistance, due to reduced rate of insulin degradation in hypothyroidism which may lower the exogenous insulin requirement. Otherwise, uncontrolled hyperglycemia may lead to an impairment in peripheral conversion of T4 to T3, reducing of T3 levels and worsening of hypothyroidism outcome with enlarged dosages of replacement therapy needed. Studies done in hypothyroid patients showed elevated HbA1c not only in the presence of diabetes but also in non-diabetic subjects. Whereas, both clinical and subclinical hypothyroidisms have been recognized as insulin resistant states [12]. In hyperthyroidism patients, the hyperglycemia may improve with treatment of thyrotoxicosis. Otherwise, underlying hyperthyroidism should be considered in diabetic patients with unexplained worsening hyperglycemia due to the increase in glucose gut absorption mediated by the excess thyroid hormones, the half-life of insulin is reduced most likely secondary to an increased rate of degradation and an enhanced release of biologically inactive insulin precursors, increased lipolysis. Restoration of euthyroidism will lower blood glucose level [13]. In our study we also found existence of middle-strength positive (0,5) correlation between HbA1c level and creatinine levels in group of DM+Hyperthyroidism (2) patients with (higher level of HbA1c is – higher level of creatinine will be), which proves strong interactions between both endocrine disorders. From one hand, the kidneys play a role in glucose

homeostasis, in patients with DM decreased renal gluconeogenesis, microvascular changes, decreased insulin clearance, and inflammation-induce insulin resistance is a base of renal injury in patients with DM [14]. From other hand, hyperthyroidism is a risk factor of kidney injury with kidney function impairment and further glucose homeostasis worsening despite treatment prescribed.

CONCLUSIONS

1. Diabetes and thyroid disorders have been shown to mutually influence each other and associations between both conditions have long been reported. Compensation of thyroid function due to adequate therapy leads to controlled hyperglycemia, less frequency of DM and better DM outcome

2. Hyperthyroidism as hypothyroidism impairs glycemic control in diabetic subjects, but hypothyroidism patients alter carbohydrate metabolism with inability to gain stable compensation of DM compering with euthyroidism and DM without thyroid dysfunction.

3. Despite increased levels of BP, both systolic and diastolic, in patients with hypothyroidism group, prevalence of AH 3rd stage and AH complications were significantly higher in hyperthyroidism which requires more strict control of blood pressure levels and AH treatment in this group of patients.

PROSPECTS FOR FUTURE STUDIES

It seems appropriate and important to study influence of DM course on thyroid function control and possible interactions between medication using in treatment of both disorders in the aim of improvement of diseases course, decreasing of complications and increasing of survival rate.

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