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The Risk of Severe Hypoglycemia in Patients with Type 2 Diabetes Mellitus Starting Insulin Therapy with Premixed Insulin Analogues Taken Twice Daily: An Observational Study in Turkish Patients

İnsülin Tedavisine Günde İki Kez (BID) Hazırkarışım İnsülin Analogu ile Başlayan Tip 2 Diabetik Hastalarda Ciddi Hipoglisemi Riski: Türk Hastalarda Gözlemsel Çalışma

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Abstract

Purpose: To assess the risk of severe hypoglycemia in Turkish patients with type 2 diabetes mellitus (T2DM) starting insulin therapy with premixed insulin analogues alone or in combination with oral antihyperglycemic medications.

Material and Method: Data from a subset of Turkish patients who participated in a 1-year, multinational, multicenter, prospective observational study were evaluated. Insulin treatment was initiated using commonly prescribed premixed regimens: insulin lispro mixture 25/75 (25% insulin lispro, 75% insulin lispro protamine suspension) or biphasic insulin aspart 30/70 (30% insulin aspart, 70% insulin aspart protamine suspension) twice daily.

Results: Of the 154 patients treated, 61 (39.6%) were male with a mean age of 56 years and a T2DM duration of 8.9 years. Twelve patients (7.8%) experienced ≥1 episode of severe hypoglycemia, but all recovered. The severe hypoglycemic rate was 0.14 episodes/patient-year. The mean glycated hemoglobin decreased by 2.7% (10.4% to 7.8%) and fasting plasma glucose by 115.9 mg/dL (265.3 mg/dL to 157.6 mg/dL) ($p<0.0001$). Self-monitored blood glucose (2-hour post morning meal) decreased by 163.3 mg/dL (327.0 mg/dL to 216.2 mg/dL; $p<0.0001$). Self-monitored blood glucose level was low, particularly at the 2-hour post evening meal. Body mass index increased by 1.4 kg/m^2, and total daily insulin dose by 4.2 IU.

Discussion: In Turkish patients with T2DM, initiation of premixed insulin analogues during routine clinical care significantly improves glycemic control during the first year of treatment, but comes with a risk for severe hypoglycemia. Improvements in physician and patient education within the Turkish population regarding hypoglycemia management may be of benefit. *Turk Jem 2013; 17: 83-8*

Key words: Premixed insulin analogues, severe hypoglycemic episode, type 2 diabetes mellitus, observational study

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Özet

Amaç: Tek başına veya oral antihiperglisemik ilaçlarla birlikte hazırkarışım insülin analogları kullanan, tip 2 diabetes mellitusu (T2DM) olan Türk hastalarda ciddi hipoglisemi oluşumunu değerlendirmek.

Gereç ve Yöntem: Bir yıl süren, çok uluslu, çok merkezli, prospektif gözlem çalışmasına katılan Türk hastaların verileri değerlendirilmiştir. İnsülin tedavisi aşağıda belirtilen, sık reçete edilen hazırkarışım insülin rejimleri kullanılarak başlanmıştır: insülin lispro mixture 25/75 (%25 insülin lispro, %75 insülin lispro protamin çözeltisi) veya bifazik insülin aspart 30/70 (%30 insülin aspart, %70 insülin aspart protamin çözeltisi) BID.

Bulgular: Çalışmaya alınan 154 hastanın 61'i (%39,6) erkekti ve ortalama yaş 56 yıl ve T2DM süresi 8,9 yıldı. Hastaların 12 tanesi (%7,8) ≥1 ciddi hipoglisemi epizodu yaşadı, fakat hepsi düzeldi. Ciddi hipoglisemi hızı 0,14 epizod/hasta yılı idi. Ortalama glikozile hemoglobin (HbA1c) %2,7 (%10,4'ten %7,8'e) ve açlık plazma glukozu 115 mg/dL (265.3 mg/dL'den 157.6 mg/dL'ye; (p<,0001) azalmıştı. Hastaların kendi ölçtükleri kan glukozu (sabah öğününden 2 saat sonra) 163,3 mg/dL azalmıştı (327,0 mg/dL'den 216,2 mg/dL'ye; p<,0001). Kendi kendine kan glukozu izlemi; özellikle akşam öğününden 2 saat sonra, düşüktü. Vücut kütle indeksi 1.4 kg/m^2 ve toplam günlük insülin dozu 4,2 IU artmıştı.

Tartışma: T2DM'li Türk hastalarda klinik bakım sırasında hazırkarışım insülin analoglarının başlanması tedavinin ilk yılındaki glisemik kontrolün anlamlı derecede iyileşmesini sağlamakta, fakat ciddi hipoglisemi riskini de beraberinde getirmektedir. Türk popülasyonundaki hekim ve hastaların eğitimlerinde hipoglisemi yönetimi hakkındaki geliştirmeler yararlı olabilir. *Turk Jem 2013; 17: 83-8*

Anahtar kelimeler: Hazırkarışım insülin analogları, ciddi hipoglisemi epizodu, tip 2 diabetes mellitus, gözlem çalışması

Introduction

Deficit of endogenous insulin secretion progresses over time in patients with type 2 diabetes mellitus (T2DM). Because of the progressive deterioration in pancreatic β-cell function, oral antidiabetic medications (OAMs) are often unable to sustain control of hyperglycemia. Thus, insulin remains the foundation of antihyperglycemic therapy (1). Although it is generally agreed that insulin therapy should be started in a timely manner in these patients, many health care professionals delay insulin therapy for various reasons, including concern over hypoglycemia and weight gain (2). Additionally, patients are reluctant to begin insulin therapy due to a variety of reasons, including fear of injections, fear of hypoglycemia, and complexity/inconvenience of insulin regimens (3).

Premixed insulin analogues, typically composed of a combination of a rapid-acting insulin analogue for prandial coverage and a protamine suspension of the analogue for basal coverage, may help mitigate the reluctance to initiate insulin therapy by eliminating potential errors due to patient self-mixing of insulin, minimizing the number of injections required, and providing greater flexibility in timing of dose relative to meal time (4,5). Nevertheless, hypoglycemia remains a potentially serious complication of any insulin regimen, and patients with T2DM have been shown to be at higher risk of severe hypoglycemia with insulin treatment compared with other treatments (6).

Several clinical trials of premixed insulin analogues have been conducted in patients with T2DM (7-11), but little information exists regarding the real-world risk of severe hypoglycemia in these patients. In addition, the choice of insulin regimen after OAM failure remains controversial (10, 11). Therefore, we undertook the present analysis of a Turkish subpopulation from a multinational observational study to assess the risk of severe hypoglycemia (primary objective) and to examine glycemic measures routinely available in clinical practice (secondary objective) with insulin therapy initiation using premixed insulin analogues in patients with T2DM suboptimally controlled with OAMs (12).

Materials and Methods

Study Design

The original study was a 12-month multinational, multicenter, open-label, prospective, observational study in patients with suboptimal glycemic control who initiated a commonly prescribed premixed insulin analogue (12). At baseline (insulin initiation), patients either continued or discontinued OAM therapy. Consistent with an observational design, patients were treated in outpatient settings by general practitioners, internists, or diabetes specialists. Treatment for diabetes was prescribed according to the usual standard of care, and treatment pattern and initiation of changes were solely at the discretion of the physician and patient in the course of standard clinical practice. Data were collected at 0 months (baseline, visit 1), 4 (±1) months (visit 2), 8 (±1) months (visit 3), and 12 (±1) months (visit 4). Only the results for the Turkish patients who participated in the study are provided in this report.

Patients and Treatment

Patients aged ≥18 years with T2DM (according to the World Health Organization (WHO) classification) and a body mass index (BMI) <40 kg/m^2, receiving at least one OAM without insulin for at least 3 months immediately before the study and, in the opinion of the physician, requiring insulin therapy to achieve proper metabolic control were enrolled. Patients were not allowed to participate if they had taken the following medications for more than 2 weeks within 3 months before entering the study or during the observation period: chronic systemic glucocorticoid therapy excluding topical and inhaled preparations, any prescription drug to promote weight loss, or thiazolidinediones.

Premixed insulin treatment, as monotherapy or in combination with OAMs, was initiated by the administration of insulin lispro low mixture 25/75 (25% insulin lispro, 75% insulin lispro protamine suspension) or biphasic insulin aspart 30/70 (30% insulin aspart and 70% insulin aspart protamine suspension), twice daily, before morning and evening meals.

Study Measures

The primary assessment was the risk of severe hypoglycemia, as determined by the number of patients with at least one severe hypoglycemic episode during 1 year of observation, and the rate (number of episodes per patient-year) of severe hypoglycemia. A severe hypoglycemic episode was defined as an event requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions and was associated with either a blood glucose level <70 mg/dL or a prompt recovery attributable to the restoration of plasma glucose to normal. Secondary measures included mean changes from baseline in glycated hemoglobin (HbA1c), fasting plasma glucose levels (measured in the clinic), self-monitored postprandial whole blood glucose levels, BMI, and total daily insulin dose after starting therapy with premixed insulin analogues.

Statistical Analyses

Estimates for the study population size for the original study were based on the incidence of severe hypoglycemia reported in the United Kingdom Prospective Diabetes Study (UKPDS) trial (6). The original study enrolled 1150 patients of whom 1139 received at least one dose of insulin (12). In the current study, a subset of 154 Turkish patients who received at least one dose of insulin was included in the analyses. The frequency of severe hypoglycemia between insulin groups was compared using Fisher's exact test. Changes (intrapatient) from baseline in HbA1c levels, fasting plasma glucose levels, postprandial blood glucose levels recorded 2 hours after the morning and evening meals, BMI, and total daily insulin dose were calculated. Differences between mean baseline and 12-month values were assessed for glycemic indices using a paired t-test, with a p-value <0.05, indicating a significant difference from baseline; 95% confidence intervals (CIs) were constructed for the mean differences.

Results

Patient Disposition and Baseline Characteristics

Of the 155 Turkish patients enrolled, 154 patients received insulin (138 insulin lispro 25/75 and 16 insulin aspart 30/70) and 1 patient was not treated. Of the 154 treated patients, 35 (23%) discontinued and 118 (77%) completed the study; 1 (0.6%) patient had no follow-up data beyond visit 1. Reasons for discontinuation included physician decision (n=17), lost to follow-up (n=15), death (n=2), and subject decision (n=1).

The characteristics of the patients are summarized in Table 1. The mean (standard deviation [SD]) age was 56 (10) years, and the duration of diabetes mellitus was 8.9 (5.4) years (Table 1). The most common OAM at baseline was metformin (46.7% of 242 medications administered); 70 (45.5%) patients stopped OAMs from baseline.

Primary Measure

Of the 154 insulin-treated patients, 12 (7.8%) reported 16 severe hypoglycemic episodes (8 with 1 episode each and 4 with 2 episodes each). No significant difference (p=1.000) was found in the frequency of severe hypoglycemia between patients treated with insulin lispro 25/75 (8.0%, 11 of 138 patients) and those treated with insulin aspart 30/70 (6.3%, 1 of 16 patients). The rate of severe hypoglycemia over the 12-month study was 0.14 episodes per patient-year. All hypoglycemic episodes were confirmed by blood glucose readings. Eight episodes (50.0% of total episodes) occurred between the morning mean and lunch, 1 (6.3%) occurred between lunch and the evening meal, 3 (18.8%) occurred between the evening meal and bedtime, and 2 (12.5%) occurred between waking and the morning meal; the timing of 2 episodes was unknown (Table 2). Most events (11 of 16) were reported in Visit 2 (Table 2). There were no reported nocturnal severe hypoglycemic episodes. Two episodes (12.5%) resulted in changed insulin regimens and 1 (6.3%) resulted in hospitalization. During 12 episodes (75.0%), the patients were aware of hypoglycemic symptoms, and during 4 episodes (25.0%), the patients were unaware of symptoms. All patients recovered.

Secondary Measures

Secondary measures are summarized in Table 3 and Figures 1 and 2. The mean change from baseline in HbA1c was -2.7% (95% CI -3.0% to -2.4%; p<0.0001). Fasting plasma glucose and self-monitored 2-hour postprandial blood glucose after the morning meal also showed significant improvement with premixed insulin analogue therapy, with mean changes from baseline of -115.9 mg/dL (95% CI -135.2 mg/dL to -96.6 mg/dL; p<0.0001) and -163.3 mg/dL (95% CI -228.6 mg/dL to -98.0 mg/dL; p<0.0001), respectively. Only 1 patient had both baseline and 12-month values for the 2-hour postevening meal time point. Over the 12-month period, the mean (SD) BMI increased from baseline by 1.4 (1.8) kg/m^2, and the mean total daily insulin dose increased by 4.2 (11.9) IU.

Table 1. Patient baseline characteristics

Characteristic	Patients, n=154
Male, n (%)	61 (39.6)
Female, n (%)	93 (60.4)
Age, years	56.2 (10.3)
Diabetes duration, years	8.9 (5.4)
Body mass index, kg/m^2	29.0 (4.6)
HbA1c, %	10.4 (1.8)
Fasting plasma glucose, mg/dL	265.3 (83.2)
Fasting whole blood glucose, mg/dL	265.5 (78.5)
Insulin prescribed at baseline, IU/day	37.7 (11.0)
Oral antihyperglycemic medications, n (%)	242
Metformin	113 (46.7)
Gliclazide	38 (15.7)
Glimepiride	35 (14.5)
Acarbose	27 (11.2)
Repaglinide	9 (3.7)
Pioglitazone	7 (2.9)
Nateglinide	6 (2.5)
Glipizide	5 (2.1)
Glibenclamide	1 (0.4)
Rosiglitazone	1 (0.4)

HbA1c=glycated hemoglobin; SD=standard deviation.
Data are presented as mean (SD), unless otherwise noted

Less than half of the patients in this observational study performed self-monitored blood glucose determinations. The time point with the highest rate of patient participation was the baseline 2-hour post morning meal blood glucose measurement, with 55 of 154 (36%) patients recording values. This number decreased to 25 patients (16%) by the end of the 12-month observational period, with only 17 patients (11%) having both baseline and 12-month recorded values. The rate of performance of the 2-hour post evening meal blood glucose measurement was even lower than that of the post morning meal blood glucose determination, with 18 (12%) patients performing the measurement at baseline and 8 (5%) patients performing the measurement at 12 months.

Discussion

Hypoglycemia is still a significant barrier to adequate glycemic control in patients with T2DM treated with insulin. In this analysis of a Turkish subpopulation with T2DM from a multinational observational study (12), the rate of severe hypoglycemia is consistent with many population-based studies of insulin-treated patients with T2DM (0.12 to 0.28 episodes/patient-year) (13-17), and higher than typically reported in controlled clinical trials of premixed insulin analogues (0.00-0.10) (7-11). The modest increase in BMI observed was not unexpected and in keeping with previous studies of premixed insulin regimens in insulin-naive patients (7-11, 18-21).

A possible explanation for the higher rate of severe hypoglycemia found in this real-world study compared with those in controlled clinical trial settings could be a lack of or minimal patient education and engagement regarding insulin therapy and management of hypoglycemia in routine clinical practice. By comparison, patients in controlled clinical trials are typically monitored by clinical staff and engaged in dialogue regarding their therapy to a degree that is often difficult to achieve in a average specialist center, and even more so in general practice settings. Thus, controlled clinical trial environments may not be fully applicable to the real-world setting (22).

Similar to the current study, a retrospective medical records analysis of Turkish patients with T2DM who received conventional insulin therapy on an outpatient basis reported a rate of severe hypoglycemia of 0.15 episodes/patient-year (13). In that study, the

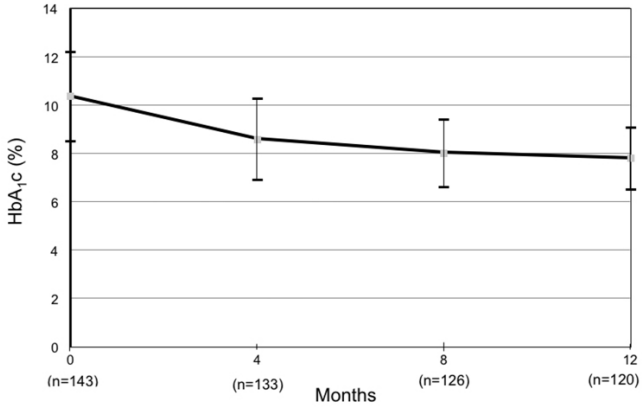

Figure 1. Glycated hemoglobin (HbA1c) over 12 months (mean±standard deviation).

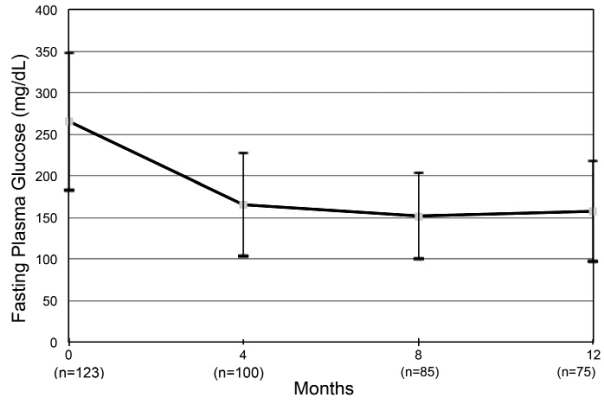

Figure 2. Fasting plasma glucose over 12 months (mean ± standard deviation).

Table 2. Timing of severe hypoglycemic events

Time of day	Visit 2 4 (±1) months		Visit 3 8 (±1) months		Visit 4 12 (±1) months
	Insulin lispro 25/75 n (n)	Insulin aspart 30/70 n (n)	Insulin lispro 25/75 n (n)	Insulin aspart 30/70 n (n)	Insulin lispro 25/75 n (n)
Between morning meal and lunch	5 (6)	0	1 (1)	0	1 (1)
Between lunch and evening meal	1 (1)	0	0	0	0
Between evening meal and bedtime	1 (1)	0	1 (1)	1 (1)	0
Between waking and morning meal	1 (1)	0	1 (1)	0	0
Unknown	1 (1)	1 (1)	0	0	0
Total[a]	9 (10)	1 (1)	3 (3)	1 (1)	1 (1)

n (n) = Number of patients with severe hypoglycemia (number of events); 138 patients received insulin lispro 25/75 and 16 received insulin aspart 30/70

[a] Three patients were counted in more than one category: One patient (insulin lispro 25/75) between morning meal and lunch at visit 2 and between evening meal and bedtime at visit 3; one patient (insulin lispro 25/75) between morning meal and lunch at visits 2 and 3; and one patient (insulin aspart 30/70) between evening meal and bedtime at visit 3 and unknown time of day at visit 2.

Table 3. Changes in measures of glycemic and metabolic control

	Baseline n Mean (SD)	12 Months n Mean (SD)	Change from Baseline n Mean (SD)
HbA1c (%)	143	120	117
	10.4 (1.8)	7.8 (1.3)	-2.7 (1.9)*
Fasting plasma glucose (mg/dL)	123	75	70
	265.3 (83.2)	157.6 (60.4)	-115.9 (80.9)*
2-hr postmorning meal blood glucose (mg/dL)	55	25	17
	327.0 (102.5)	216.2 (80.1)	-163.3 (127.0)*
2-hr postevening meal blood glucose (mg/dL)	18	8	1
	255.4 (51.2)	196.8 (44.4)	-69.0 (N/A)
Body mass index (kg/m^2)	154	120	120
	29.0 (4.6)	30.6 (4.4)	1.4 (1.8)
Insulin dose (IU/day)	154	120	120
	37.7 (11.0)	42.1 (15.3)	4.2 (11.9)

HbA1c=glycated hemoglobin; SD=standard deviation

* P<0.0001 determined from a paired t test comparing differences between mean baseline and 12-month values.

authors reported that only 10% of patients with T2DM regularly attended a diabetes teaching program and only 5% of patients performed self-monitoring of blood glucose. Patient-reported reasons for severe hypoglycemic episodes, which were not collected in the current study, included dietary mistakes (65.5%), exercise (27.5%), and insulin overdose (7%) (13).

Intensification of diabetes therapy to include insulin is often delayed until patients have markedly high HbA1c values (23,24). This occurs for a variety of reasons on the part of both physicians and patients (25). Indeed, the current study population had a mean HbA1c of 10.4% at the time of insulin initiation, an indication that T2DM had progressed significantly in these patients. Although the mean duration of diabetes at baseline (8.9 years) was similar to, or less than other populations reported to have lower baseline HbA1c levels (26-28), it is important to note that the diabetes duration value was obtained from patient recall of the date of diagnosis, which could be prone to error. In addition, patients could have gone undiagnosed for some time. Thus, there appears to be an important opportunity within the Turkish diabetes community to screen and treat patients with T2DM sooner.

Despite the apparent advanced progression of their disease, the patients in this study responded well in terms of glycemic control to relatively low insulin doses and small insulin dose increases, with significant improvement in HbA1c, fasting plasma glucose, and self-monitored postprandial blood glucose recorded 2 hours after morning meal. This may suggest that, in this patient population, insulin resistance may play a minor role in patients with T2DM (29), and may indicate an opportunity to bring patients into glycemic control without the need for high insulin doses.

A limitation of this study includes the potential for patient recall bias, which could have resulted in underreporting or overreporting of hypoglycemia. In addition, if the patients were not clear on the reporting criteria for hypoglycemia, it is possible that there may have been confusion regarding the severity of their hypoglycemic events. However, the patients were asked to recall severe hypoglycemic episodes rather than mild hypoglycemia, and it has been shown that unlike mild hypoglycemia, retrospective recall of severe hypoglycemia is relatively robust (14,30). Another possible limitation is that patient participation in self-monitoring of blood glucose was low, especially at the 2-hour postevening meal. Thus, results for postprandial blood glucose values represent only a portion of the patient population. For these reasons, the results of the present study should be interpreted with caution. The lack of a requirement for the study design to record possible complications of diabetes such as, diabetic neuropathy or nephropathy, also represents a possible limitation.

In conclusion, initiation of insulin therapy with premixed insulin analogues in Turkish patients with T2DM in normal clinical practice significantly improves glycemic control during the first year of treatment, but comes with a risk for severe hypoglycemia. An important opportunity exists to better educate Turkish patients regarding self-monitoring of blood glucose and strategies to avoid hypoglycemia. As with all patients with T2DM, education regarding diet and exercise to help control weight gain, manage hyperglycemia and hypoglycemia, and improve insulin sensitivity is of great importance.

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HFE Gene Mutation Among Turkish Patients with Type 2 Diabetes Mellitus

Türk Tip 2 Diabetik Hastalar Arasında HFE Gen Mutasyonu

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Abstract

Purpose: Hereditary haemochromatosis (HH) is a genetic disease with autosomal recessive trait. Recent studies demonstrated the importance of C282Y gene mutation in the aetiology of HH. Free iron accumulating in pancreas deteriorates insulin secretion and synthesis which can lead to insulin resistance and the development of type 2 diabetes mellitus (T2DM) in patients with HH. There has been no study determining the prevalence of haemochromatosis gene (HFE) mutations and HH in diabetic patients in Turkey. We planned this study in order to investigate the C282Y and H63D mutation that cause HH in T2DM.

Material and Method: In this study, we included185 patients with T2DM. Patients older than thirty-five years, not taking vitamin supplementation, iron preparates and/or oral contraceptives and those without any signs of active bleeding were included while patients with any infectious, systemic or immune disease were excluded from the study. Serum transferrin saturation (TS), ferritin, iron, and total iron binding capacity levels were measured after 12 hours of fasting.

Results: Ten (5.4%) cases with TS of more than 45% were detected at the first evaluation. The test was repeated in those cases and 6 patients with TS of more than 45% were left according to the second measurement. H63D and C282Y gene polymorphisms were not present in these patients.

Discussion: We did not find any correlation between the existence of T2DM and HFE polymorphisms. We assume that screening for HH in T2DM in our population is not needed. *Turk Jem 2013; 17: 89-91*

Key words: Hemochromatosis, Type 2 diabetes, transferrin saturation

Özet

Amaç: Herediter Hemokramotozis (HH) otozomal resesif özelliğinde genetik bir hastalıktır. Önceki çalışmalar,HH etyolojisi için C282Y gen mutasyonunun önemini göstermiştir. HH'lu hastalarda pankreasta serbest demir birikmesi, insülin sekresyonunu ve sentezini bozarak, insülin resistansı ve tip 2 diabet mellitüs (DM) gelişimine öncelik etmektedir. Türkiyedeki diabetik hastalarda HFE gen mutasyonu ve HH prevalansı belirlemeye yönelik herhangi bir çalışma bulunmamaktadır. Biz bu çalışmada, tip 2 DM de HH sebep olan C282Y ve H63D mutasyonunu araştırmayı planladık.

Gereç ve Yöntem: Bizim çalışmamıza tip 2 DM tanısı olan 185 hasta dahil edildi. Hastalar 35 yaşın üzerinde,vitamin desteği ,demir preparatı ve/veya oral kontraseptif tedavi almayan ve aktif kanama işareti olmayan hastalar dahil edilirken, infeksiyon, sistemik ve immün sistem hastalığı bulunanlar çalışma dışında bırakıldı. 12 saat açlık sonrası serum transferrin saturasyonu (TS), ferritin, demir ve demir bağlama kapasitesi ölçüldü.

Bulgular: İlk değerlendirmede 10 vakada (%5.4) transferrin saturasyonunun % 45' in üzerinde bulundu. Bu vakalarla test tekrarlandı ve ikinci değerlendirmede 6 vakada TS %45 'in üzerinde bulundu. Bu hastaların hiçbirinde H63D ve C282Y gen polimorfizmi saptanmadı.

Tartışma: Biz tip 2DM ve HFE poliformizmi arasında bir korelasyon bulamadık. Bizim toplumumuzda tip 2 DM li hastalarda, HH için mutasyon taramayı önermiyoruz. *Turk Jem 2013; 17: 89-91*

Anahtar kelimeler: Hemokromatozis, Tip 2 diabetes mellitüs, transferrin saturasyonu

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Introduction

Hereditary haemochromatosis (HH) is a genetic disorder characterized by increased dietary iron absoption and accumulation in body tissues such as liver, pancreas, joints and pituitary gland. Iron accumulation in body tissues may lead to cirrhosis, hypogonadism and arthralgia (1). Even though diabetes mellitus is a well-known complication of HH, the percentage of people presenting with typical type 2 diabetes mellitus (T2DM) having polymorphisms in the HFE gene is not exactly known (2). The HFE gene product is a HLA-like molecule which is presented at cell surface. It is bound to ß2-microglobulin, where it is proposed to modify the affinity of transferrin to its receptor. Although C282Y gene predicts serum iron indices (3-5), reports of C282Y allele frequency in T2DM are conflicting (6-8).

The C282Y mutation in the HFE gene is the main one which causes haemochromatosis. 83% of hemochromatosis patients are homozygous for this mutation (9). The H63D polymorphism, which is the second variant of HFE gene, is not per se associated with hemochromatosis, but it acts synergistically with C282Y mutation (9). Body iron stores are shown to be associated with abnormal glucose tolerance and insulin resistance (10). Nonetheless, the results are open to discussion. Many studies tried to affirm the hypothesis that heterozygosity for hereditary hemochromatosis-causing mutations could be a risk factor for diabetes (10). Kwan et al. found an increased frequency of C282Y mutations in patients with T2DM and they stated that the C282Y gene mutation was a potential genetic marker for T2DM (11). In a study by Fernandes-Real et al., the C282Y allele frequency was similar in patients with T2DM and controls, however, the H63D allele frequency was significantly increased in patients with T2DM. Many studies failed to show this association (12). The prevalence of C282Y and H63D mutations was not found to be increased in patients with T2DM compared to non-diabetic population in some other studies (13-16). Thus, we investigated the association of the C282Y and H63D mutations with T2DM in the Turkish population.

Materials and Methods

One hundred eighty-five patients (110 female and 75 male) with T2DM diagnosed according to the ADA criteria were included in this study. Patients older than thirty-five years, not using vitamin supplements, iron preparates or oral contraceptives, and with no active bleeding were included. Those with any infectious, systemic or immune disease were excluded from the study. Serum transferrin saturation (TS), ferritin, iron, and total iron binding capacity were evaluated after 12 hours of fasting. The test was repeated in subjects whose serum TS levels were more than 45%. TS levels of more than 45% were detected in 6 patients. H63D and C282Y mutations were analyzed in these patients. Serum iron levels and serum total iron binding capacity were measured using an automatic spectrophotometric analyzer. Serum ferritin levels were measured by immunometric assays. TS% was calculated by dividing serum iron levels by total serum iron binding capacity multiplied by 100%. DNA was extracted from EDTA-anticoagulated blood samples collected from the patients using standard methods. HFE C282Y genotyping was performed by the PCR-RFLP method using modified oligonucleotide primers sequence to improve allelic discrimination (5'-CTA CCA GGG CTG GAT AAC CTT G, and, 5'-TGG CTC TCA TCA GTC ACA TAC C) (17). H63D genotyping was performed similarly as described above. All patients were Turkish and they participated in the study after signing an informed consent form. The study protocol was approved by the Ethics Committee of the Ministry of Health Dışkapı Y.B. Education and Research Hospital.

Results

The average age of the patients was 57.3±10.1 years and the duration of T2DM was 11.2±7.2 years. Serum TS levels of more than 45% were detected in 10 patients (5.4%). The test was repeated in these patients and 6 patients were found to have the same results. These patients were analyzed for H63D and C282Y gene polymorphisms, but none of the mutations were detected (Table 1).

Discussion

The C282Y mutation in the HFE gene may lead to haemochromatosis. Furthermore, 83% of hemochromatosis patients are YY homozygotes (9). The H63D polymorphism is the second variant of HFE gene and acts synergistically with C282Y mutation. (9). The relationship between accretion of iron and increased risk of type 2 diabetes had been attributed to insulin synthesis and secretion inhibitory effect of iron (18-19). Increased body iron may cause oxidation of free fatty acids that bring out free radicals (20). Increased free fatty acid oxidation diminishes glucose utilization in muscle tissue and increases gluconeogenesis in the liver, leading to insulin resistance (18-20). Studies on non-cirrhotic haemochromatosis and on hypertransfused patients with

Table 1. H63D and C282Y mutations of the patients (Transferrin saturation > 45%)

Age (year)	Ferritin (ng/ml)	Iron (µg/dl)	Iron binding capacity (µg/dl)	TS (%)	H63D mutation	C282Y mutation
65	357	120	235	51	negative	Negative
76	261	134	194	45.5	negative	Negative
65	187	154	311	49,5	negative	Negative
69	135	151	331	45.6	negative	Negative
42	110	113	229	49,3	negative	Negative
55	355	161	307	52,4	negative	Negative

ß-thalassemia support the evidence that accumulation of iron leads to development of insulin resistance (21-22). Clarke et al. studied the prevalence of HFE gene mutation in a limited number of Turkish people and found that the H63D allele frequency was 17.7% while C282Y mutation was not present (23). Recently, 4633 subjects (3827 men, 806 women with a mean age of 35±8.0) were investigated for hereditary haemochromatosis in terms of C282Y and H63D mutations in a study by Barut et al. (24) and 11 (10 men, 1 woman) subjects were found to be heterozygous while 1 case was homozygous for the H63D mutation, however, the C282Y mutation was not detected in any of them. Simsek and collegues (25), has found H63D mutation in 60 out of 143 HH patients in whom 49 of them were heterozygous and 11 of them were homozygous for this mutation. They also declared that none of their patients had C282Y mutation.

We did not detect C282Y mutation in our study population consistent with the results above, but the absence of H63D can be attributed to the insufficient number of subjects involved in our study.

One study reported the increased prevalence of HFE mutation in diabetic patients compared to control subjects and also indicated that the C282Y mutation was more common among patients with diabetic nephropathy when compared with normoalbuminuric ones (26). However, our results were similar to the results of other studies which did not show increased prevalence of C282Y and H63D mutation among diabetic patients. Routine screening for HH in diabetic patients is not recommended but HH can be suspected as an aetiologic factor in patients who required early insulin therapy. Genetic analyses must be performed for selected patients in our population after phenotypic scanning. Patients susceptible to haemochromatosis with elevated serum ferritin levels and TS can undergo genetic analyses earlier.

The lack of a control group is the main limitation of this study. We recommend genetic analyses for HFE gene mutation in diabetic patients who have clinical, biochemical and phenotypical characteristics of HH. Further studies with larger sample size are needed to investigate the prevalence and importance of HFE gene mutation in the Turkish population with diabetes.

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Özgün Araştırma *Original Article*

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Hipertansif Tip 2 Diyabetiklerde Telmisartan ve Losartanın İnsülin Duyarlılığına Etkileri

The Effects of Telmisartan and Losartan on Insulin Sensitivity

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Özet

Amaç: Anjiotensin Reseptör Blokörleri (ARB) insülin direncini düzeltmektedir. ARB grubundan telmisartanın Renin-anjiotensin- sistemi inhibisyonundan bağımsız, parsiyel PPAR-gamma aktivitesi göstererek insülin duyarlılığını arttırdığı gösterilmiştir. Bir başka ARB olan losartanda bu aktivite bulunamamıştır. Çalışmamızda tip 2 diyabetik hastalarda telmisartan ve losartanın insülin direnci üzerine etkilerini karşılaştırmayı amaçladık.

Gereç ve Yöntem: Çalışmaya üç aydır telmisartan yada losartan alan , sulfonilüre tedavisi ile metabolik kontrolü sağlanmış 2 diyabetli hastalar alındı. Hastaların antropometrik ölçümleri alındı, açlık plazma glukozu, HbA1C, bazal insülin ve serum adiponektin düzeyleri belirlendi; HOMA-IR hesaplandı. Hiperinsülinemik-öglisemik klemp testiyle insülin duyarlılığını yansıtan M değerleri bulundu. Takiben hastaların almış olduğu ARB kesildi. Onbeş günlük ilaçtan temizlenme periyodunu takiben önceden losartan almış olan gruba (Grup1) telmisartan (80mg/gün), önceden telmisartan almış gruba (Grup 2) losartan (50 mg/gün) verildi. 12 hafta takip sonunda hastalara bahsedilen antropometrik ölçümler ve laboratuvar testleri ile hiperinsülinemik öglisemik klemp testi tekrarlandı.

Bulgular: Çalışmayı 1. Gruptan dokuz, 2. Gruptan sekiz hasta tamamladı. Başlangıç özellikleri açısından gruplar arasında anlamlı farklılık yoktu. Çalışma bitiminde Grup 1'de kan basıncı, açlık plazma glukozu, HbA1C, bazal insülin düzeyi, serum adiponektin düzeyileri, HOMA-IR ve M değerlerinde başlangıca göre anlamlı farklılık yokken vücut ağırlığı ve vücut kitle indeksinde istatistiksel anlamlı azalma tespit edildi (p=0,034 ve p=0,023). Buna karşın Grup 2' deki hastalarda bahsedilen hiçbir parametrede çalışma başlangıcı ve bitişi arasında fark yokken hiperinsüliemik-öglisemik klemp testiyle belirlenen insülin duyarlılığında anlamlı artış saptandı (p=0,028).

Tartışma: Bu bulgularla kısa süreli tedavide tip 2 diyabetik hastalarda losartanın insülin duyarlılığını, telmisartan anlamlı kilo kaybı yaptığı halde bu ilaca göre daha belirgin düzelttiği sonucuna varıldı. *Turk Jem 2013; 17: 92-7*

Anahtar kelimeler: Telmisartan, losartan, insülin direnci

Abstract

Purpose: Telmisartan has been reported to increase insulin sensitivity by acting as a partial PPAR-gamma agonist, regardless of its renin-angiotensin system inhibition, but losartan has no such activity. In this study, we compared the effects of telmisartan and losartan on insulin sensitivity among type 2 diabetic patients.

Material and Method: Age-, sex- and weight-matched patients, who had been on telmisartan or losartan treatment for at least 3 months, were included. Their anthropometric measurements were performed, blood pressures were recorded. Fasting venous blood samples were obtained for analyzing the levels of glucose, HbA1C, insulin and adiponectin. HOMA-IR was calculated. An euglycemic hyperinsulinemic clamp procedure was performed in each subject and M index was calculated. Thereafter, telmisartan and losartan were withdrawn in both groups. A cross-over design was planned; following a wash-out period of 15 days, losartan group (Group 1) was given telmisartan 80 mg/day, telmisartan group (Group 2) was administered losartan 50 mg/day. After 12 weeks of therapy, all measurements, calculations and the euglycemic hyperinsulinemic clamp test were re-performed.

Results: General characteristics of the patients at inclusion were similar. Nine cases in group 1 and 8 cases in Group 2 concluded the follow-up. In Group 1, among all follow-up parameters, only weight exhibited a significant decrease at final evaluation (p=0,034). In Group 2, only M value was found to increase (p=0,028).

Discussion: Our findings indicated that losartan improved insulin sensitivity in patients with concomitant hypertension and type 2 diabetes, and telmisartan use resulted in more weight loss. *Turk Jem 2013; 17: 92-7*

Key words: Telmisartan, losartan, insulin resistance

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Giriş

Hipertansiyon, insülin direnci ve hiperinsülinemi ilişkisi iyi bilinmektedir. Tedavisiz esansiyel hipertansif hastalarda açlık ve tokluk insülin düzeyleri normotansif kontrollerden yüksek bulunmuş ve vücut kitle indeksine göre düzeltme yapıldığında plazma insülin düzeyi ile kan basıncı arasında direkt ilişki bulunmuştur (1-3). Çeşitli popülasyonlarda yapılmış geniş prospektif bir çalışmada esansiyel hipertansiyonlu hastaların, non-hipertansif bireylere göre tip 2 diyabet gelişimi açısından daha fazla risk altında bulunduğu saptanmıştır (4).

Renin-Anjiotensin Sisteminin (RAS), kan basıncı regülasyonunda oynadıkları anahtar rol dışında insülin direnci ve diyabet gelişimi üzerine de etkileri olduğu bilinmektedir. Aynı şekilde insülin direncinin de doku RAS üzerinde etkileri vardır. İnsülin direncinde postranskripsiyonal mekanizmalarla dokularda anjiotensin reseptörü 1(AT1R) upregülasyonu ve anjiotensin II (AT II) üretim ve etkinliğinde artış meydana gelir (5). AT II'nin insüline bağlı oluşan vazodilatasyonu ve glukoz transportunu inhibe ettiğini gösteren kanıtlar vardır (6,7). RAS inhibisyonu kas kan akımında düzelme yaparak (8), sempatik aktiviteyi azaltarak (9), serum iyon düzeylerinde değişme yaparak (10), vazodilatasyondan bağımsız olarak insülin sinyalizasyon yolağında düzelmeler yaparak ve buna bağlı periferik glukoz kullanımını arttırarak (11) ve yağ dokusu ile adipokinler üzerine olan etkilerle (12) insülin direncini azaltabilir. Aynı zamanda RAS inhibisyonunun, serum potasyum ve magnezyum iyonları üzerindeki iyonik dengeyi düzeltici etkisinin ve pankreatik beta hücre mikrosirkülasyonunu düzeltmesinin insülin sekresyonu üzerine olumlu katkıları olacağı düşünülmektedir (13).

Anjiotensin dönüştürücü enzim inhibitörleri (ACEİ) ve Anjiotensin reseptör blokörleri (ARB) gibi RAS inhibisyonu yapan ilaçların insülin direncini belirgin düşürmeleri ve antidiyabetik etkilerinden dolayı, günümüzde bu gurup ilaçlar diyabet gelişimi açısından metabolik pozitif etkileri olan popüler ajanlar olmuşlardır. ACEİ ve ARB'lerin RAS inhibisyonu üzerinden olan koruyucu etkileri benzer bulunmuştur, meta-analizlerde bu grup ilaçlarla RAS inhibisyonunun tip 2 diyabet gelişimi relatif riskini yaklaşık %22 azalttığı hesaplanmıştır (14).

Yakın zamanda bazı ARB'lerin antidiyabetik etkilerini parsiyel PPAR-gamma (peroksizom proliferatör aktive edici reseptör-gamma) agonizması yaparak gösterdiği bulunmuştur (15). PPAR-gamma aktivasyonu ile yağ dokusunda preadipositlerin olgun adipositlere diferansiyasyonu sağlanır ve yağ dokusunda insüline duyarlığını arttırıcı yönde etki olur.Yine diferansiye olmuş yağ hücrelerinden serbest yağ asitleri, tümör nekroze edici faktör alfa, interlökin-6 ve rezistin gibi insülin direnci üzerine olumsuz etkileri olan sitokinlerin salınımı azalırken, insülin duyarlaştırıcı adiponektin salınımı artar (16). AT1R'lerinin çıkarıldığı hücre modellerinde bu PPAR-gamma aktivitesinin devam ettiği bulunmuş, bundan dolayı bu etkinliğin RAS inhibisyonundan bağımsız olduğu sonucuna varılmıştır (15). ARB'ler arasında, PPAR-gamma uyarıcı etkinin terapötik konsantrasyonlarda sadece telmisartanda bulunduğu, bunun dışında yüksek dozlarda kısmen irbesartanın ve daha az olarak da candesartanın benzer aktiviteye sahip olduğu belirlenmiştir (17). Losartan ve diğer ARB'lerin herhangi bir konsantrasyonda PPAR-gamma aktivitesi gözlemlenmemiştir (17,18).

Çalışmamızda, tedavi gören tip 2 diyabetli hastalarda antihipertansif ajan olarak kullanılan telmisartan ve losartanın insülin direnci üzerine olan etkilerini karşılaştırmayı hedefledik. Bu şekilde terapötik dozlarda hem RAS inhibisyonu hem de parsiyel PPAR-gamma agonizması üzerinden ikili etki gösteren telmisartanın, klinik uygulamada bilinen PPAR-gamma aktivitesi olmayan klasik ARB'lerden anlamlı üstünlük gösterip göstermediğini araştırmayı amaçladık.

Gereç ve Yöntem

Hasta Seçimi

Çalışmaya Başkent Üniversitesi Adana Uygulama ve Araştırma Hastanesi Endokrinoloji ve Metabolizma Hastalıkları kliniğine başvuran, yeni tanı almış, daha önce medikal tedavi görmemiş, tip 2 diyabetik, hafif-orta şiddette hipertansiyonu olan 20 hasta dahil edildi. Tip 2 diyabet tanısı için Amerikan Diyabet Birliğinin 2004 yılındaki kılavuzu esas alındı (19).Yine hafif-orta şiddette hipertansiyon tanısı Joint National Committee VII kriterlerine göre evre 1 hipertansiyonu kapsayan tedavi görmeyen hastalar için kullanıldı (20). Sigara içenler, kronik alkolizm sorunu olanlar, son 3 hafta içinde arteryel kan basınçları ortalaması 140/90 mm/Hg üzerinde olan kontrolsüz hipertansif olgular, tip 1 diyabetik hastalar, glukozile hemoglobin (HbA1C) >8 % olan kötü kontrollü diyabetikler, gebeler, tek böbreği olanlar ve malignite, herhangi bir endokrinolojik bozukluk, karaciğer ya da böbrek yetmezliği gibi kronik hastalıklar nedeni ile takipte olan hastalar ile 65 yaş üzeri olanlar çalışma dışı bırakıldı.

KA-05/256 proje numarası ile Başkent Üniversitesi Tıp Fakültesi merkez etik kurulu izni alındıktan sonra çalışmaya dahil edilen hastalara gönüllü denek bilgilendirme formu okutularak onayları alındı.

Hazırlık Dönemi

Çalışmaya alınan hastalara diyabetlerine yönelik sulfonilüre ya da meglitinid gurubu insülin sekretogog ajanlar ile oral antidiyabetik monoterapi başlandı ve hastalar başlanacak antihipertansif tedavi yönünden iki gruba ayrıldı. Grup 1 hastalara (n=10; 5 kadın, 5 erkek) 50 mg/gün losartan ve Grup 2 hastalara (n=10; 3kadın, 7 erkek) 80 mg/gün telmisartan başlandı. Her iki guruba uygun beslenme rejimleri önerildi. Aylık kontrollerle kan şeker ve kan basıncı regülasyonu sağlandı.

Çalışma Başlangıcı

Üç aylık tedavi sonunda 3 gün standart karbonhidratlı diyete alınan hastalara 12 saatlik açlık sonrası arteryel kan basıncı, bel çevresi ve vücut ağırlığı ölçümleri yapıldı, vücut-kitle indeksi (VKİ) kg/m^2 olarak hesaplandı. Venöz kan örneklerinden serum potasyum, kreatinin, glukozile hemoglobin (HbA1C) düzeyi, açlık plazma glukozu ile bazal insülin düzeyleri ölçüldü. {Açlık Glukoz (mmol/l) X Açlık İnsülin (mU/ml) } / 22.5 formülü ile HOMA-IR değerleri hesaplandı. Alınan venöz kanın bir kısmı plazma adiponektin düzeyi bakılmak üzere saklandı. Her hastaya de Fronzo tarafından tariflenen yönteme dayanarak hiperinsülinemik öglisemik klemp testi (HECT) uygulanarak hesaplanan M değerleri kaydedildi (21).

Ara verme periyodu: Daha sonra her iki gruptaki hastaların kullanmakta olduğu telmisartan ve losartan gurubu

antihipertansiflere iki hafta süre ile ara verildi (wash-out periyodu). Bu süreçte hastaların hipertansif acil veya acele durum riskine karşı günlük kan basıncı takipleri alındı, hiçbir hastada çalışmadan çıkarılmayı gerektirecek kan basıncı yükselmesi olmadı.

Takip periyodu: İki haftalık ilaçsız periyodu tamamlayan hastalardan Grup 1 (önceden losartan başlanmış olan grup)'e 80 mg/gün dozunda telmisartan, Grup 2 (önceden telmisartan başlanmış olan grup)'ye ise 50mg/gün losartan verildi. Diyet uyumları ve günlük fizik aktivitelerinde belirgin bir değişiklik yapılmaması önerilen hastaların aylık kontrollerle kan basıncı ve kan şekeri takipleri yapıldı. Hiçbir hastada oral antidiyabetik veya antihipertansif ilaç dozunda değişikliğe gerek görülmedi.

Çalışma Bitimi

Üçüncü ayın sonunda tüm hastalara yukarda belirtilen antropometrik ölçümler ve biyokimyasal tetkikler tekrarlandı, serum adiponektin düzeyi için kan örneği alındı ve HECT yapılarak M değerleri kaydedildi.

Hastaların boy ve vücut ağırlıkları standart terazide ölçüldü. Kan basınçları standart kol manşonlu sfingomanometre ile istirahat halinde 5 dakika ara ile alınan üç ölçüm ortalaması olarak kaydedildi. Biyokimya analizöründe (Roche modular DP) enzimatik kalorimetrik yöntemle plazma glukozu (glukoz oksidaz metodu), kinetik kalorimetrik yöntemle kreatinin, iyon selektif elektrot yöntemi ile de potasyum düzeyleri çalışıldı. Plazma açlık insülin düzeyleri mikropartikül Enzim İmmunassey yöntemi ile (Axsym Abbott Diagnostics Division) ve adiponektin düzeyleri ise enzim linked immunosorbent assey (ELISA) yöntemi ile (Biovendor Human Adiponectin Elisa, Tecan Sunrise) çalışıldı.

İstatistiksel değerlendirme için Windows SPSS 11.0 programı kullanıldı. Her iki grup hasta özellikleri ve bakılan parametrelerin ortalamaları cross-tabs yapılarak belirlendi. Gruplar arası karşılaştırma independent samples T test kullanılarak yapıldı. Her bir grubun kendi içinde hasta özellikleri ve bakılan parametrelerinin, çalışma başı ve bitimindeki değişikliklerinin karşılaştırılması için paired samples T test kullanıldı. İstatistiksel anlamlılık için p değerinin<0,05 olması şartı arandı.

Bulgular

Çalışmaya her iki gruptan 10'ar hasta olmak üzere başlangıçta 20 hasta dahil edildi. Birinci gruptan 1 ve ikinci gruptan 2 hasta takiplerine gelmedikleri için çalışmadan çıkarıldı. Çalışmayı 1. gruptan dokuz (4 kadın, 5 erkek), 2. gruptan sekiz (1 kadın , 7 erkek), toplam 17 hasta tamamladı. Grup 1'deki hastaların yaş ortalaması 51,2±6,4 yıl ve grup 2'deki hastaların yaş ortalaması ise 44,6±6,2 yıl olarak saptandı.Her iki gruptaki hastaların başlangıç ve bitimindeki karakteristik özellikleri tablo 1 ve 2'de verilmiştir.

1. Vücut ağırlığı ve VKİ: Çalışmanın başında ortalama vücut ağırlıkları ve VKİ yönünden her iki grup arasında istatistiksel anlamlı farklılık yoktu (p=0,39).

Çalışma bitiminde Grup 1'deki hastalarda vücut ağırlıklarında ve VKİ'nde istatistiksel anlamlı azalma tespit edildi (p=0,034 ve p=0,023). Grup 2'deki hastaların ise çalışma sonundaki ortalama vücut ağırlığında ve VKİ'nde başlangıca göre anlamlı değişiklik gözlenmedi (p=0,27 ve p=0,34).

2. Kan basıncı: Çalışma başlangıcında sistolik kan basıncı (SKB) her iki grupta farksız iken (p=0,67), Grup 2'deki hastaların ortalama diyastolik kan basıncı (DKB) düzeyleri Grup 1 hastalara göre anlamlı olarak daha düşüktü (p=0,043).

Çalışma sonunda SKB ve DKB yönünden her iki grupta da başlangıçtaki ölçümlere göre istatistikel anlamlı değişiklik saptanmadı (tablo1 ve 2).

3. Açlık Plazma Glukozu (APG) ve Glikozile Hemoglobin (HbA1c) düzeyleri: Çalışmanın başında her iki grup arasında başlangıç APG düzeyleri arasında istatistiksel fark yokken (p=0,49), grup 2'de ölçülen HbA1c düzeyleri diğer gruba göre anlamlı düşük saptandı (p=0,032).

Her iki grupta da çalışma sonunda ortalama APG ve HbA1c düzeylerinde başlangıç ölçümlere göre anlamlı değişiklik tespit edilmedi (Tablo 1 ve 2).

4. Adiponektin: Çalışma başlangıcında ortalama adiponektin düzeyleri açısından her iki grup arasında istatistiksel fark yoktu (p=0,38). Çalışma sonu her iki grubun adiponektin düzeylerinde çalışma başlangıcına göre anlamlı bir değişiklik saptanmadı (p=0,27 ve p=0,087).

Tablo 1. Grup 1'deki (önceden losartan başlanıp telmisartana geçilen grup) hastaların çalışma başlangıcında ve bitimindeki karakteristik özellikleri ve çalışma başlangıç ve bitimi arasındaki değişim

Parametre	Çalışma Başlangıcı	Çalışma Sonu	P değeri*
Vücut Ağırlığı (kg)	91,7±17,4	90,71±16,53	0,034
VKİ (kg/m^2)	33,41±5,30	33,1±5,04	0,023
SKB (mm/Hg)	124±15	125,1±13,25	0,67
DKB (mm/Hg)	80±3,0	77± 8,7	0,28
Açlık plazma glukozu (mg/dl)	129,4±46,1	127,8±27,69	0,12
Açlık insülini (ulU/ml)	16,5±9,6	14,86±10,69	0,072
HOMA-IR	5,1±2,9	4,62±3,16	0,091
HbA1C (%)	7,1±1,1	7,06±0,83	0,37
Adiponektin (mcg/ml)	7,4±2,2	8,44±3,41	0,27
M değeri	3,1±1,3	4,37±2,54	0,16

* p değeri için istatistiki anlamlılık sınırı <0,05 olarak belirlenmiştir.

5. İnsülin, HOMA-IR, ve M değeri: Her iki grupta da çalışma başlangıcında açlık plazma insülini, HOMA-IR ve HECT ile hesaplanan M değerleri açısından anlamlı istatistiksel fark yoktu (sırasıyla p=0,072,p=0,39 ve p=0,48).

Çalışma bitiminde Grup1'deki hastaların ortalama açlık plazma insülin düzeyleri , HOMA-IR ve HECT ile hesaplanan M değerlerinde başlangıca göre anlamlı bir değişiklik bulunamadı (Tablo 1).

Grup 2'deki hastaların ise açlık insülin düzeyi ve HOMA-IR değerlerinde başlangıca göre hafif ancak istatistiksel olarak anlamlı bulunmayan bir azalma mevcuttu (Tablo 2). Buna karşın bu hastaların HECT sonrası hesaplanan M değerlerinde başlangıca göre istatistiksel anlamlı bir artış olduğu belirlendi (p=0,028).

6.Serum kreatinin ve potasyum düzeyleri: Takip süresince çalışmaya alınan hastaların hiçbirinde tedavi değişikliği yaptıracak nitelikte serum kreatinin ya da potasyum düzeyi yükselmesi saptanmadı .

Tartışma

Çalışmamızda telmisartandan losartana geçilen grupta (Grup 2), losartandan telmisartana geçilen gruba (Grup1) göre HECT ile belirlenen insülin duyarlığında daha belirgin düzelme saptadık. Buna karşın telmisartana geçilen grupta diğer gruba kıyasla vücut ağırlığında başlangıca göre anlamlı azalma tespit ettik. Her iki grupta da kan basıncı, açlık plazma glukozu, bazal insülin seviyeleri, HOMA-IR değerleri ve adiponektin düzeyleri arasında farklılık bulamadık.

Hem telmisartan hem de losartanın insülin duyarlığını arttırdığı, diyabet oluşumunu azalttığı ve diyabetik hastalarda açlık plazma glukozu ile HbA1C düzeylerini düşürdüğü çeşitli deneysel ve klinik çalışmalarla gösterilmiştir (18,22-25). Bu iki ARB'nin insülin direnci ve glukoz metabolizması üzerine olan olumlu etkileri RAS blokajına bağlanmış, telmisartanda ek olarak var olan parsiyel PPAR-gamma agonistik özelliğinin de RAS blokajından bağımsız olarak insülin duyarlığındaki artışa katkıda bulunduğu bildirilmiştir (17). Telmisartan, terapötik dozlara uyan plazma konsantrasyonlarında PPAR-gamma uyarıcı etkisi olan tek ARB'dir. Losartan ve diğer ARB'lerin terapotik konsantrasyonlarda PPAR-gamma aktivitesi gözlemlenmemiştir (17,18). Çalışmalarda telmisartanla, sentetik PPAR-gamma agonisti olan pioglitazon arasında önemli yapısal benzerlikler bulunmuş ve telmisartanın, PPAR-gamma sentetik ligandı gibi davrandığı düşünülmüştür (18). Ancak yapılan moleküler çalışmalar, telmisartanın ful PPAR-gamma agonistler ile aynı ligand bağlayıcı bölgeye bağlanmasına rağmen bunlara oranla %70-75 daha az PPAR-gamma aktivasyonu yaptığını göstermiştir (18). Ayrıca telmisartanın enerji alımından bağımsız olarak diyete bağlı kilo artışını zayıflattığı gösterilmiştir (18,26). Bu durum, telmisartanın adiposit diferansiyasyonu ve adipogenezin zayıf bir uyaranı olmasından kaynaklanmaktadır. (18). Telmisartanın, PPAR-gamma bağımlı lipolitik yolakları aktive ettiği dokularda yağ asidi katabolizmasını arttırdığı gösterilmiştir (27). Temisartanın vücut ağırlığı üzerine olan bu olumlu etkisi Losartanla gösterilememiş, bu nedenle bu etkinin RAS inhibisyonundan bağımsız olduğu bildirilmiştir (28). Literatürde metabolik etkinlik açısından telmisartan ve losartanın karşılaştırıldığı üç deneysel ve klinik çalışma mevcuttur. Benson ve arkadaşlarının çalışmalarında yüksek karbonhidrat diyetine alınan ratlarda 5 haftalık tedavinin sonunda telmisartan grubunda serum glukoz, insülin ve trigliserid düzeylerinin losartan ve kontrol grubuna göre belirgin düştüğünü gözlemlemişlerdir. Ayrıca bu çalışmada telmisartanın ratların vücut ağırlığında, losartan ve kontrol grubuna göre %10'luk bir azalma yaptığını tespit emişlerdir(18). Vitale ve arkadaşlarının yaptıkları çalışmada ise yeni tanı konmuş hipertansiyonu ve metabolik sendromu olan hastalarda telmisartanla açlık glukoz, insülin ve HOMA skorlarının losartana göre belirgin düştüğünü saptamışlardır(29). Bahadır ve arkadaşlarının çalışmasında ise metabolik sendromu olan hipertansif hastalarda HOMA-IR ile hesaplanan insülin direnci üzerine telmisartanın ve losartanın birbirinden farksız ve nötral etkide oldukları raporlanmıştır (30). Çalışmamız, bahsedilen karşılaştırma çalışmalarından ilginç olarak farklı sonuçlanmıştır.Bu durumun bir kaç sebebi olabilir. Öncelikle çalışmalarda kullanılan denekler diyabetik değildi ve ayrıca yorumlar yalnızca insülin ve glukoz düzeylerine göre ve bunlara dayanarak belirlenen HOMA-IR hesaplamalarıyla yapılmıştı. Normal fizyolojide insülinin pulsatil bir salgı kinetiğine sahip olması (31) ve rutin ölçüm yöntemlerinde insülin-proinsülinin birlikte ölçülmesi (32) nedeniyle insülin duyarlılığının belirlenmesinde yanılmalara neden olabileceğinden

Tablo 2. Grup 2'deki (önceden telmisartan başlanıp losartana geçilen grup) hastaların çalışma başlangıcında ve bitimindeki karakteristik özellikleri ve çalışma başlangıç ve bitimi arasındaki değişim

Parametre	Çalışma başlangıcı	Çalışma sonu	P değeri*
Vücut Ağırlığı (kg)	89,8±11,7	90,6±13,7	0,27
VKİ (kg/m^2)	31,57±4,29	31,84±4,86	0,34
SKB (mm/Hg)	124±15	124,1±8,85	0,62
DKB (mm/Hg)	74±6,0	79,9±7,7	0,87
Açlık plazma glukozu (mg/dl)	130,9±31,7	121,75±25,74	0,29
Açlık insülini (ulU/ml)	13,2±7,1	10,81±5,54	0,37
HOMA-IR	4,2±2,6	3,42±2,32	0,63
HbA1C (%)	5,9±0,5	6,27±0,95	0,35
Adiponektin (mcg/ml)	7,7±2,8	7,84±2,86	0,087
M değeri	2,3±1,1	4,26±1,956	0,028

*p değeri için istatistiki anlamlılık sınırı <0,05 olarak belirlenmiştir.

çok kullanışlı görünmemektedir. Bu çalışmadan farklı olarak bizim çalışmamızda diyabetik hasta popülasyonu kullanıldı ve insülin duyarlığı halen tüm dünyada altın standart olarak kabul edilen HECT ile belirlendi (21). Bu nedenle sonuçları önceki çalışmalardan farklı çıkmakla beraber güvenilir bir çalışma durumundadır. Çalışmamızda, Bahadır ve arkadaşlarının sonuçları ile (30) benzer olarak her iki grup hastada da çalışma sonu açlık plazma insülin düzeyi, açlık plazma glukozu ve hesaplanan HOMA-IR değerlerinde çalışmanın başlangıcına göre anlamlı bir değişim olmamıştır. Ancak, losartana geçilen grupta HECT ile hesaplanan insülin duyarlığında anlamlı düzelme saptanmıştır. Hassasiyeti ve güvenilirliği tartışılmaz olan HECT sonuçları ile HOMA-IR hesaplamasından elde olunan sonuçların farklı çıkması özellikle kısıtlı sayıda hastada yapılan çalışmalarda seçilecek yöntemin önemini gözler önüne sermektedir.

Çalışmamızda her iki ilacın adiposit diferansiyasyonu ve adipogenez üzerine olan etkilerini karşılaştırabilmek amacıyla serum adiponektin konsantrastonlarını ölçtük. Gruplar arasında çalışma başında adiponektin düzeyleri açısından anlamlı bir fark yoktu. Yine çalışma bitiminde her iki grupta da başlangıca göre anlamlı bir değişiklik tespit etmedik. Literatürde losartan ve telmisartanın adiponektin düzeylerine karşılaştırmalı etkilerini inceleyen tek çalışmanın Erbe ve arkadaşlarının çalışması olduğunu tespit ettik ki bu çalışmada da bizim bulgularımıza benzer şekilde her iki ilaç da adiponektin seviyeleri üzerine belirgin etkinlik göstermiyordu (17). Yapılan çalışmalarda AT1R blokajı ile adiposit diferansiyasyonunda ve adiponektin sentezinde artış meydana geldiği deneysel olarak gösterilmiştir(12). Bu yaklaşım iki ilaç arasında adiponektin düzeyleri üzerine etki açısından fark olmamasının nedenini açıklayabilir. Çalışma süresince hastaların beslenme ve fizik aktivite alışkanlıkları ile almış oldukları antidiyabetik tedavide bir değişiklik yapılmaması, çalışmanın sonucuna etkili olabilecek karmaşaları ortadan kaldırmasına rağmen telmisartana geçilen grupta başlangıca göre istatiksiksel anlamlı kilo kaybı ve VKİ azalması gözlenmiştir (p=0,034 ve p=0,023). Bu sonuç literatürle uyumludur (18,26). Telmisartanın yapmış olduğu ağırlık azalmasının losartanla gösterilememesi bu durumun RAS inhibisyonundan bağımsız olduğunu düşündürmektedir (18). Kilo kaybının insülin duyarlığını arttırdığı bilinmektedir. Losartanın, telmisartanın aksine kilo kaybı yapmadan insülin direnci üzerine daha fazla etkili olması, losartanın insülin duyarlığı üzerine telmisartandan daha etkili bir ajan olduğunu düşündürmektedir. Bu durumun bize göre açıklaması: RAS inhibisyonunun, parsiyel PPAR-gamma aktivitesine göre insülin duyarlılığı üzerinde daha belirleyici olabilmesi ve losartanın doku düzeyinde telmisartandan daha potent RAS inhibitörü olabilmesidir. Bu hipotezin geçerli olabilmesi için in-vitro deneysel karşılaştırmalı çalışmalara ihtiyaç vardır.

Sonuç olarak çalışmamızda; metabolik kontrollü tip 2 diyabetik hastalarda, kısmi PPAR-gamma agonistik etki gösteren bir ARB olan telmisartanın, PPAR-gamma üzerine etkisi bulunmayan losartana göre vücut ağırlığı üzerine olumlu etkileri olmasına karşın, losartanın insülin direncini telmisartandan daha fazla düşürdüğünü tespit ettik. Losartanın tip 2 diyabetik hipertansif olgularda metabolik olumlu etkileri de göz önüne alınarak kullanılabilecek bir antihipertansif ajan olduğunu düşünüyoruz.

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Contributors to Secondary Osteoporosis in Patients Referred for Treatment with Teriparatide

Teriparatid Tedavisi için Refere Edilen Hastalarda Sekonder Osteoporoza Katkıda Bulunan Faktörler

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Abstract

Purpose: Teriparatide is an anabolic agent belonging to a new class of antiosteoporosis drugs. The Turkish Social Security Institution covers teriparatide for patients with osteoporosis who have 2 osteoporotic fractures, are older than 65 years, and have a T-score of less than -4. We evaluated possible secondary contributors to osteoporosis in patients referred for treatment with this agent.

Material and Method: All patients referred to our center for teriparatide treatment over 2 year were evaluated for clinical risk factors for osteoporosis, medical history, and medications.

Results: Sixty-eight patients (63 women and 5 men, mean age:71.3±9.4 (50-89 years) were referred. Twenty-nine patients (42.6%) had received osteoporosis therapy before referral, consisting of bisphosphonate (n=20), strontium ranelate (n=6), calcitonin (n=2), or calcitonin and bisphosphonate (n=1). The mean duration of the previous therapy was 46.4± 38.5 (3-120 months). In all, 50 of the 68 patients (73.5%), including all of the men, had a contributor to secondary osteoporosis. Vitamin D deficiency was the most frequent contributor in 34 patients (52.3%). Other common contributors were hyperthyroidism and hypogonadism. Only 3 of 18 patients with hyperthyroidism and none of the patients with hypogonadism had been diagnosed previously, and 16 of the 24 patients receiving vitamin D supplementation still had deficiency of this vitamin.

Discussion: Most of our patients had a contributor to secondary osteoporosis, which often had not been identified previously. Identifying and correcting such disorders might improve the treatment of osteoporosis and reduce the risk of subsequent fracture. *Turk Jem 2013; 17: 98-101*

Key words: Secondary osteoporosis, fracture, teriparatide

Özet

Amaç: Ülkemizde Teriparatid etken maddeli osteoporoz ilacı yalnızca endokrinologlar tarafından yazılabilmektedir. Teriparatid, sosyal güvenlik kurumu tarafından; '65 yaşını doldurmuş, T skoru -4 veya daha düşük olan, 2 veya daha fazla osteoporoza bağlı kırığı olan hastaya' ödenmektedir. Bu çalışmada amaç, Teriparatid tedavisi için refere edilen hastalarda sekonder osteoporoz nedenlerini ortaya koymaktı.

Gereç ve Yöntem: 2010-2012 yıllarında, Teriparatid tedavisi için refere edilen 63 kadın, 5 erkek hasta çalışmaya dahil edildi. Bu hastalarda osteoporoz risk faktörleri ve sekonder osteoporoz nedenleri ayrıntılı olarak değerlendirildi.

Bulgular: Ortalama yaşları 71,3±9,4 (50-89 yaş) idi. Hastaların hepsinde osteoporotik kırık mevcuttu. Hastaların 39'u (%57,4) daha önceden osteoporoza yönelik herhangi bir tedavi almazken, 29'u (%42,6); daha önceden bisfosfonat (20), stronsiyum ranelat (6), kalsitonin (2), bisfosfonat ve kalsitonin (1) tedavisi almışlardı. Tedavi alanlarda ortalama tedavi süresi 46,4±38,5 (3-120) aydı. Hastaların 28'inde (%26,5) sekonder osteoporoza yönelik etyolojik bir neden tespit edilmedi. Erkek hastaların (n=5) hepsinde sekonder bir neden vardı. Vitamin D eksikliği en sık nedendi (n=34; %52,3). Diğer en sık görülen nedenler tiroroksikoz ile hipogonadizmdi. Tirotoksikoz tanısı alan 18 hastadan sadece 3'ü daha önceden tanı almıştı. D vitamini almakta olan 24 hastanın 16'sında hala D vitamini düzeyleri düşüktü.

Tartışma: Ciddi, kırıklı osteoporozla başvuran her hastada tedaviye başlanmadan önce muhakkak sekonder nedenler araştırılmalıdır. *Turk Jem 2013; 17: 98-101*

Anahtar kelimeler: Sekonder osteoporoz, kırık, teriparatid

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Introduction

Osteoporosis is a systemic skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone tissue, which leads to increased bone fragility and a consequent increase in fracture risk (1). In addition to the current definition of osteoporosis according to the World Health Organization (WHO) - a T-score of ≤-2.5 -, many other risk factors are associated with fracture risk (2). These include clinical risk factors, the risk of falling, prevalent morphometric vertebral fractures, and secondary osteoporosis (3-6). After a clinical vertebral or non-vertebral fracture, patients are at increased risk for subsequent fractures. Patients presenting with fractures should therefore be screened to exclude diseases that can mimic osteoporosis, and possible causes of osteoporosis and contributory factors should be investigated (1-5).

Prevention and treatment of osteoporosis consists of nondrug, drug, and/or hormonal treatment. Diet, exercise, and cessation of smoking are the three main components of the nondrug treatment of osteoporosis. Available antiresorptive drug therapies include bisphosphonates and raloxifene, a selective estrogen receptor modulator. Strontium ranelate has both anabolic and antiresorptive properties. Intermittent administration of recombinant human parathyroid hormone has been shown to stimulate bone formation. Teriparatide is an anabolic agent belonging to new class of antiosteoporosis drugs (7). In contrast to antiresorptive agents, these drugs stimulate bone formation, activating bone remodeling (7). Parathyroid hormone 1-34, teriparatide, is available in the United States and Europe for the treatment of severe osteoporosis in both men and women at a dose of 20 µg/day. The Turkish Social Security Institution (SGK) covers teriparatide therapy for patients with osteoporosis who have 2 osteoporotic fractures, who are older than 65 years, and who have a T-score of less than -4. Only endocrinologists can prescribe this drug in Turkey; other specialists caring for patients with osteoporosis must refer their patients to endocrinologists for teriparatide treatment.

Given the importance of identifying secondary contributors of osteoporosis in patients with fracture, and the advent of this new treatment for osteoporotic patients with fractures, we wish to describe the characteristics of patients referred to our clinic for osteoporosis treatment with teriparatide.

Materials and Methods

This prospectively planned, descriptive study was conducted in the outpatient clinic of the department of endocrinology and metabolism at Trabzon Kanuni Training and Research Hospital in Trabzon, Turkey. All patients who were referred for teriparatide treatment were recruited for the study.

Patients were evaluated for the clinical risk factors for osteoporosis, medical history, and medication. We recorded age, age at menopause, current or previous calcium and vitamin D supplementation, current or previous antiresorptive therapy, history of cigarette smoking, and alcohol intake. Physical examination was performed, and body weight and height were measured.

All patients underwent dual x-ray absorptiometry and plain, 2-sided thoracolumbar radiography. Laboratory examinations performed for all patients were as follows: kidney, liver, and thyroid function tests (blood urea nitrogen, creatinine, sodium, potassium, alanine aminotransferase, free tetraiodothyronine, thyroid-stimulating hormone), complete blood count, follicle-stimulating hormone, estradiol for women and total testosterone for men, calcium, phosphate, serum 25(OH) vitamin D, parathyroid hormone, and alkaline phosphatase. Additional tests were performed when needed.

We performed overnight dexamethasone suppression tests for suspected cases of Cushing's syndrome. In patients with hypogonadism, magnetic resonance imaging of the hypophysis or/and ultrasonography of gonads (ovarian, scrotal) was performed when needed. Patients with primary hyperparathyroidism underwent 24-hour urinary calcium collection. Glomerular filtration rate was calculated when needed. Vitamin D deficiency was defined as a level of <20 ng/mL.

We used SPSS software (version 13.0; SPSS Inc., Chicago, IL) for statistical analyses. Only descriptive statistics were calculated.

Results

Between December 2010 and April 2012, 63 women and 5 men were referred to our clinic for treatment with teriparatide. Fifty-two patients (76.5%) were referred by physiatrists, 14 (20.6%) by orthopedists, and 2 (2.9%) by internists. All patients had 2 or more fractures, and 28 (41.2%) had at least 1 systemic disease (Table 1).

In all, 29 (42.6%) patients had received previous treatment for osteoporosis: 20 (29.4%) had received bisphosphonates, 6 (8.8%) had received strontium ranelate, 2 (2.9%) had received calcitonin, and 1 (1.5%) had received calcitonin and bisphosphonate (Table 1). Of note, 116 of the 24 (66.7%) 24 patients receiving vitamin D supplementation (combined with calcium) still had vitamin D deficiency.

In all, 50 of the 68 patients (73.5%) were found to have 1 or more contributors to secondary osteoporosis (Table 2), many of which had been undetected until referral. Among the 18 patients found to have hyperthyroidism, only 3 already had a diagnosis of hyperthyroidism and were taking the antithyroid drug propylthiouracil; we diagnosed the remaining 15 cases. The diagnoses of hypogonadism (n=5) and hyperparathyroidism (n=1) also were newly established. Nine patients with hyperthyroidism had been taking antiresorptive treatment; only 3 of them had been diagnosed previously. One of the male patients with hypogonadism also had been taking antiresorptive therapy.

Discussion

In this study, nearly three quarters of our osteoporotic patients with fracture had a secondary contributor to osteoporosis. In many cases, these contributors had not been previously identified.

In a study of 173 otherwise healthy women with osteoporosis, Tannenbaum and colleagues (4) identified secondary contributors to osteoporosis in 55 women (32%). Contributors to secondary osteoporosis in this study included hypercalciuria (9.8%), malabsorption (8.1%), hyperparathyroidism (6.9%), vitamin D deficiency (4.1%), exogenous hyperthyroidism (2.3%), Cushing's

Table 1. Clinical and demographic characteristics of patients

	All patients (N=68)	Women (n=63)	Men (n=5)
Age, years	71.3 ± 9.4 (50-89)	72.1 ± 8.9 (50-89)	62 ± 11.8 (51-81)
Weight, kg	55.9 ± 9 (40-89)	54.8 ± 7.8 (40-82)	69.8 ± 13 (60-89)
Height, cm	151 ± 0.7 (135-175)	150 ± 0.5 (135-165)	169 ± 0.6 (160-175)
Body mass index, kg/m^2	24.2 ± 3.4 (14.7-35.5)	24.2 ± 3.4 (14.7-35.5)	24.4 ± 3.2 (22.5-29.1)
Smoking status, n (%)			
Former smoker	3 (4.4%)	2 (3.2%)	1 (20%)
Current smoking	4 (5.9%)	1 (1.6%)	3 (60%)
Never smoked	61 (89.7%)	60 (95.2%)	1 (20%)
Age at menopause	—	45.5 ± 5.1 (35-60)	—
Medication, n (%)a	28 (41.2%)	26 (41.3%)	2 (40%)
Previous therapy for osteoporosis, n (%)	29 (42.6%)	28 (44.4%)	1 (20%)
Duration of previous osteoporosis treatment, mo	46.4 ± 38.5 (3-120)	46.8 ± 39.3 (3-120)	36 (only 1 patient)
Supplemented vitamin D ± calcium, n (%)	33 (48.5%)	32 (50.8%)	1 (20%)
Calcium, mg/dL	9.4 ± 0.6 (7.8-10.8)	9.4 ± 0.6 (7.8-10.8)	9.4 ± 0.9 (8.3-10.5)
Phosphate, mg/dL	3.7 ± 0.7 (2.5-6.8)	3.7 ± 0.8 (2.5-6.8)	3.6 ± 0.4 (3.2-4)
Vitamin D, ng/dL	17.4 ± 11 (4-55)	17.5 ± 11.1 (4-55)	15.9 ± 10.9 (8.1-23.6)
Parathyroid hormone, pg/mL	70.2 ± 32.6 (14.4-170.2)	70.6 ± 32.9 (14.4-170.2)	65.6 ± 31.2 (23.2-108)
Alkaline phosphatase, U/L	176.5 ± 80 (72-438)	171.1 ± 72.2 (72-438)	225.2 ± 133.2 (103-432)
T-score			
Lumbar spine	-4.5 ± 0.6 (-6.3--2.8)	-4.6 ± 0.5 (-6.3--3.4)	-3.7 ± 0.8 (-4.3--2.8)
Femoral neck	-3.1 ± 0.9 (-5.9--0.9)	-3.1 ± 0.7 (-5.9--0.9)	-3.1 ± 0.4 (-3.5--2.7)
Total hip	-3 ± 1 (-6.5--0.7)	-3.1 ± 1.1 (-6.5--0.7)	-2.6 ± 0.7 (-3.5--1.9)

Values are mean ± SD (range) unless indicated otherwise. Normal ranges for laboratory variables are: calcium, 8.3-10.6 mg/dL; phosphate, 2.4-5.1 mg/dL; 25-OH vitamin D, >20 ng/dL; parathyroid hormone, 11.1-79.5 pg/mL; alkaline phosphatase, 70-290 U/L.

aAntihypertensives (n=14), antidepressants (n=6), oral hypoglycemic agents (n=2), inhalers for chronic obstructive pulmonary disease (n=2), antiischemic agents for coronary artery disease (n=2), vitamin B12 for pernicious anemia (n=2), L-thyroxine (n=2), propylthiouracil (n=3), diuretic for congestive heart failure (n=1), nonsteroidal antiinflammatory drugs (n=6), warfarin for mitral stenosis (n=2), proton pump inhibitor (n=1), and methotrexate and prednisolone for rheumatoid arthritis (n=1)

disease (0.6%), and hypocalciuric hypercalcemia (0.6%). The authors underlined the importance of recognizing undiagnosed causes of osteoporosis (4). Of note, the presence of clinical fracture was ignored in this study, and only postmenopausal women with osteoporosis were included.

A study from Belgium evaluated 100 consecutive patients (73 women and 27 men) older than 50 years who presented with a clinical fracture (6). Overall, 27 patients had 34 known contributors to secondary osteoporosis, but 53 new contributors were detected in 50 patients. Among the overall contributors, 77% was similar to that found in our cohort, as is the fact that most of the new contributors were vitamin D deficiency (n=42). Other common contributors in this study were renal disorders (n=14), pulmonary disease (n=5), hyperthyroidism (n=3), and diabetes mellitus (type not indicated; n=5). Although Type 1 diabetes has been associated with osteoporosis, data conflict about the relationship with Type 2 diabetes (8). We did not include diabetes as a possible contributor to secondary osteoporosis because all of our diabetic patients had Type 2 disease.

The Belgian study also detected hypogonadism in men (6), which in our study had previously gone undetected. Women with hypogonadism are usually diagnosed earlier than men with the disorder, given that menstrual irregularities can be alarming. We detected hypogonadism only while searching for possible contributors to secondary osteoporosis. However, hypogonadism is one of the best characterized risk factors for osteoporosis in men (9, 10), and the 40% incidence of the disorder in men in our study is similar to that found by Bours and colleagues (42.5%) (11). In their study, the most common contributors overall were chronic obstructive pulmonary disease (10.4%), glucocorticoid use (8.5%), rheumatoid arthritis or systemic lupus (5.2%), and premature ovarian failure (4%).

The second most frequent contributor in our study was hyperthyroidism, similar to findings from other studies (4, 6, 11). Among 18 patients with the disorder, only 3 had a diagnosis of hyperthyroidism upon admission to our clinic. Hyperthyroidism, either exogenous or endogenous, is closely associated with a loss of bone mass and increased fracture risk. When adequate treatment is established, fracture risk declines (12). A recent review has advocated evaluating patients with subclinical hyperthyroidism for osteoporosis and treating in cases of reduced bone mass (13).

Table 2. Contributors to secondary osteoporosis

Contributor, n (%)	All patients (n=68)	Women (n=63)	Men (n=5)
Vitamin D deficiency	34 (52.3%)	29 (46%)	5 (100%)
Hyperthyroidism	18 (27.7%)	16 (25.4%)	2 (40%)
Hypogonadism[a,b]	5 (7.4%)	3 (4.6%)	2 (40%)
Malnutrition (due to gastrectomy)	3 (4.4%)	3 (4.6%)	—
Chronic obstructive pulmonary disease	2 (2.9%)	2 (3.2%)	—
Primary hyperparathyroidism	1 (1.4%)	1 (1.5%)	—
Other contributor[c]	12 (17.6%)	12 (18.5%)	—
Total[d]	50 (73.5%)	45 (69.2%)	5 (100%)

[a]Patients with premature ovarian failure (n=3) are included.

[b]Among men with hypogonadism, 1 had primary hypogonadism and 1 had panhypopituitarism due to a hypophysis macroadenoma.

[c]Warfarin use (n=2), glucocorticoid use (n=1), selective serotonin reuptake inhibitor use (n=6), chronic proton pump inhibitor use (n=1), rheumatoid arthritis (n=1), chronic renal failure (n=1).

[d]Some patients had more than 1 contributor. The total number shows the number of patients with any (1 or more) contributor.

Primary hyperparathyroidism, chronic renal failure, chronic obstructive pulmonary disease, rheumatoid arthritis, and malnutrition are other well-known contributors to secondary osteoporosis (14), as is the use of warfarin, glucocorticoids, anticonvulsant drugs, heparin, gonadotropin-releasing hormone analogs, and cyclosporine (15). Data continue to emerge regarding a possible risk of secondary osteoporosis with the use of selective serotonin reuptake inhibitors and long-term proton pump inhibitor therapy (16,17), leading us to include such patients in our analysis.

In summary, most of the patients in our observational cohort had a contributor to secondary osteoporosis, many of which had previously gone undetected. Identifying and correcting these disorders is possible and might improve the treatment of osteoporosis and reduce the risk of subsequent fractures. We suggest that clinicians take a detailed history from patients who have severe osteoporosis and clinical fracture to screen for contributors to secondary osteoporosis.

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Original Article *Özgün Araştırma*

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Plasma Osteoprotegerin Levels Before and After Treatment of Thyroid Dysfunctions

Tiroid Disfonksiyonlarında Tedavi Öncesi ve Sonrası Plazma Osteoprotegerin Seviyeleri

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Abstract

Purpose: Osteoprotegerin (OPG) is a soluble decoy receptor for the receptor activator of nuclear factor kappaB ligand, thereby inhibiting bone resorption. In this study, we aimed to evaluate plasma OPG levels in patients with thyroid dysfunctions and determine whether its levels change after restoration of euthyroidism.

Material and Method: OPG levels were studied at the time of diagnosis and after the restoration of euthyroidism at least for 8 weeks in patients diagnosed with overt thyrotoxicosis and hypothyroidism.

Results: Seventeen hypothyroid, 17 thyrotoxic patients and 17 age-, sex- and body mass index-matched healthy controls were analyzed. Mean basal plasma OPG levels were 5.42±2.66, 5.04±1.62 and 5.24±0.93 pmol/l in thyrotoxic, hypothyroid and healthy controls, respectively (p=0.844). After restoration of euthyroidism, OPG was 5.52±2.37 pmol/l in thyrotoxic and 4.33±1.37 pmol/l in hypothyroid patients, indicating no significant difference compared to baseline values (p=0.846 and p=0.109, respectively). We also did not observe any correlation between basal OPG levels and basal thyrotropin and thyroid hormone levels.

Discussion: Thyroid dysfunctions seem to affect bone functions by mechanisms other than OPG, however, more clinical studies with larger sample sizes are needed to clarify the underlying mechanisms of thyroid dysfunction-related changes in bone metabolism. *Turk Jem 2013; 17: 102-7*

Key words: Osteoprotegerin, hypothyroidism, thyrotoxicosis

Özet

Amaç: Osteoprotegerin (OPG), reseptör aktivatör nükleer faktör kappa B ligand için yalancı reseptör görevi görür ve bu şekilde kemik yıkımını inhibe eder. Bu çalışmanın amacı tiroid disfonksiyonu olan hastalarda plazma OPG seviyelerinin değerlendirilmesi ve ötiroidizm sağlandıktan sonra OPG seviyesinde değişiklik olup olmadığının belirlenmesidir.

Gereç ve Yöntem: Aşikar hipotiroidi ve tirotoksikoz tanısı alan hastalarda tanı anında ve en az 8 hafta ötiroidizm sağlandıktan sonra OPG seviyeleri ölçüldü.

Bulgular: Çalışmaya 17 hipotiroid, 17 tirotoksik hasta ve 17 yaş, cinsiyet ve vücut kitle indeksi açısından eşleştirilmiş sağlıklı kontrol grubu alındı. Ortalama bazal plazma OPG seviyeleri tirotoksik hastalarda 5,42±2,66 pmol/l, hipotiroid hastalarda 5,04±1,62 pmol/l ve kontrol grubunda 5,24±0,93 pmol/l bulundu (p=0,844). Ötiroidizm sağlandıktan sonra ortalama OPG seviyeleri tirotoksik hastalarda 5,52±2,37 pmol/l, hipotiroid hastalarda 4,33±1,37 pmol/l olarak bulundu. Her iki grupta da tedavi öncesi ve sonrası OPG seviyelerinde anlamlı değişiklik olmadı (tirotoksik hastalar için p=0,846 ve hipotiroid hastalar için p=0,109). Bazal OPG ile bazal tirotropin ve tiroid hormonları arasında anlamlı korelasyon saptanmadı.

Tartışma: Bu çalışmanın sonuçlarına gore tiroid fonksiyon bozukluklarında görülen kemik metabolizma değişikliklerinde OPG rol almamaktadır. Tiroid disfonksiyonlarının kemik üzerine etkilerinin hangi mekanizmalarla oluştuğunun belirlenmesi için daha fazla sayıda hastanın alındığı klinik çalışmalara ihtiyaç vardır. *Turk Jem 2013; 17: 102-7*

Anahtar kelimeler: Osteoprotegerin, hipotiroidi, tirotoksikoz

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Introduction

Bone remodeling is under regulation of various hormones, cytokines, transcription factors and intracellular signaling proteins. Receptor activator of nuclear factor kappaB ligand (RANKL) is a hematopoietic growth factor that plays a role in osteoclastogenesis via activating receptor activator of nuclear factor kappaB (RANK) in osteoclasts. Osteoprotegerin (OPG) protects the skeleton from excessive bone resorption by acting as a decoy receptor for RANKL and preventing it from binding to its receptor RANK (1,2). It is expressed in many tissues apart from osteoblasts, including heart, kidney, liver, spleen and bone marrow. In general, up-regulation of RANKL is associated with down-regulation of OPG, such that the ratio of RANKL to OPG changes in favor of osteoclastogenesis. OPG also appears to protect large blood vessels from medial calcification, based on the observation of renal and aortic calcification occurring in OPG knockout mice (3). There are also studies showing an association between high plasma levels of OPG and cardiovascular diseases, diabetes and chronic renal failure (4,5).

It is believed that high circulating thyroid hormones induce a high turnover state in bone with increased activity of osteoblasts and osteoclasts. The osteoclast stimulation, however, predominates and structural integrity of the skeleton decreases in hyperthyroidism. General belief is that reduction in bone mineral density in overt thyrotoxicosis is due to the effect of high circulating levels of thyroid hormones, not the effect of suppressed thyrotropin (TSH) levels. However, in a recent study, Abe et al. demonstrated a critical role for TSH in maintenance of bone mass independently from circulating thyroid hormones (6). In their study, TSH receptor (-/-) knockout mice were shown to have high bone turnover osteoporosis, revealing that TSH is a negative regulator of bone turnover. They speculated that the skeletal loss that occurs in hyperthyroidism is due to low TSH levels, not as opposed solely to high thyroid hormones. Patients with hypothyroidism may actually have a higher than normal bone mass prior to thyroxine replacement. Data from cell and organ cultures have identified the role of T3 in the production of cytokines, growth factors and markers of bone turnover (7). Therefore, altered T3 is thought to be the cause of decreased bone turnover in hypothyroidism.

Plasma OPG levels in patients either with hyperthyroidism or with hypothyroidism, separately, were investigated in a few studies reporting inconsistent results. High basal OPG levels were observed with both of these thyroid dysfunctions and lower OPG levels were shown with treatment of both conditions (8-12). However, there are no publications investigating OPG levels in overt hypo and hyperthyroidism in the same study in the literature. In this study, our aim was to evaluate OPG levels in overt thyrotoxicosis and hypothyroidism before and after restoration of euthyroidism in a descriptive matched case-control study.

Materials and Methods

Patients diagnosed with overt thyrotoxicosis and hypothyroidism in our clinic were screened for the study. All patients and control subjects gave informed consent and local ethics committee approval was obtained in accordance with the ethical standards of the Helsinki Declaration. Inclusion criteria were as follows: ≥18 years old, newly diagnosed overt hypothyroidism or thyrotoxicosis without medication, body mass index (BMI)<30 kg/m^2. Patients with a previous history of bone fracture, taking medication for osteopenia or osteoporosis (bisphosphonates, vitamin D, calcium supplementation, etc.), using oral contraceptives or estrogen hormone replacement therapy, patients with known diabetes and/or using antidiabetic medications including thiazolidinediones and patients with organ failure or malignancy were excluded. Patients with central hypothyroidism were excluded as well. Patients were matched with healthy controls according to age, sex and BMI. All female patients and controls were premenopausal.

Complete physical examination was performed by the same physician in all subjects. As an open study, laboratory parameters of TSH, free T3 (FT3), free T4 (FT4), anti-thyroid peroxidase antibody (anti-TPO), and antithyroglobulin antibody (anti-Tg) levels were checked at the time of diagnosis and after the restoration of euthyroidism with appropriate therapy provided at least for 8 weeks. Healthy control subjects were tested once. Blood samples were taken after an overnight fasting from an antecubital vein between 08.30 and 09.30 am at resting position. Serum concentrations of TSH, FT3 and FT4 were measured with electrochemiluminescence immunoassay. Anti-TPO and Anti-Tg were measured using radioimmunoassay and chemiluminescent sequential immunometric assay, respectively. Plasma samples for OPG were obtained also at the time of diagnosis and after the restoration of euthyroidism at least for 8 weeks in patients and for once in control group and stored at -80 °C. After collection of all samples, they were thawed for once and studied in the same day. The time from freezing of the first sample to thawing of all the samples was approximately 10 months. OPG levels were determined by enzyme immunoassay using an ELISA kit produced by BioVendor® Research and Diagnostic Products. Presented reference range was 4.1±2.3 pmol/l. Limit of detection, defined as concentration of analyte giving absorbance higher than mean absorbance of blank plus 3 standard deviation was calculated from the real human OPG values in wells and was 0.13 pmol/l. Intraassay and interassay coefficient of variations were 2.4%-7.0% and 3.4%-7.4%, respectively. The antibodies used in this method were specific for human OPG with no detectable cross-reactivity to human RANKL.

Overt thyrotoxicosis and hypothyroidism were diagnosed in compliance with the American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the evaluation and treatment of hyperthyroidism and hypothyroidism (13). Normal values for TSH were 0.27-4.2 mIU/ml, for FT3 3.1-6.8 pmol/l, for FT4 12-22 pmol/l, for Anti-TPO 0-30 IU/ml and for Anti-Tg 0-20 IU/ml. Where needed, thyroid ultrasonography, scintigraphy and radioactive iodine uptakes were performed to define the underlying cause and to plan the management. Patients with thyrotoxicosis were administered propylthiouracil (dosage tapered down from 300 mg/day) and/or propranolol (40-120 mg/day for 2 weeks) according to underlying pathology to maintain thyroid functions within normal limits. Hypothyroid patients were administered L-thyroxine and initial dosage was

chosen considering age and cardiovascular risk. Thyroid function tests were re-evaluated in thyrotoxic and hypothyroid patients in every 3-4 weeks.

All data were analyzed with SPSS (Statistical Packing of Social Science for Windows) 9.05. The Kolmogorov-Smirnov test was used to find out whether parameters were normally distributed or not in each group. All parameters except basal TSH and Anti-TPO were normally distributed in patients with hypothyroidism and thyrotoxicosis. In control group, anti-TPO and anti-Tg were not normally distributed, while other parameters were normally distributed. Comparison of means between 3 groups was made using the One-way ANOVA for parametric variables, and the Kruskall-Wallis test for nonparametric variables. The Chi-square test was used to investigate the difference between the groups regarding the categorical variables. For paired data, statistical analyses before and after therapy were carried out with the paired student t-test for parametric variables and the Wilcoxon test for nonparametric variables. Pearson's correlation and Spearman's correlation analysis were performed in order to document possible associations between parametric and nonparametric variables, respectively.

Results

Twenty patients with overt hypothyroidism and 23 patients with overt thyrotoxicosis were included in the study. Data of 17 hypothyroid, 17 thyrotoxic patients and 17 control cases were analyzed, because 3 hypothyroid and 6 thyrotoxic patients were not euthyroid at the end of the study. Mean age, sex distribution and anthropometric measures were similar in all groups. Baseline characteristics of patients and control group are shown in Table 1.

Underlying causes of hypothyroidism were Hashimoto's thyroiditis in 14 patients, postoperative hypothyroidism in 2 and postradioactive iodine hypothyroidism in 1 patient. Thyrotoxicosis was due to Graves' disease in 14 patients, subacute thyroiditis in 2 patients and autonomous thyroid nodule in 1 patient. Anti-TPO and anti-Tg autoantibodes were measured in all patients and controls. Anti-TPO was positive in 15 patients with hypothyroidism, 8 patients with thyrotoxicosis and in 1 subject in the control group. Anti-Tg was positive in 13, 7 and 1 patients with hypothyroidism, thyrotoxicosis and control group, respectively (Table 1). There was no significant correlation between basal OPG and anti-TPO and anti-TG levels (rs=-0,102, p=0.477 for anti-TPO and rs=-0,214, p=0.131 for anti-TG). Table 2 compares the clinical and biochemical characteristics of the patients before and after treatment of thyroid dysfunctions. In both groups, BMI did not change with restoration of euthyroidism.

Plasma OPG levels were (mean±stdev) 5.42±2.66, 5.04±1.62 and 5.24±0.93 pmol/l in thyrotoxic, hypothyroid and healthy controls, respectively. Although, baseline OPG levels were lowest in patients with hypothyroidism and highest in patients with thyrotoxicosis, no statistically significant difference among study groups and controls were detected (Table 3). Mean OPG levels after restoration of euthyroidism in thyrotoxic and hypothyroid patients were (mean±stdev) 5.52±2.37 and 4.34±1.37 pmol/l, respectively. OPG seemed to increase in thyrotoxic and decrease in hypothyroid patients with treatment, however, no significant alteration was detected compared to baseline state in both groups (p=0.846

Table 1. Baseline characteristics of patients and controls

	Hypothyroidism (n=17)	Thyrotoxicosis (n=17)	Controls (n=17)	p
Age	41.1±11.8	37.6±11.0	38.2±10.2	0.613
BMI (kg/m^2)	25.4±3.1	23.4±3.7	25.6±2.5	0.093
TSH (mIU/ml)				
Mean	85.15±22.77	0.01±1.11	1.58±0.16	<0.001
Median	101 (26.84-101)	0.005 (0.005-0.041)	1.64 (0.44-269)	<0.001
FT3 (pmol/l)				
Mean	2.30±0.93	18.35±12.05	4.94±0.12	<0.001
Median	2.90 (0.537-3.090)	11.85 (6.90-44.0)	(4.94-4.1-5.65)	<0.001
FT4 (pmol/l)				
Mean	5.48±2.51	50.08±29.50	15.75±0.53	<0.001
Median	5.64 (1.43- 11.08)	35.02 (23.1-100.0)	16.1 (12.1-19.0)	<0.001
Anti-TPO (IU/ml)				
Mean	2287.23±1081.21	762.91±1085.48	19.29±46.91	<0.001
Median	3000 (7-3000)	76 (0-3000)	7.6 (3.6-201)	0.002
Anti-Tg (IU/ml)				
Mean	683.12±980.68	173.42±336.43	24.18±87.6	0.006
Median	249 (0-3950)	43 (0-1300)	0 (0-363)	0.011
Anti-TPO positivity (n)	15	8	1	<0.001
Anti-Tg positivity (n)	13	7	1	<0.001

BMI: Body mass index, TSH: Thyrotropin, FT3: Free T3, FT4: Free T4, Anti-TPO: Anti-thyroid peroxidase antibody, anti-Tg: Antithyroglobulin antibody, NA: Not applicable

and p=0.109, respectively) (Table 3). The mean change in OPG in hypothyroid patients was -0.71±1.71 pmol/l, while the mean change in thyrotoxic patients was +0.10±2.17 pmol/l (p=0.234).

Analyzing all groups together, there was no correlation between basal OPG levels and basal TSH and thyroid hormone levels (rs=-0.002 and p=0.990 for TSH, rs=0.057 and p=0.692 for fT3, rs=0.030 and p=0.832 for fT4). Changes in TSH, FT3 and FT4 levels (before-after the restoration of euthyroidism) showed no correlation with changes in OPG levels (Table 4).

Discussion

In the present study, we found no significant difference in basal OPG levels in both hypothyroid and thyrotoxic patients compared with euthyroid healthy subjects. Additionally, achievement of euthyroidism in both groups did not result with any change in OPG levels. In the literature, there are few studies investigating OPG in thyroid dysfunctions, but with inconsistent results. To our knowledge, there are 3 clinical trials studying OPG levels in hypothyroid patients. In all, OPG was found to be higher than in controls and

Table 2. Characteristics of thyrotoxic and hypothyroid patients before and after restoration of euthyroidism

	Hypothyroidism			Thyrotoxicosis		
	Basal	**Post-treatment**	**p**	**Basal**	**Post-treatment**	**P**
BMI (kg/m^2)	25.4±3.1	24.8±3.0	0.103	23.4±3.7	24.1±4.3	0.125
TSH (mIU/ml)						
Mean	85.15±22.77	1.86±1.25	<0.001	0.01±1.11	2.06±1.10	<0.001
Median	101 (26.84-101.0)	1.82 (0.29-4.20)	<0.001	0.005 (0.005-0.041)	1.73 (0.38-4.14)	<0.001
FT3 (pmol/l)						
Mean	2.30±0.93	4.89±0.80	<0.001	18.35±12.05	4.60±0.63	<0.001
Median	2.90 (0.54-3.09)	4.79 (3.44-6.42)	<0.001	11.85 (6.90-44.0)	4.58 (3.19-6.13)	<0.001
FT4 (pmol/l)						
Mean	5.48±2.51	17.90±2.54	<0.001	50.08±29.50	14.42±1.80	<0.001
Median	5.64 (1.43-11.08)	17.86 (12.73-21.85)	<0.001	35.02 (23.1-100.0)	13.71 (12.31-17.32)	<0.001

BMI: Body mass index, TSH: Thyrotropin, FT3: Free T3, FT4: Free T4

Table 3. Basal and post-treatment plasma osteoprotegerin levels in patients and control group

	Hypothyroidism	**Thyrotoxicosis**	**Controls**	**p**
Basal OPG levels (pmol/l)	5.04±1.62	5.42±2.66	5.24±0.93	0.844
Post-treatment OPG levels (pmol/l)	4.34±1.37	5.52±2.37	-	0.083
p	0.109	0.846	NA	-

OPG: Osteoprotegerin, NA: Not applicable

Table 4. Correlation between changes in osteoprotegerin and changes in thyrotropin, free T3 and free T4 levels after treatment of thyroid dysfunctions

	Hypothyroidism						Thyrotoxicosis					
ΔOPG	ΔTSH		ΔFT3		ΔFT4		ΔTSH		ΔFT3		ΔFT4	
	r	p	r	p	r	p	r	p	r	p	r	p
	-0.580	0.825	-0.356	0.161	-0.209	0.421	0.341	0.180	0.339	0.183	0.280	0.276

OPG: Osteoprotegerin, TSH: Thyrotropin, FT3: Free T3, FT4: Free T4,

r: Pearson correlation coefficient

$\Delta = \frac{\text{Last volue-basal volue}}{\text{Basal volue}}$

two of them showed decreasing OPG levels after achievement of euthyroidism (8,9,14). An additional study compared OPG levels in TSH suppressed state and after withdrawal of L-thyroxine in patients with differentiated thyroid cancer and reported increased OPG when intentional hypothyroidism occurred (10). These studies suggested that OPG acting as an inhibitor of osteoclastogenesis may constitute a link between hypothyroidism and the decrease in bone resorption.

If so, thyrotoxicosis - a disease known to be related with increased bone turnover in favor of osteoclastogenesis - is expected to be associated with decreased OPG levels. On the contrary, OPG in overt thyrotoxicosis has been assessed only in two trials yet, and found to be also increased in cumulatively 114 patients with Graves' disease and 21 patients with autonomous thyroid nodules (11,12). Additionally, OPG was reported to decrease with restoration of euthyroidism in both studies. Besides, the relationship between subclinical hyperthyroidism and OPG was examined in differentiated thyroid cancer patients receiving L-thyroxine therapy for suppression of TSH and conflicting results were obtained. Although some authors declared increased OPG in exogenous TSH suppression (15,16), some suggested no difference compared to healthy subjects (17,18). However, the common finding of all was the lack of change in OPG levels after institution of high TSH with administration of rhTSH.

The precise mechanism by which thyroid hormone dysfunctions change serum OPG has not been expounded yet in existing studies. It was shown that OPG and RANKL are also produced in the thyroid gland by thyroid follicular cells, and OPG mRNA and protein secretion are regulated by cytokines and TSH (1). In hyperthyroidism, one of the possible explanations for increased OPG was induction of in vitro expression of OPG mRNA in bone cells by T3 (19).

Findings of our study were not consistent with most of the previous studies showing high OPG in both hypothyroidism and hyperthyroidism. Similar trends of change in OPG levels in two conditions which are known to have contrary effects on bone metabolism give rise to more questions on the results of those previous publications. There is evidence that TSH regulates bone function by mechanisms different from those used by RANKL/OPG cytokines. Abe et al. showed that osteoclast formation is increased in TSH receptor -/- mice although RANKL expression was decreased, considering lack of effect of RANKL on osteoclastogenesis (6). They also suggested that TNF-alpha is a proosteoclastic signal mediating the effects of TSH receptor deletion because they found that expression of TNF-alpha is enhanced dramatically in vivo and that a neutralizing antiTNF antibody inhibits the enhanced osteoclastogenesis ex vivo in TSH receptor -/- bone marrow cell cultures. Giusti et al. did not find an acute direct effect of TSH on OPG and RANKL in patients with a history of differentiated thyroid cancer, thus, confirming the view that the inhibitory role of TSH on osteoclastogenesis is achieved through mechanisms other than osteoblast-osteoclast cross-talk via the OPG/RANK/RANKL system (17). Moreover, recently, it has been shown that, circulating OPG is not correlated with serum TSH receptor antibodies in patients with Graves' hyperthyroidism (11). These data provide clues that, TSH does not regulate OPG production in bone, although some regulation may occur in other tissues. Lack of any significant change in OPG levels during thyroid dysfunctions in our study seems to be relevant in accordance with those experimental data, described above. None of the previous clinical publications investigated overt hypo and hyperthyroid patient populations in the same study with the same methods. Exclusion of methodological selection bias while evaluating any possible change in OPG levels in hypothyroidism and thyrotoxicosis in our study population might explain inconsistency of our data with the literature.

Menopausal status, autoimmunity and inflammation are three important factors that might modify serum OPG levels. Postmenopausal women without estrogen replacement therapy displayed 2 to 3 fold higher RANKL expression index on bone marrow stromal cells and lymphocytes compared to postmenopausal women on estrogen therapy (20). Premenopausal status of our study population might have masked possible difference in OPG levels across the study groups. In addition, our patient groups were heterogeneous in terms of etiologies of hypothyroidism and thyrotoxicosis. Hofbauer et al. detected OPG mRNA levels three times more abundant in surgical thyroid specimens of Graves' disease compared with other thyroid diseases suggesting a possible role of autoimmunity on serum OPG levels (1). Conducting a study investigating OPG levels in hypothyroid or hyperthyroid patients with the same etiology to exclude influence of autoimmunity and inflammation may be more elucidative. It is generally impossible to know for how long patients with thyroid dysfunctions have these disorders. In this study, euthyroidism was maintained in 7.17±4.0 months in thyrotoxic and in 4.7±2.49 months in hypothyroid patients. The durations of thyroid dysfunctions and the time elapsed after achievement of euthyroidism might be too short for significant changes to occur.

Recently, Riches et al. showed the presence of a neutralizing autoantibody against OPG in a patient with celiac disease, autoimmune hypothyroidism and high-turnover severe osteoporosis (21). Consequently, they demonstrated the presence of this antibody in 3 of 15 patients with celiac disease, but not in any of 14 patients with primary hypothyroidism and 10 healthy controls. They suggested a possible association of OPG antibodies with the development of osteoporosis in patients with celiac disease. Although no patient with autoimmune hypothyroidism was positive for OPG antibody in that study, possible confounding effect of an antibody should still be considered in our patient groups which included autoimmune thyroid diseases. We think that evaluation of bone turnover markers would help us to make more precise implications about the effects of thyroid dysfunctions on bone metabolism, yet the purpose of our study was not directed to this subject. As another limitation of our study, we could not measure RANKL concentration before and after restoration of euthyroidism in order to calculate RANKL bioactivity index (RANKL/OPG ratio). Finally, small number of cases in our groups may be considered as another limitation.

In conclusion, we demonstrated that OPG levels in hypothyroid and thyrotoxic patients are similar with that in euthyroid subjects and achievement of euthyroidism in these patients does not

change OPG levels. Impact of thyroid dysfunctions on bone metabolism seems to be regulated by mechanisms other than OPG. However, further studies with larger sample size are needed to come to a definite conclusion about the effects of TSH or thyroid hormones on OPG, RANKL and bone turnover.

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Original Article *Özgün Araştırma*

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The Prevalence of Incidental Adrenal Mass Found Using Diagnostic Imaging Techniques

Görüntüleme Tekniklerinde Adrenal Insidentaloma Prevelansı

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Abstract

Purpose: Incidentally-found adrenal masses detected by imaging studies performed for unrelated reasons have become more common in the clinical practice. Our study aims to assess the nature and prevalence of incidental adrenal masses discovered on CT or MRI in patients without malignancy.

Material and Method: We analyzed the reports of 8378 abdomen or chest CT and 820 abdominal MRI examinations performed on 4973 patients in our hospital. We found 629 (12.6%) incidental adrenal masses. We excluded 194 (3.9%) patients with known cancer or high-risk adrenal metastasis. The remaining 435 (8.7%) adrenal masses constituted the study group. This group consisted of 274 (5.9%) patients [123 (44.9%) women and 151 (55.1%) men] with masses greater than 1 cm in diameter and 161 (2.8%) patients with masses less than 1 cm.

Results: The mean age of the patients was 62.55±13.23 years. Unilateral adenoma was the most common type of adrenal masses (n=112, 40.9%). Less commonly observed adrenal masses were: unilateral [n=79 (28.8%)] and bilateral [n=35 (12.8%)] macronodular hyperplasia, unilateral [n=33 (12%)] and bilateral [n=2 (0.7%)] diffuse adrenal thickness, bilateral adenoma [n=7 (2.6)], unilateral [n=3 (1.1%)] and bilateral [n=3 (1.1%)] micronodular hyperplasia. The masses were most commonly found in the left adrenal gland (165, 60.2%). They were found at lower rates in the right adrenal gland (66, 24.1%) and bilateral adrenal glands (43, 15.7%). The mean sizes of left and right adrenal masses were 1.89±1.11 cm and 2.02±0.86 cm, respectively.

Discussion: Patients harbouring adrenal incidentalomas should be evaluated for the possibility of malignancy and/or hormone activity. The lack of controlled studies impedes specific management and recommendations for adrenal incidentalomas. Large prospective controlled studies on this topic are needed. *Turk Jem 2013; 17: 108-10*

Key words: Adrenal mass, incidentaloma, prevalence

Özet

Amaç: Rutin yapılan görüntüleme çalışmalarında, tesadüfen tespit edilen adrenal kitleler klinikte sık karşımıza çıkmaktadır. Bu çalışmamızda malignitesi olmayan hastalarda yapılan CT ve MRI tetkiklerinde, adrenal insidentaloma yaygınlığını değerlendirmeyi amaçladık.

Gereç ve Yöntem: Hastanemizde 4973 hastada yapılan 8378 karın ve göğüs bilgisayarlı tomografi ile 820 karın magnetik rezonans tetkiklerinin raporları incelendi. Altı yüz yirmi dokuz olguda (%12.6) adrenal kitle saptandı. Malignitesi ve adrenal metastaz riski yüksek olan 194 (%3,9) hasta çalışmaya alınmadı. Dört yüz otuz beş (%8,7) adrenal kitlesi olan hasta çalışmaya dahil edildi.

Bulgular: Çalışmaya dahil edilen 435 hastanın, 274'ünde (5,9%) 1 cm'den büyük ve 161'inde (2,8%) 1 cm'den küçük adrenal kitle olduğu belirlendi. 1cm'den büyük kitlesi olan hastaların 123'ü kadın, 151'i erkek hastaydı ve yaş ortalamaları 62,55±13,23 idi. Hastalarda en sık tek taraflı adenom (n=112, 40,9%), daha az sıklıkta da tek taraflı [n=79 (28,8%)] ve bilateral [n=35 (12,8%)] makronodüler hiperplazi, tek taraflı [n=33 (12%)] ve bilateral [n=2 (0,7%)] difüz adrenal kalınlık, bilateral adenoma [n=7 (2,6%)], tek taraflı [n=3 (1,1%)] ve bilateral [n=3 (1.1%)] mikronodüler hiperplazi tespit edildi. Hastaların en sık sol adrenal bezinde kitle tespit edildi (165, 60,2%). Sağ adrenal bez ve bilateral adrenal tutulum daha nadirdi (n,%: 66, 24,1% and 43, 15,7%, sırasıyla). Ortalama sağ ve sol adrenal bez boyutları sırasıyla 1.89±1.11 cm ve 2,02±0,86 cm idi. Unilateral [n=79 (28,8%)] and bilateral [n=35 (12.8%)] macronodular hyperplasia, unilateral [n=33 (12%)] and bilateral [n=2 (0,7%)] diffuse adrenal thickness, bilateral adenoma [n=7 (2,6%)], unilateral [n=3 (1,1%)] and bilateral [n=3 (1,1%)] micronodular hyperplasia.

Tartışma: Adrenal insidentalomalı hastalar malignite yada hormon aktivitesi açısından mutlaka değerlendirilmelidirler. Adrenal insdentalomalar için spesifik tedavi ve öneriler için daha geniş prospektif çalışmalara ihtiyaç vardır. *Turk Jem 2013; 17: 108-10*

Anahtar kelimeler: Adrenal kitle, insidentaloma, prevelans

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Introduction

Adrenal incidentalomas (AIs) are masses coincidentally found during abdominal or thoracic imaging performed for other reasons. It is difficult to know the true prevalence of this entity because of varied definitions and variability in methods used for imaging. The prevalence of adrenal tumors when established by computed tomography (CT) varies from 2.5 to 4% for abdomen CT, and 4.2% for thorax CT in adult populations (1-3). The prevalence of AI detected at autopsy is less than 1% in patients younger than 30 years of age, increasing to 7% in patients 70 years of age or older (4).

These masses are mainly non-secreting and benign. However, it is still an important clinical problem, because there can be a risk for malignancy or hormonal hyperfunction. All adrenal incidentalomas should be evaluated for these potential problems (3,5).

The primary aim of this study was to determine the number of cases of AI diagnosed by CT scans of the thorax and abdomen and magnetic resonance imaging (MRI) scans of the abdomen performed on adult patients attending our hospital between 2009 and 2012.

Material and Methods

Patients

We performed a retrospective review of the medical records of all patients with incidental adrenal mass discovered on CT or MRI between January 2009 and December 2012 at our institute. We analyzed the reports of 8378 abdomen or chest CT and 820 abdominal MRI examinations performed on 4973 patients in our hospital during this period. We found 629 (12.6%) incidental adrenal masses while browsing. We excluded 194 (3.9%) patients with a known malignancy or high-risk adrenal metastasis. The remaining 435 (8.7%) adrenal masses constituted the study group. This group consisted of 274 (5.9 %) patients with masses greater than 1 cm in diameter and 161 (2.8%) patients with masses less than 1 cm. The number and size of the adrenal mass in each patient was recorded.

A laboratory database review of the patients with AI was performed. Biochemical and radiological data, and demographic details were recorded. According to the guidelines, a sufficient endocrine evaluation included a 1 mg overnight dexamethasone suppression test to assess for Cushing's disease, a 24-hour collection of urinary metanephrines and normetanephrines, and plasma aldosterone and renin activity (5).

Imaging Methods and Analysis

Abdominal and chest CT scans comprised the initial scans. A helical CT (4-MDCT Asteion, Toshiba Medical Systems) was used for all investigations. Abdominal CT, both unenhanced and contrast-enhanced scans, were used to diagnose incidental adrenal lesions. Scans were completed during the portal venous phase (60-70 seconds) after 100 ml low-osmolar contrast material was administered intravenously. Collimation was 3 to 7 mm depending on the scanner used, body part to be imaged and the year of investigation. The majority of chest CT examinations were unenhanced. For contrast-enhanced chest CT 100 ml low osmolar contrast material was given intravenously during routine procedures.

Characterization of the incidentally-discovered adrenal mass was completed by using unenhanced CT, dedicated adrenal CT with contrast washout, or adrenal MRI with chemical shift imaging.

Adrenal CT was performed as follow-up investigation to identify the adrenal mass discovered. Unenhanced slices were obtained with 2.5 mm collimation through the adrenal glands. The field of view was 25-28 mm on average. The region of interest (ROI), an ellipse in the adrenal mass, was identified and measured. If the ROI was greater than 10 H, 100 ml non-ionic contrast material was administered intravenously at 3 ml/s. Imaging was repeated 60 s after injection and again 10-15 minutes later, keeping imaging parameters constant.

Adrenal MRI was completed with a variety of equipment including 1.5 T systems (Signa HDx, GE Healthcare). Where possible, a phased-array body coil was preferred. A 2-D gradient-refocused echo sequence was used to obtain T1-weighted inphase and opposed phase axial breath hold images. The parameters were: TR range: 110 milliseconds, in-phase TE range: 4.6 milliseconds, and opposed-phase TE range: 2.4 milliseconds. Additional parameters were: flip angle: 80°, field of view: 44x44 cm, slice thickness: 4 mm, intersection gap: 0.5 mm, and 1 signal acquisition. A T2-weighted sequence was included in all investigations, though the technique varied.

Results

The patients with masses greater than 1 cm comprised 274 patients [123 female (44.9%) and 151 male (55.1%)] (5.9%). The mean age of the patients was 62.55±13.23 years. The most common kind of adrenal mass was unilateral adenoma (n=112, 40.9%). Less commonly observed adrenal masses were: unilateral [n=79 (28.8%)] and bilateral [n=35 (12.8%)] macronodular hyperplasia, unilateral [n=33 (12%)] and bilateral [n=2 (0.7%)] diffuse adrenal thickness, bilateral adenoma [n=7 (2.6)], unilateral [n=3 (1.1%)] and bilateral [n=3 (1.1%)] micronodular hyperplasia The masses were most commonly seen in the left adrenal gland (165, 60.2%). They were less common in the right adrenal gland and bilateral adrenal glands (n,%: 66, 24.1% and 43, 15.7%, respectively). The mean sizes of left and right adrenal masses were 1.89±1.11 cm and 2.02±0.86 cm, respectively (Table 1). Evaluation of adrenal incidentalomas in the hormone system was performed in only 13 patients (4.7%). The results were non-functional masses, Cushing's syndrome, primary aldosteronism, and pheochromocytoma (n,%=8, 2.9%; 3, 1.1%; 1, 0.4%, 1, 0.4%) respectively.

Discussion

Adrenal masses are being discovered more frequently with the development of imaging techniques. There have been some studies on the prevalence of AI, with different results. The prevalence of AI in a study by Herrera et al. analyzing CT scans done between 1985 and 1989 was 0.4% (6). Using a similar method, Song et al. examined the CT scans in 65231 patients performed between 2000 and 2003 and reported a prevalence of 5% (7). Developments in imaging technology during the time between the two studies may be responsible for the increase in AI prevalence. Additionally,

Table 1. General data of the 274 patients	
Age (year)	62.55±13.23
Gender	
M	151 (55,1%)
F	123 (44,9%)
Side of the mass	
Right	66 (24,1%)
Left	165 (60.2%).
Bilateral	43 (15.7%)
Diagnostic technique	
CT (Abdominal+thorax)	8378
Abdominal MRI	820
Mass size	
Left adrenal	1.89±1.11 cm
Right adrenal	2.02±0.86 cm

Davenport et al. examined thorax and abdomen CT scans performed for any reason between 2006 and 2007 and found that the prevalence of AI detected by thorax CT and abdomen CT was 0.81% and 0.98%, respectively (8). They linked these low rates to the fact that more specific scanning for adrenal adenoma is done in a research protocol while a typical radiology department focuses on the patient's presenting complaint. In our study, when the results of radiological examination done for any reason were retrospectively evaluated, it was found that AI prevalence was 5.9%. In spite of not performing any specific radiological investigation for AI, contrary to the other studies, we determined a higher rate of incidence.

When AI is identified, it should definitely be evaluated to see if the lesion shows hormonal activity or not and whether it is benign or malignant. The guidelines for this evaluation have been determined by the NIH state-of-the-science statement on management of the clinically inapparent adrenal mass (5).

Each patient should be evaluated for pheochromocytoma, primary hyperaldosteronism, Cushing's syndrome and for the presence of virilising or feminising tumours. According to the test results, surgical or non-surgical treatment of the mass should be given. In a study, Mantero et al. investigated 1096 patients with identified AI between 1980 and 1995. According to the results of hormonal work-up, 85% of the masses were nonhypersecretory, 9.2% were subclinical Cushing's syndrome, 4.2% were pheochromocytoma and 1.6% were aldosteronomas (9). In their study, Golgowski et al., found excess hormone synthesis in 13.6% of subjects, pheochromocytoma in 7.4%, subclinical hypercortisolism in 4.8%, and primary hyperaldosteronism in 1.4% of patients with AI (10). In a study by Kasperlik-Zaluksa et al., of 1790 AI patients, 1590 subjects were found to have benign tumors and malignancy was detected in 200 patients. Subclinical adrenal hyperfunction was detected in 140 patients (8%), most frequently pre-Cushing's syndrome (6%), while subclinical hyperaldosteronism and hyperandrogenism were diagnosed in only 1%. Pheochromocytoma was found in 58 patients (3% of the whole group) (11). Comlekci et al. investigated clinical haracteristics, metabolic parameters and follow-up findings in 376 patients with AI. 73.5% of subjects had non-functional masses while 12.5% had subclinical Cushing's syndrome (12). In our study, only few patients with AI were evaluated for hormonal activity. Although all patients diagnosed with AI were referred to the endocrinology department, those with no complaints, or who attributed their complaints to some other cause, did not attend the endocrine clinic, thus, hormonal investigation could not be performed in the majority of patients. Apart from internal medicine and endocrinology clinics, initiatives to increase awareness on the need for evaluation of incidentally-found adrenal masses from the point of view of malignancy and hormonal hyperfunction may help to solve this problem.

Studies in recent years have frequently emphasized the relationship of AI with metabolic syndromes, insulin resistance and coronary artery disease. Studies on AI patients have discovered a frequent correlation between AI and metabolic syndrome characteristics, such as impaired glucose tolerance, elevated blood pressure and high triglyceride levels (13). A study by Dalmazi et al. found the relationship of increasing patterns of subclinical hypercortisolism with increased prevalence of adverse metabolic and cardiovascular events, independently of other potential risk factors (14). Evaluation and monitoring of all patients with AI should include screening for metabolic syndromes, diabetes mellitus and coronary artery disease. In this study, the first on AI prevalence in Turkey, we observed that the prevalence of AI detected during radiological investigations for any reason was higher compared to that in previous papers. In our center, a special training would contribute to raising awareness on the need for careful evaluation of incidentally-found adrenal masses from the point of view of malignancy and hormonal hyperfunction. In addition, prospective, multi-centre studies on this topic are needed in our country.

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The Relationship Between Coronary Artery Disease and Undiagnosed Glucose Metabolism Disorders in Patients who Have Undergone Angiography

Anjiyografi Geçiren Hastalarda Bilinmeyen Glukoz Metabolizma Bozuklukları ve Koroner Arter Hastalıkları ile Olan İlişkisi

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Abstract

Purpose: Diabetes mellitus (DM) and coronary artery disease (CAD), seen frequently in the general population, are major causes of morbidity and mortality. DM, controllable through treatment, is one of the most important risk factors for the development of cardiovascular diseases.

Material and Method: Our study included patients who had undiagnosed glucose metabolism disorders and had undergone an angiography under elective conditions. To diagnose the glucose metabolism disorders, these patients were given the oral glucose tolerance test (OGTT) (75 g) within 5-10 days after angiography.

Results: In our study, 24.5% (n=79) of patients had isolated impaired fasting glucose, 9.3% (n=30) had isolated impaired glucose tolerance, 21.1% (n=68) had both impaired fasting glucose and impaired glucose tolerance, and 5% (n=16) had DM. None of these patients knew about their condition beforehand. Only 40.1% (n=129) of patients had normal OGTT results.

Discussion: If patients with suspected CAD found to have blocked arteries after an angiography are screened for DM, glucose metabolism disorders can be diagnosed early. When caught early, the long-term complications can be avoided, resulting in significant savings for health care costs. *Turk Jem 2013; 17: 111-5*

Key words: Diabetes mellitus, coronary artery disease, oral glucose tolerance test

Özet

Amaç: Diabetes Mellitus (DM) ve koroner arter hastalıkları (CAD) toplum genelinde sık olarak görülen ve ciddi oranda morbidite veya mortaliteye neden olan hastalıklardır. DM kontrol edilemediği takdirde uzun dönemde başta kardiyovasküler sistem olmak üzere bir çok sistemde komplikasyonlar meydana getirmektedir. Çalışmamızda koroner arter hastalarındaki bilinmeyen DM, bozulmuş açlık glukozu (BAG) ve glukoz toleransı bozukluğu (GTB) sıklığı ve aralarındaki ilişkisi araştırılmıştır.

Gereç ve Yöntem: Çalışmamız elektif şartlarda anjiyografi işlemi uygulanan ve öncesinde bilinen DM, BAG veya GTB hastalığı bulunmayan bireyler üzerinde gerçekleştirilmiştir. Tüm hastalara anjiyografi sonrası 5.-10. günlerde 75 g oral glukoz tolerans testi uygulanmıştır.

Bulgular: Çalışmamızda katılımcıların %24,5'inde (n=79) izole BAG, %9,3'ünde (n=30) izole GTB, %21,1'inde (n=68) BAG ve GTB birlikteliği ve %5'inde (n=16) ise DM saptanmıştır. Anjiyografi geçiren hastaların yanlız %40,1'inin (n=129) OGTT sonuçları normal yorumlanmıştır.

Tartışma: DM erken saptandığı takdirde uzun dönemde meydana gelen ciddi komplikasyonlarından korunulabilir. Özellikle koroner arter hastalığı ile DM arasındaki ilişki bilinmeli ve koroner anjiyografi geçiren tüm hastalar altta bulunabilecek glukoz metabolizma hastalıkları açısından araştırılmalıdır. *Turk Jem 2013; 17: 111-5*

Anahtar kelimeler: Diabetes mellitus, oral glukoz tolerans testi, koroner arter hastalığı

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Introduction

Diabetes Mellitus (DM) and cardiovascular diseases are chronic diseases seen frequently in our day, especially in developed countries. According to data from 2008, there are approximately 13 million people with coronary artery disease (CAD) in the U.S. Cardiovascular disease, in particular, is the leading cause of death in adults all over the world (1,2,3). Furthermore, two thirds of these deaths are due to CAD. DM is responsible for 5% of deaths in adults all over the world (3). According to the World Health Organization (WHO) there are more than 220 million people with DM in the world. This number is expected to increase by more than two-fold in the year 2030 (3). Studies have shown that many factors, including gender, race, age, and family history contribute to the development of CAD. In addition to these factors which predetermine one's risk of developing CAD, there are also factors that can be changed or treated, such as high levels of low-density lipoprotein (LDL) cholesterol and triglycerides, low levels of high-density lipoprotein (HDL) cholesterol as well as DM, obesity, hypertension, smoking, and a sedentary lifestyle (4,5,6).

DM, which can be controlled through treatment, is one of the most important risk factors for the development of cardiovascular diseases. DM patients are two to four times more likely to develop a cardiovascular disease (7). In a study conducted by Türkiye Diyabet Epidemiyoloji Araştırma Projesi-2 (TURDEP-2), it was found that the prevalence of DM in the Turkish population was 13.7%. However, 45.5% of those with DM are not getting treatment because they are not aware that they have the disease (8). In the GAMI (Glucose in Acute Myocardial Infarction) study, it was seen that patients with acute myocardial infarction in Sweden had abnormal blood glucose metabolism (9). CAD occurs at an earlier age in DM patients and coronary lesions tend to be both more complex and extensive in these patients (10). The cause of death in more than 80% of DM patients is due to CAD and the complications that result from CAD (11).

In summary, we aimed to determine the frequency of glucose metabolism disorders in patients with undiagnosed CAD and the relationship between glucose metabolism disorders and CAD.

Material and Methods

How Patients were Selected for İnclusion in this Study

We included patients with suspected CAD and who had undergone an angiography under elective conditions, from June 2009 to June 2010 in the Department of Cardiology at Gülhane Military Medical Academy Hospital (GATA). In order to determine who would be included in this study, while waiting in the clinic after their angiography, the patients were given one to one interviews. Furthermore, we evaluated the results of the routine preoperative laboratory tests. During the interviews, the purpose of this study was explained to the patients and signed consent forms were collected from those who agreed to participate. Following this, questionnaires containing socio-demographic data were given to the patients to fill out and the results from routine blood tests and complete blood count tests that were requested prior to angiography, were recorded. Each patient was given the oral glucose tolerance test (OGTT) (75 g) within 5-10 days after the angiography. After the OGTT, the results of the blood tests were recorded. In total, 322 patients, who had undergone angiography for suspected CAD, were included in this study. We aimed to research unknown glucose metabolism disorders (Diabetes Mellitus, impaired fasting glucose and, impaired glucose tolerance) and their effects on the coronary arteries.

2.2 Conditions that Need to be met by the Patient for Inclusion in this Study

1. Patient must have willingly had an angiography
2. Patient must have undiagnosed glucose metabolism disorder
3. Patient must have had no acute myocardial infarction at least 3 months prior to the angiography
4. Patient must willingly consent to the study
5. Patient must have no history of autoimmune disease and/or cancer

The patients went to the Endocrinology and Metabolism Diseases Department in GATA to have the OGTT administered. The doctor responsible for the patients in this study performed a systemic examination and had the patient rest sitting down, in a quiet room, for a 15-minute period before taking his/her blood pressure. In patients where no problems were found, the OGTT was administered. During the OGTT, 0- and 2-hour venous blood samples were taken from patients and sent to the Department of Biochemistry in GATA where they were immediately analyzed.

The Examination Process of Laboratory Parameters

The patients were told not to introduce a new diet to their daily regimen for a period of three days before OGTT and to continue eating what they have always been eating. In order to avoid a false-negative test result, the patients were reminded to eat at least 150 g of carbohydrates per day. The patients were not asked to limit their physical activity. After fasting for a 10-hour period, a blood sample was taken from each patient and glucose and insulin levels were examined. The patients were given a 75 g oral glucose in 300 ml water and asked to drink it within 5 minutes, in a sitting position. At the 120 minute mark, measured from the time the patients started drinking, another blood sample was taken and blood glucose levels were measured for the second time. The patients' states of glucose metabolism were evaluated.

Evaluation of Coronary Angiography Results

Critical CAD is defined as ≥50% narrowing of the luminal diameter of any epicardial artery and/or a side branch with a diameter greater than 2.5 mm. Patients with CAD were grouped according to the number of blocked vessels. After examining angiography reports, the severity of the blockages was recorded separately.

Statistical Analysis

At the end of this study, when evaluating the findings, SPSS 15.00 for Windows (Chicago-USA) was used. Descriptive statistical methods for categorical variables are given in the form of numbers and percentages, and for continuous variables arewere given in the form of mean±standard deviation. The Chi-square test was used when examining the relationship between glucose metabolism disorders and the number of clogged arteries. The compliance of the data with normal dispersion was examined using the Shapiro-Wilk test. The results of the Shapiro Wilk test show that there is no

normal distribution because p<0.001 in all groups. The Mann-Whitney U test was used to compare the normal and the impaired fasting glucose groups whereas the Kruskal-Wallis test was used to compare the normal, impaired glucose tolerance and the DM groups. A p value of less than 0.05 was considered significant. The Bonferroni adjusted Mann-Whitney U test was used to determine the subgroup pairs that caused the differences between the three groups. In this case, a p value of less than 0.017 was considered significant.

Ethics Committee Approval

Ethical approval for our study was given by the ethics committee of our hospital. During the study period, the patients were informed about the study and written informed consent forms were signed by the patients. All patients' data have been kept confidential. Furthermore, nothing was implemented on the patients except those stated in the ethics committee application form. No conflict of interest exists in this study.

Results

The mean age of the patients was 54.04±11.52 years. 66.2% (n=213) of patients were male and 33.8% (n=109) of patients were female. The medical history revealed that 76.4% (n=246) of patients had no history of cardiovascular disease or had undergone any procedure. 15.5% (n=50) of patients have had a myocardial infarction, 5% (n=16) had undergone a percutaneous transluminal coronary angioplasty (PTCA) and 3.1% of patients had undergone a coronary artery bypass. When the history of smoking was examined, we saw that 31.05% (n=100) of patients had never smoked, 49.8% (n=159) of patients had smoked, but had quit at least one year before participating in this study, and 19.57% (n=63) of patients continued to smoke. None of the patients were diagnosed with DM or a glucose metabolism disorder. However, 28.6% (n=92) suffered from hypertension.

In our study, 24.5% (n=79) of patients had isolated impaired fasting glucose, 9.3% (n=30) had isolated impaired glucose tolerance, 21.1% (n=68) had both impaired fasting glucose and impaired glucose tolerance, and 5% (n=16) had DM. None of these patients knew about their condition beforehand. The rate of patients newly diagnosed with DM, after being diagnosed with CAD based on their angiography results, was 6.78%.

According to the measurements at 0 minute during the OGTT, the patients were divided into two groups: impaired fasting glucose group and normal group. When the left anterior descending artery, circumflex artery and the right coronary artery of blocked arteries were compared between the two groups, there was a statistically significant difference between the two (in order p=0.001, p=0.001, p=0.003). However, a statistically significant difference was not found in the left coronary artery (p=0.300) (Table 1).

According to the measurements at 120 minute after the OGTT test, the patients were divided into three groups: impaired glucose tolerance group (IGT), DM group and a normal group. When the left coroner artery, left anterior descending artery, circumflex artery and the right coronary artery of blocked arteries were compared between the three groups, there was a statistically significant difference (p=0.005, p=0.031, p=0.037, p=0.021, respectively) (Table 2). The Bonferroni adjusted Mann-Whitney U test was used to determine the subgroup pairs that caused the differences between the three groups. No statistically significant difference was not found in the coronary arteries between the normal and IGT groups (p=0.431, p=0.705, p=0.469, p=0.154, respectively); only a difference in the left anterior descending artery was found between the IGT and DM groups (p=0.041, p=0.08, p=0.041, p=0.077, respectively), and a difference was found in the coronary arteries between the normal and DM group (p=0.001, p=0.013, p=0.010, p=0.009).

When the number of coronary arteries affected by glucose metabolism disorder that detected at the 0 and 120 minute measurements during the OGTT was compared, a statistically significant difference was found between the two groups (p=0.001, p=0.002, respectively) (Table 3).

Discussion

In our study, we found that 5% of patients who have undergone coronary angiography had previously unknown DM. Furthermore, 59.9% of our patients had a glucose metabolism disorder (DM, impaired glucose tolerance or impaired fasting glucose). According

Table 1. Comparison of the average rates of blocked coronary arteries between the impaired fasting glucose group and the normal group and the statistically significant difference between the two groups

Name of Coronary Artery	Normal		Impaired Fasting Glucose		P*
	Mean Median	Std. Deviation Min - Max	Mean Median	Std. Deviation Min - Max	
LCA	0.11 0	1.06 0-20	0.81 0	5.81 0-60	0.300
LAD	19.20 10	27.91 0-100	31.95 20	36.92 0-100	0.001
CX	11.06 0	24.68 0-100	24.65 10	34.83 0-100	0.001
RCA	10.11 0	20.31 0-100	24.31 10	24.31 0-100	0.003

LCA: Left Coronary Artery LAD: Left Anterior Coronary Artery CX: Circumflex Artery RCA: Right Coronary Artery *: Mann-Whitney U Test

to the angiography results in all patients who were diagnosed with DM, we found a blockage in the coronary arteries. This is an important finding because it shows the frequency of CAD in DM patients. When we examined the number of pathological coronary arteries in our patients who were newly diagnosed with DM, we observed that in 75% of 3 arteries, in 12.5% of 2 arteries and in 12.5% of 1 artery were blocked. None of our patients had normal angiography results. 23% were found to have healthy coronary arteries. In addition, 50% of patients who were newly diagnosed with DM had serious blockage and 50% had mild blockage in their arteries. In participants with normal glucose metabolism, only one in four had serious blockage. Furthermore, there was a statistically significant difference in the degree of stenosis between the DM and normal groups. These findings are important because they seem to indicate that DM increases the severity of CAD. Moreover, in our study, we detected a statistically significant difference between the state of coronary artery blockage and blood sugar levels.

The Funagata Diabetes study has clearly shown the increased mortality rates in patients with impaired glucose tolerance and CAD (12). The DECODE study has shown that the risk of developing CAD increases as a result of chronic hyperglycemia. The results of these two studies support the findings of our study (13). According to the TURDEP-2 study, 7.5% of the Turkish population (approximately 5.5 million people) has undiagnosed DM (8). According to Harris et al., the prevalence of undiagnosed DM in the U.S. is 2.7% (approximately 5.4 million people) and according to Garancini et al., the prevalence of undiagnosed DM in Italy is 2.5% (approximately 1.5 million people) (14,15). In our study, newly diagnosed DM rates in patients who have undergone angiography are about twice of that of the studies mentioned above. In our study, the prevalence of DM in newly diagnosed patients was similar to the that found in the TURDEP-2 study. However, in contrast to the TURDEP-2 study, the prevalence of other glucose metabolism disorders that were diagnosed in our study was twice as high. The rate of patients newly diagnosed with DM after being diagnosed with CAD based on their angiography results, was 6.78%. This result is about three times higher than that of the US population study results. The high frequency of undiagnosed DM in patients with CAD who have undergone angiography, in comparison to the normal population, is an important finding. However, the rate of newly diagnosed DM

Table 2. Comparison of the average rates of blocked coronary arteries between the impaired fasting glucose group, the normal group, and DM group and the statistically significant difference between the three groups

Name of Artery	Normal		IGT		DM		P*
	Mean Median	Std. Dev. Min-Max	Mean Median	Std. Dev. Min-Max	Mean Median	Std. Dev. Min-Max	
LCA	0.10 0	0.97 0-20	1.02 0	7.10 0-60	1.25 0	3.41 0-10	**0.005**
LAD	24.38 10	31.97 0-100	24.06 10	34.15 0-100	40.00 25	36.14 10-100	**0.031**
RCA	15.57 0	28.48 0-100	18.71 0	33.19 0-100	31.25 10	36.30 0-100	**0.037**
CX	15.00 0	27.97 0-100	18.76 10	30.17 0-100	25.00 20	24.22 0-75	**0.021**

IGT: Impaired Glucose Tolerance DM: Diabetes Mellitus LCA: Left Coronary Artery LAD: Left Anterior Coronary Artery CX: Circumflex Artery RCA: Right Coronary Artery Std. Dev.: Standard Deviation *: Kruskal-Wallis Test

Table 3. Number of blocked arteries according to the results of the Coronary Angiography and its relationship with the results of the OGTT

Number of Blocked Coronary Arteries	OGTT 0				P*	OGTT 120						P*
	Normal		IFG			Normal		IGT		DM		
	n	%	n	%		n	%	n	%	n	%	
0	56	17.4	30	9.3	0.001	58	18.0	28	8.7	0	0	0.002
1	42	13.0	26	8.1		46	14.3	20	6.2	2	0.6	
2	37	11.5	27	8.4		48	14.9	14	4.4	2	0.6	
3	39	12.1	63	19.6		56	17.4	34	10.6	12	3.7	
4	0	0	2	0.6		0	0	2	0.6	0	0	

OGTT: Oral Glucose Tolerance Test IFG: Impaired Fasting Glucose
IGT: Impaired Glucose Tolerance DM: Diabetes Mellitus *: Chi-square test

patients in our study is lower than the rate found in the GAMI study performed in Sweden (9). The GAMI study consisted of patients with acute myocardial infarction whereas our study consisted of patients who had undergone angiography in elective conditions. Therefore, we assume that the difference resulted from the differences in the patient groups used in both studies. According to the Society of Endocrinology and Metabolism of Turkey, impaired glucose intolerance and impaired fasting glucose could be described as pre-diabetes (16). In general, patients with impaired glucose tolerance receive the diagnosis of DM within 4-6 years. Therefore, if glucose metabolism disorders are identified early, complications as a result of these disorders can be avoided. As seen in our findings, one in five patients who have undergone angiography and who have normal fasting blood glucose, have impaired glucose tolerance.

In the TURDEP-2 study, the researchers reported that 7.1% of the general population had impaired glucose tolerance levels. According to the results of our study, impaired glucose tolerance levels in the general population were five times greater than this. The results from a study by Gui et al. conducted in China in 2010 support the results of our study (17). The results from the Gui et al. study indicated that 50% of patients who had CAD had normal OGTT results, 9.3% had isolated impaired fasting glucose, 23.02% had isolated impaired glucose tolerance, and 17.62% had both impaired fasting glucose and impaired glucose tolerance. In our study, 24.5% (n=79) of patients had isolated impaired fasting glucose, 9.3% (n=30) had isolated impaired glucose tolerance, and 21.1% (n=68) of patients had both impaired fasting glucose and impaired glucose tolerance. When viewed from this aspect, both studies had similar findings.

In conclusion, we found that 69.45% of patients diagnosed with impaired glucose tolerance had blockage, in various diameters, in at least one coronary artery. Only 26.71% of patients with normal OGTT results were diagnosed with CAD. This result is particularly important because it shows the relationship between impaired glucose tolerance and CAD. Another noteworthy finding in our study was that approximately one in three patients who had undergone coronary angiography had a positive family history of CAD. In addition, 62.5% of patients who were newly diagnosed with DM had at least one first-degree relative diagnosed with DM. These results prove once more the importance of family history.

Approximately one in three DM patients are unaware that they have the disease (8,18,19). This leaves patients vulnerable to complications down the line (19,20,21). Complications related to CAD tops the list. Disability and death resulting from impaired glucose metabolism can be avoided if caught early (20,22). Therefore, even if patients who have undergone angiography have no complaints, their fasting and postprandial glucose levels should be examined. Furthermore, when early diagnosis is made, annual health care spending on DM and CAD will decrease. This issue is particularly important for primary health care providers as they are often the first point of contact with these patients.

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Cervical Approach to Substernal Goiter: Do we Need Sternotomy? Cerrahpaşa Experience

Substernal Guatırda Servikal Yaklaşım: Sternotomiye ihtiyacımız var mı? Cerrahpaşa Deneyimi

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Abstract

Purpose: The purpose of this study was to evaluate the clinical and surgical differences between substernal goiter and non substernal goiter according to institutional experience.

Material and Method: Twenty-nine patients with substernal goiter and 62 randomly chosen non substernal goiter patients from January 2009 to October 2012 were compared retrospectively according to their pre-operative and post-operative data. Cervical approached total thyroidectomy was applied to patients with substernal goiter.

Results: Thirteen of twenty-nine substernal goiter patients were male (44.8%) and 16 were female (55.2%). Body mass index, age, gender in both groups were compared and found to be similar. No post-operative complication was observed. Pathology results revealed malignancy in 24.1% of patients.

Discussion: Patients with substernal goiter can be safely treated through the cervical approach with low complication rates in expert hands. *Turk Jem 2013; 17: 116-20*

Key words: Substernal goiter, sternotomy, cervical approach

Özet

Amaç: Bu çalışmanın amacı substernal uzanımlı tiroid patolojisi olan hastalarla substernal uzanımı olmayan tiroid patolojisi olan hastaların, klinik ve cerrahi farklarını tecrübemize göre değerlendirmektir.

Gereç ve Yöntem: Çalışmamız Ocak 2009 ve Ekim 2012 tarihleri arasında elektif şartlarda substernal uzanımlı tiroid patolojisi olan 29 hastanın, aynı tarihler arasında substernal uzanımlı olmayan tiroid patolojisi olup, rastgele yöntemle seçilmiş 62 hastanın preop ve postop verileri retrospektif karşılaştırılarak yapılmıştır. Substernal guatırlı hastalara servikal yaklaşımlı total tiroidektomi uygulandı.

Bulgular: Substernal guatırı olan 29 hastanın: 13'ü erkek (%44,8), 16'sı kadındır (%55,2). Her iki grup, BMI, yaş, cinsiyet dağılımı baz alınarak karşılaştırılmış; birbirine benzer gruplar olarak değerlendirilmiştir. Hastaların hiçbirinde komplikasyon gelişmedi. Bu hastaların %24,1'inin patolojisi malign geldi.

Tartışma: Substernal guatırlı hastalar deneyimli cerrahlar tarafından, servikal yaklaşımla güvenli bir şekilde tedavi edilebilmektedir. *Turk Jem 2013; 17: 116-20*

Anahtar kelimeler: Substernal guatır, sternotomi, servikal yaklaşım

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Introduction

Substernal Goiter (SG) is described as the extension of the thyroid tissue into the mediastinum. This structure might be unilateral or bilateral. Despite difficulties in estimating the overall incidence of SG, extensive thyroidectomy series show an incidence of 1-20% (1-4). It is generally seen in the fifth to sixth decade of life and female/male ratio is approximately 4:1. Neurovascularity generally originates in the cervical region, however, a limited number of studies have demonstrated that substernal thyroid tissue might originated in the mediastinum. While SGs usually extend into the anterior mediastinum (85-90%), 10-15% of them extend into the posterior mediastinum (2,5,6). Enlarged thyroid tissue may compress the trachea or esophagus and can cause symptoms such as dysphagia or dyspnea. However, in some studies, 5 to 50% of patients were found to be asymptomatic (1,2,7,8). Compression of the large venous structures may lead to venous congestion (7,9). The initial diagnosis is based upon clinical history and the findings of routine analyses, and radiological evaluations, then, is verified with intra-operative evidences. Surgery is considered to be the primary approach and the gold standard for the treatment of SG due to the fact that malignancy is observed in about 7 to 20% of patients with SG. Surgery can be done through cervical approach, sternotomy, thoracotomy or a combination of these techniques. The general consensus is that most SG patients can be treated through cervical approach, however, some cases may need thoracic intervention. Sternotomy is performed in about 0 to 11% cases. This wide range may be explained by the absence of a common SG definition (6,7,10-13). Most of the SG studies have been published as series of author's self-experience, evaluation of their own surgical techniques and comparison of other studies on SG. This study compared statistically similar groups of SG patients to non-substernal goiter (NSG) patients in whom same surgical technique was applied and investigated the possible differences between the two groups.

Materials and Methods

This study retrospectively compared the pre-operative, per-operative and post-operative data from 29 SG patients (group 1) with those from 62 randomly selected NSG patients (group 2) who have been admitted to Cerrahpaşa Medical Faculty, Department of General Surgery between January 2009 and October 2012. The diagnosis of SG was made by per-operatively confirmed pre-operative radiological investigation or per-operative observation of substernal thyroid tissue. Contrast-enhanced computed tomography (CT) of the neck and thorax was performed in only symptomatic patients. Chest X-ray was considered to be a pre-operative routine and made in all patients. Extension of the thyroid gland caudally beyond the sternal notch in chest X-ray was accepted as substernal. A sample of chest X-ray with tracheal deviation is given in Figure 1. Major symptoms, such as dyspnea, dysphagia, and hoarseness were questioned and, height, weight, submental distance, and neck circumference were recorded in all patients. Use of fiber-optic laryngoscope during intubation, duration of operation, duration of anesthesia, weight of specimens, and whether the thyroid was divided from isthmus or not were noted. Pre-operative and post-operative calcium and albumin levels were analyzed. All calcium levels were corrected for albumin before statistical calculations.

Pre-operative and post-operative vocal cord examinations were made in patients for hoarseness and the patients were evaluated for nerve paralysis at the Department of Otorhinolaryngology. Routinely recommended systemic antibiotic prophylaxis was not used. Total thyroidectomy was performed by energy-based devices (Harmonic FOCUS® or Ligasure™ LF1212). Surgical drains were used in all cases. Surgical knots were not applied according to sutureless thyroidectomy technique (14).

Study was conducted in accordance with the Helsinki Declaration and was approved by the Institutional Ethics Committee.

Statistical Analysis

The groups were compared in regard to BMI, age, submental distance, neck circumference, duration of operation, post-operative calcium levels, amount of drainage, duration of anesthesia and weight of specimens by using a chi-square test, Fisher's exact test, student's t-test, Mann-Whitney-U test, and the Shapiro-Wilk test all statistical analyses were performed by using IBM SPSS 20.0 for Windows. A p value of less than 0.05 was considered statistically significant.

Results

BMI, age, submental distance, neck circumference, duration of operation, post-operative calcium levels, amount of drainage, duration of anesthesia, and weight of specimens were analyzed. In group 1 (n=29), 13 patients were male (44.8%) and 16 were female (55.2%); in group 2 (n=62), 22 patients were male (35.5%), and 40 patients were female (64.5%). No reasonable relationship was found between gender and location of elongated thyroid tissue (p=0.393). No significant differences were detected between the groups in mean values of BMI (p=0.674), age (p=0.096), submental distance (p=0.399), neck circumference (p=0.03), and post-operative calcium level (p=0.029) (Table 1). A significant difference was found between the two groups in weight of specimens (p<0.001), duration of anesthesia (p=0.005), duration of the surgery (p<0.001), and average amount of drainage (p=0.002) (Table 1). We were unable to resect the glands in five Group 1 patients (17.2%) as unblock specimen and if compared with Group 2, significant difference was established (p=0.005). Dyspnea was the most common symptom in SG patients, 13 patients (51.7%) presented to the clinic with dyspnea as an admission symptom. No analysis was made between the two groups due to the limited number of symptoms (Table 1).

There was a significant difference in the size of the tyroid gland between patients with compression symptoms and asymptomatic patients. Increased specimen weight resulted in an increase in symptoms (p=0.01). Dyspnea was the most common symptom. There was no relationship between gender and distribution of symptoms (p>0.05). Chest X-ray showed tracheal deviation in 25 patients in group 1 (86.2%) and 11 subjects in group 2 (30.6%). There were significant differences in X-ray findings between the groups (p<0.001). None of the Group 2 patients were investigated with CT;

on the other hand, in the Group 1 patients, CT was performed in four patients with heavy dyspnea, one patient with dysphagia and in two asymptomatic patients with serious enlarged thyroid gland based on physical examination findings (Figure 2). Thyroid ultrasound (US) showed substernal enlargement in 10 (34.5%) patients in group 1, while no substernal extension was detected in group 2 (p<0.001). Two subjects in group 1 were considered hard-to-intubate patients, thus, fiber-optic intubation was performed in these patients. There were no substantial differences detected for intubation between the groups (p=0.09). Sternotomy or thoracotomy was not applied; all patients were operated via cervical approach. In group 1, the thyroid glands were resected in 24 patients as unblock (83.3%), unblock resection was not possible in five patients (16.7%). Only one patient in group 2 presented with post-operative hoarseness which found to be due to vocal cord trauma. One patient in group 1 (3.4%) and 2 subjects in group 2 (8.1%) presented with post-operative complications. There was no significant difference in terms of surgical complications between the two groups (p=0.66)., Pathological evaluation of the specimens from 7 group 1 patients

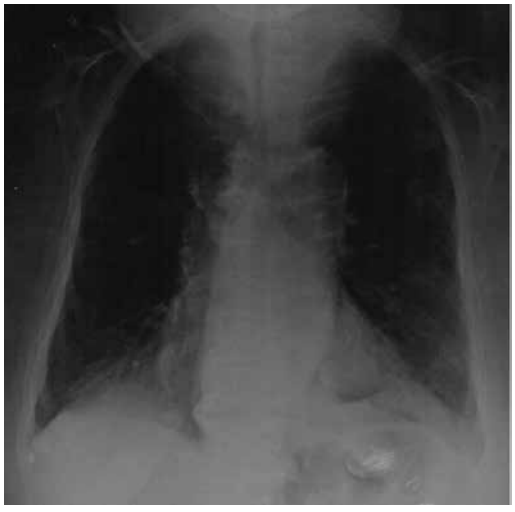

Figure 1. Tracheal deviation on a pre-operative chest- X-ray

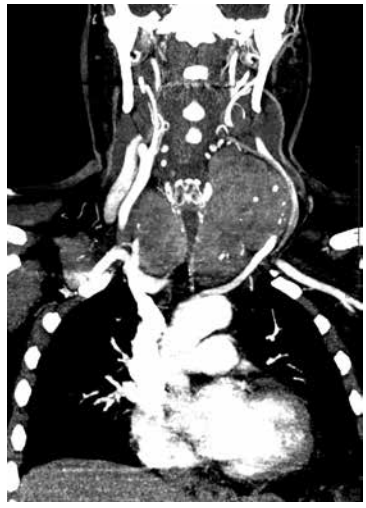

Figure 2. Mediastineal extension of thyroid gland on CT image

Table 1. Measured values of each group

	Group 1 (n=29)	Group 2 (n=62)	Total	p-value
Age (years)	54.24±14.07	49.53±11.63	51.03 ± 12.58	0.096
BMI (kg/m^2)	28.91±5.18	28.41±5.31	28.57 ± 5.25	0.674
Sternomental distance (cm)	15.48±2.99	14.98±2.50	15.14 ± 2.66	0.399
Neck circumferences (cm)	39.35±4.84	37.19±4.08	37.88 ± 4.42	**0.03**
Duration of operation (min)	31.69±9.79	41.90±12.88	38.65 ± 12.85	**<0.001**
Duration of anesthesia[a] (min)	49.24±12.92 49 (30-100)	58.69±15.52 60 (30-85)	55.68±15.32 50 (30-100)	**0.005**
Weight of specimens[a] (g)	155.90±180.34 108 (27-792)	45.82±51.14 30 (8-296)	80.90±120.63 37 (8-792)	**<0.001**
Amount of drainage[a] (ml)	51.55±29.13 45 (9-150)	37.10±21.19 35 (12-155)	41.70±24.78 37 (9-155)	**0.002**
Symptoms (n)				
Asymptomatic	15 (51.72%)	50 (80.65%)	65 (71.43%)	0.004
Symptomatic	14 (48.28%)	12 (19.35%)	26 (28.57%)	
Dyspnea	13 (44.83%)	3 (4.84%)	16 (17.58%)	
Dysphagia	1 (3.45%)	8 (12.9%)	9 (9.89%)	
Vocal cord palsy	0 (0%)	1 (1.61%)	1 (1.1%)	

Continues values were denoted as mean ± standard deviation. If the distribution was not normal median (minimum – maximum) values also were given.

[a] Data was not distributed as normal.

P values with statistical significance were typed in bold.

(24.1%) and 16 group 2 patients (25.8%) demonstrated malignancy. In those patients cytology was unknown prior to surgery. There was no significant difference in pathological diagnosis between the two groups (p=0.864).

Discussion

SG is defined as enlargement of the thyroid tissue into the mediastinum. After the first description of SG in 19th century, continuous developments in surgery and anesthesia changed the methods of the evaluation and treatment of SG radically. Thyroidectomy was considered as one of the brutal surgical interventions in the medical history; these operations are now performed with low mortality and morbidity rates. In contrast to female/male ratio of 4 to 1 in the literature, female/male ratio was 16/13 in this study (1-4). Clinically, some patients are admitted to hospital with compression symptoms, while, some patients remain asymptomatic (2,7,8). In this study, this percentage was calculated as high as 50% (14 patients).

Radiological imaging is considered to be an important part of the diagnosis. Chest X-ray does not provide a definitive diagnosis of SG, but may raise a suspicion of tracheal and esophageal deviation. In this study, 25 SG patients (88.2%) showed findings of deviation. The percentage of patients with normal chest radiograph findings was about 20-30% in other studies (2). However, in this study, the percentage was 13.8. This wide percentage dispersion is due to the fact that no certain standardization has been decided for radiographic imaging. Calculation of deviation angles can be helpful in creating standardization of deviation degrees. Thyroid US examinations diagnosed only 34.5% of the patients. Some other clinical studies showed that US was inefficient in diagnosing SG. In this study, US was generally done out of our clinic; any difference in results was considered normal given the differences in the experience of radiologists, and properties of US devices (2,3,6). Because of these heterogeneous US results, CT of the neck is accepted appropriate for patients with deviation findings on chest X-ray and for clinically symptomatic patients. CT examination helps us to evaluate substernal elongation and anatomical neighborhood with other mediastineal organs.

CT based diagnosis of SG was confirmed per-operatively for each patient. In this study, some of the patients were diagnosed by scintigraphy, however, inadequate number of patients in whom scintigraphy was performed prevented evaluation of the accuracy of scintigraphy in the diagnosis of SG. Scintigraphy shows the activity of the thyroid tissue enlarging to the mediastinum, but absence of nuclear activity cannot exclude SG. MRI can be used as a diagnostic method, but shows no advantage over CT (2,6,7). In this study, none of the patients were evaluated with MR imaging. To summarize, chest X-ray raise suspicion over SG, however, USG is not effective. CT and MRI may provide definitive diagnosis, but since these examinations are not cost-effective, they are not included in the routine tests. They must be used for the evaluation of patients with prominent symptoms.

Two of the subjects were accepted as hard-to-intubate patients according to chest X-ray images and examinations performed by anesthesiologists. These patients were intubated with the help of fiber-optic devices. In this study, there were no significant difference in the type of intubation between the two groups (p=0.09). Other studies showed that there is no difference in intubation between patients with SG and patients with nonsternal goiter. SG patients can be intubated with fiber-optic devices and standard way, even if there is a serious deviation, the fiber-optic devices remain unnecessary (2,10).

SG and malignancy might be seen together. However, malignancy rates do not differ from other thyroid pathologies. Most studies showed an incidence between 6-21% (2,7,8,10,13). In this study, the malignancy rate was 24.1%. There was no statistically significant difference in the frequency of malignancy between patients with SG and those with NSG (p=0.864). Still, total thyroidectomy is indicated in SG patients with possible malignancy. Malignancy in SG does not affect pre-operative and post-operative complications.

Potential complications of total thyroidectomy are vocal cord paralysis, bleeding, hypoparathyroidism, hypocalcaemia, and rarely, tracheomalasia. Most clinicians demonstrated that post-operative complications do not differ prominently between total and standard thyroidectomy (3,5,6). Only some of them found meaningful results in patients with hypoparathyroidism (15). In this study, the patients were pre-operatively and post-operatively examined by otorhinolaryngologists for vocal cord pathology. Only one patient was diagnosed with temporary unilateral vocal cord paralysis and when compared with all other complications, there were no significant differences between SG and NSG patients (p=0.66).

Surgery is considered to be the primary approach and the gold standard for the treatment of SG. Surgery can be done via cervical approach, sternotomy, thoracotomy or a combination of these techniques. The general consensus is that most of the patients can be treated with cervical approach but some cases need thoracic intervention. Sternotomy is performed in about 0-11% of cases. This wide range may be explained by the lack of a common SG definition (2,5,6,11-13). In this study, sternotomy or thoracotomy were not applied, all patients were operated through cervical approach. In terms of bigger glands, we fixed each gland with 2-0 silk suture in order to rotate and elevate the gland much more comfortably; sharp and blunt dissections were applied to pull out the thyroid gland from the thoracic region and, vessel ligation devices were used instead of surgical knots to maintain hemostasis.

Conclusions

SG is a rare thyroid disease with no common definition. CT must be used for the evaluation of patients with heavy symptoms. Patients with SG can be safely treated through the cervical approach with low complication rates in expert hands.

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Sepsiste Steroid Kullanımı

Steroid Use in Sepsis

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Özet

Sepsis, enfeksiyon varlığında, enfeksiyonun sistemik belirti ve bulgularının olması olarak tanımlanır. Sepsis olgularının yaklaşık dörtte biri ölümle sonuçlanmaktadır. Bu nedenle hızlı ve doğru sepsis yönetimi önemlidir. Kritik hastalık sürecinde hipotalamo-hipofizyo-adrenal aksta ve kortizolün hücre içi etkinliğinde olan değişiklikler nedeniyle, sepsiste adrenal yetmezliği değerlendirmek için güvenilir bir laboratuvar testi bulunmamaktadır. Klinik araştırmalar sepsiste steroid tedavisinin morbidite ve mortaliteye etkileri konusunda çelişkili sonuçlar yayınlanmıştır. Güncel sepsis tedavi kılavuzları, güçlü kayıtlara dayanmasa da, sıvı ve vazopressör tedaviye yanıtı olmayan sepsis hastalarında steroidin düşünülmesini önermektedirler. Bu önerinin kesinlik kazanması için randomize kontrollü çalışmalardan elde edilmiş daha güçlü kanıtlara ihtiyaç vardır. *Turk Jem 2013; 17: 121-4*

Anahtar kelimeler: Sepsis, steroid, adrenal yetmezlik

Abstract

Sepsis is defined as "systemic signs and symptoms of infection in the presence of infection". Nearly one fourth of sepsis cases eventually die. Therefore, rapid and correct management of sepsis is important. There is no reliable test to evaluate adrenal insufficiency in sepsis due to the changes in the hypothalamic-pituitary-adrenal axis and intracellular effects of cortisol during the critical illness. Clinical studies reported conflicting results regarding the effects of steroid therapy on mortality and morbidity in sepsis. Contemporary sepsis management guidelines - although not based on strong evidence - suggest consideration of steroid use in septic patients who do not respond to intravenous fluids and vasopressors. Stronger evidence obtained from randomized controlled trials is needed for this suggestion to be certain. *Turk Jem 2013; 17: 121-4*

Key words: Sepsis, steroid, adrenal failure

Giriş

Sepsis, enfeksiyon varlığında, enfeksiyonun sistemik belirti ve bulgularının olması olarak tanımlanır. Doku perfüzyonununu bozulması ve organ disfonksiyonunun ortaya çıkması ise ağır sepsis olarak isimlendirilir. Sepsis hastasında uygun hidrasyona rağmen hipotansiyonun düzelmemesi septik şoktur (1).

Sepsis olgularının yaklaşık dörtte biri ölümle sonuçlanmaktadır (2,3). Bu nedenle hızlı ve doğru sepsis yönetimi önemlidir.

İlk kez günümüzden yaklaşık kırk yıl önce endotoksik şokta steroid tedavisinin sağkalımı artırdığını gösteren hayvan deneyleri yayınlanmış, bunun üzerine steroid tedavisi klinik çalışmalarda ele alınmaya başlanmıştır (4,5).

Klinik araştırmaların bir kısmında kullanılan steroid dozu, 30-120 mg/kg/gün dozda metilprednizolon veya eşdeğeri dozuna kadar çıkılmıştır. Fakat bu dozda tedavinin olumsuz sonuçları gözlenmiştir. Yapılan bir metaanalizde yüksek doz steroidin septik hastalarda mortaliteyi artırdığı kanıtlanmıştır (6). Fakat izleyen yıllarda klinik çalışmalardan fizyolojik dozda steroidin yararı konusunda çok sayıda kanıt gelmiştir (7-11).

Kritik Hastalıkta HPA Aksinda Neler Değişir?

Strese maruz kalmak, organizmada birbiriyle bağlantılı ama aynı zamanda karmaşık, merkezi ve periferal uçları olan bir dizi yanıt başlatır. Bu yanıtlar sağkalımı artırma amacına yöneliktir. Stres yanıtı olarak adlandırılan bu durum başlıca iki sistem tarafından; sempatik sinir sistemi ve hipotalamo-hipofizyo-adrenal aks (HPA) tarafından yönetilir (12). HPA aksının aktive olması sonucunda steroid sentezi artar ve steroid, stresle başa çıkılabilmesi için gereken immün, kardiovasküler ve metabolik değişiklikleri düzenler. Adrenal korteksten salınan başlıca glukokortikoid, kortizoldür.

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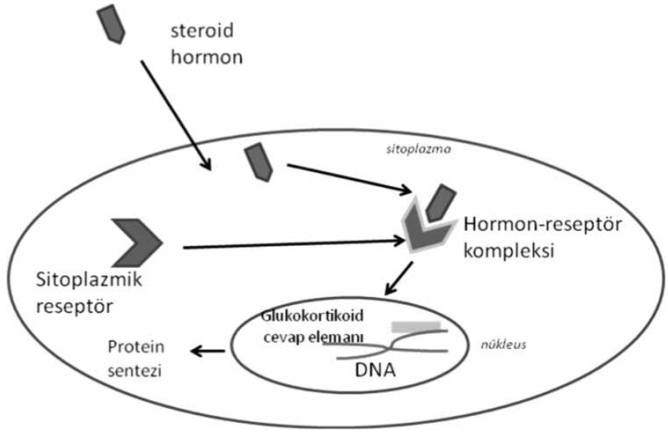
Kortizol adrenalde depolanan bir hormon değildir ve yarı ömrü 70-120 dakika kadardır (13). Kortizol dolaşımda %90 oranında kortizol bağlayıcı globuline (CBG) bağlı olarak taşınır (13). Hücrede kortizol, hücreiçi glukokortikoid reseptörüne (GR) bağlanır. Bağlanmayla beraber steroid-reseptör kompleksi aktive olur ve nukleusa doğru hareket eder. Steroid-reseptör kompleksi, nükleusta, DNA üzerinde, glukortikoid yanıt elemanları (GRE) adı verilen özel bölgelere bağlanır. Böylece ilgili genlerin transkripsiyonu ve protein sentezi gerçekleşir (15) (Şekil 1). Kortizol binlerce gende transkripsiyon işini yönetmekten başka, diğer transkripsiyon faktörlerinin çalışmasına da müdahale edebilir. Bunlardan en önemlisi nükleer faktör kapa betadır (NF-κB). NF-κB, interlökinler ve tümör nekroz faktörü gibi önemli sitokinlerin sentezinden sorumludur ve kortizol NF-κB'yi inhibe etmektedir (16).

Akut hastalıkta, kortizol üretiminde, taşınmasında ve hücresel etkilerinde bazı değişiklikler olduğu saptanmıştır. Akut hastalıkta CBG düzeyi neredeyse yarı yarıya azalmakta ve böylece serbest kortizol düzeyi artmaktadır (17). Deneysel modellerde, proinflamatuvar sitokinlerin ve endoktoksinlerin, GR sayısını, GR translokasyonunu, steroid reseptör kompleksinin DNA'ya olan afinitesi azalttığı gösterilmiştir. Bu durum, daha önce kronik obstrüktif akciğer hastalığı gibi kronik inflamatuvar süreçte varlığı gösterilen steroid direncinin, akut inflamasyonda da olduğunu düşündürmektedir. Bir başka çalışmada mikrodiyaliz yöntemiyle interstisyumdan ölçülen kortizolün, plazma kortizolü ile sadece orta düzeyde korele olduğu kanıtlanmıştır. 18 Bu da, dolaşımdaki kortizol düzeyinin dokudaki etkinin doğrudan bir göstergesi olmayabileceği anlamına gelmektedir.

Bu değişiklikler sepsiste adrenal yetmezliğin nasıl tanımlanacağı konusunu çıkmaza sokmaktadır. Ama klinisyeni bekleyen sorunlar bununla sınırlı değildir. Genel bir görüş adrenal yetmezlik tanısını ACTH uyarı testiyle koymaktır. 250 mcg intravenöz ACTH sonrası kortizolde 9mcg/dL ya da daha fazla artış oluyorsa (delta kortizol) adrenal yetmezlik tanısı dışlanır (19). Bu testle görece adrenal yetmezlik tanısı konan sepsis hastalarında steroid tedavisinin mortaliteyi azalttığını gösteren çalışmalar vardır (7,9). Ne var ki, yakın zamanda bu testin güvenilir olmadığını düşündüren bir araştırma sonucu yayınlanmıştır. Sepsis hastalarında steroid tedavisinin etkisini araştıran çok merkezli randomize kontrollü bir çalışmada ACTH testine yanıt versin ya da vermesin tüm sepsis hastalarında, steroid tedavisinin mortaliteye etkisi olmadığı gösterilmiştir (20). ACTH uyarı testi adrenal bez fonksiyonu hakkında fikir verebilir ama HPA aksının normal olup olmadığını göstermez. Bu nedenle kılavuzlar, septik hastalarda steroid tedavisinin ACTH uyarı testine göre planlanmasını önermemektedir (21,22).

Serbest kortizol düzeyi ölçümü de kılavuzlarda önerilmemektedir (21,22). Çünkü serbest kortizol ölçümü her laboratuvarda yapılamamaktadır. Ayrıca septik hastada serbest kortizolün normal değerleri net olarak ortaya konmuş değildir. Anestezi indüksiyonu için yoğun bakımda entübasyon öncesi kullanılan etomidatın da HPA aksını baskıladığı bilinmektedir (23).

Bütün bu etkenler, görece ya da mutlak adrenal yetmezlik tanısını koymak için klinisyenin elinde iyi bir laboratuvar testinin olmadığını açıkça göstermektedir. 2008 yılında yayınlanan bir kılavuzda



Şekil 1. Steroidin etki mekanizması

Tablo 1. Annane ve ark. çalışması ile CORTICUS çalışmasının karşılaştırılması

Annane ve ark. çalışması	CORTICUS
Fransa'da çok merkezli	Avrupa'da çok merkezli
Çift kör randomize plasebo kontrollü	Çift kör randomize plasebo kontrollü
Vazopresöre cevapsız septik şok	Septik şok
İlk 8 saatte	İlk 72 saatte
N: 300	N: 500
Plasebo kolunda 28 gün mortalite %61	Plasebo kolunda 28 gün mortalite %31
Cerrahi hasta % 40	Cerrahi hasta%64
4x50mg hidrokortizon ve 50 mcg fludrokortizon	4x50mg hidrokortizon
Sonuç : görece adrenal yetmezliği olanlarda % 30 azalmış mortalite	Sonuç: ACTH (250mcg) testinden bağımsız olarak mortalitede fark yok
	Tedavi kolunda şoktan çıkış daha hızlı (ACTH cevaplı grupta)
	Yeni enfeksiyon ve enflamasyonda geri dönüş(rebound şok) riski yüksek (istatistiksel olarak anlamlı değil)

görece ya da mutlak adrenal yetmezlik tanımları yerine, "kritik hastalıkla ilişkili adrenal yetersizlik" tanımı önerilmektedir (22).
Bu tanım; adrenal steroid yapımının azlığından başka, doku düzeyinde olan ve ölçülmesi mümkün olmayan değişiklikleri de kapsamakta ve eşik bir laboratuvar değeri belirtmemektedir.

Klinik Çalışmalar ve Metaanalizler

Sepsiste steroid kullanımıyla ilgili, farklı sonuçları olan çok sayıda klinik çalışma vardır. Son yıllarda bu çalışmalar metaanalizlerle incelenmiştir. Annane ve arkadaşları 12 çalışmayı dahil ettikleri bir derlemede düşük doz hidrokortizonun şoktan çıkışı hızlandırdığını ve 28 günlük mortalite oranını belirgin şekilde azalttığını bildirmişlerdir (RR, 0,84; 95% CI, 0,72–0,97; p=0,02). 6 Minecci ve arkadaşları da yaptıkları metanalizde benzer sonuçlar elde etmişlerdir (24). Sligl ve arkadaşları ise daha seçici davranarak 6'sı iyi derecede randomize kontrollü olan 8 çalışmayı değerlendirdikleri bir metaanalizde, steroidin şoktan çıkışı hızlandırdığını ama mortaliteye etkisi olmadığını öne sürmüşlerdir (RR, 1,00; 95% CI, 0,84-1,18) (25). 2013 yılında yayınlanan sepsis kılavuzunda, kanıtlar arasında yer alan bir değerlendirmeye göre, sepsiste hidrokortizon tedavisinin kullanıldığı 6 seçilmiş çalışmadan mortalitesi nisbeten düşük olan üç çalışmada, hidrokortizon tedavisinin mortaliteye etkisi yoktur. Mortalitesi daha yüksek olan diğer üç çalışmaya bakıldığında ise, mortalitede anlamlı olmayan bir azalma izlenmiştir (22).
Sepsiste steroid kullanımıyla ilgili yapılmış en kapsamlı iki çalışmadan biri Annane ve arkadaşlarının Fransa'da yaptığı çok merkezli çalışma, diğeri de Avrupa'sa yapılan çok merkezli CORTICUS çalışmasıdır. Her iki çalışma da, randomize çift kör ve plasebo kontrollü olarak tasarlanmıştır.
Annane ve arkadaşları 300 sepsis hastasını çalışmaya almışlardır. Vazopresöre tedaviye yanıtı olmayan septik şok olgularına 4x50 mg hidrokortizon ve 50 mcg fludrokortizon tedavisi beş gün boyunca verilmiştir. Hastalara tedavi sepsis tanısından sonraki 8 saat içinde başlanmıştır. Çalışmada ACTH uyarı testi sonrası delta kortizolü <9mcg/dL olan olgular yanıtsız kabul edilmiştir. ACTH yanıtsız olgularda hidrokortizon tedavisinin hem şoktan çıkışı hızlandırdığı hem de mortatilteyi azalttığı gösterilmiştir (7). Bu çalışmaya göre steroid verilen grupta, enfeksiyon ve gastrointestinal kanama sıklığında bir artış yoktur.
CORTICUS çalışmasında ise 500 septik şok hastası çalışmaya alınmıştır. Hidrokortizon 4x50 mcg dozunda ilk 72 saatte başlanmıştır. Fakat bu çalışmada, ACTH testine yanıtı olsun olmasın, tüm olgularda steroidin mortalite etkisi olmadığı saptanmıştır. Şoktan çıkış, ACTH yanıtı olduğu halde steroid alan grupta daha hızlı görünmektedir. Steroid alan grupta şokun geri dönmesi ve enfeksiyon riski istatistiksel olarak anlamsız olsa da artmıştır. CORTICUS yazarları septik şokta steroid tedavisini önermemektedirler (20). İki çalışmanın özeti karşılaştırmalı olarak Tablo1 de gösterilmiştir. CORTICUS çalışmasında plasebo kolunda 28 günlük mortalite oranı daha düşüktür yani bu çalışmada nisbeten iyi durumdaki sepsis hastalarının olduğu söylenebilir. CORTICUS da cerrahi hastası oranı daha fazladır. Fransa'da yapılan çalışmada ise sadece vazopressöre yanıtı olmayan sepsis hastalarının alınması, tedavinin daha hızlı başlanması ve plasebo kolundaki mortalitenin daha yüksek olması başlıca farklardır.

Kılavuzlar Ne Diyor?

Sepsisle Ilişkili Adrenal Yetersizlik Tanı ve Tedavisinde Güncel Klinik Yaklaşım:
Amerikan Kritik Bakım Tıbbı kılavuzu 2008 yılında yayınlanmıştır. Bu kılavuz, özellikle sıvı ve vazopresör tedavisine yanıtı olmayan septik şok olgularında hidrokortizon tedavisinin düşünülmesini önermektedir. Bu öneri yazarlarca, zayıf ve orta derecede kanıtlara dayandırılmış bir öneri olarak nitelendirilmiştir (22). Tanı için bu kılavuzun önerdiği eşik değer kortizol düzeyinin 10 mcg/dL'den az olması ya da cosintropin testi sonrası kortizol artışının (delta kortizol) 9 mcg/dL'den az olmasıdır. Sepsis hastalarında eşik değeri bilinmediğinden, serbest kortizol ölçümü önerilmemektedir. Doza gelince; kılavuz, 200 mg/gün hidrokortizonu 4 bölünmüş dozda vermeyi ya da 100mg puşe hidrkortizon sonrası 10mg/saat infuzyon vermeyi (240 mg) önermektedir.
Aynı yıl yayınlanan Kanada acil Hekimleri derneği sepsis kılavuzu, hangi hastalara steroid verilmesi gerektiği konusunda aynı öneriyi yapmıştır. Öneri D derecesindedir yani çelişkili sonuçlara dayalıdır (26). Bu kılavuza göre verilmesi gereken hidrokortizon dozu 200-300 mg/gündür. Tedavi verilmeden önce ACTH uyarı testi yapmak opsiyoneldir ama sonuçlar beklenmeksizin klinik gerekliliğe dayanarak steroid verilmelidir. Kanada kılavuzu, acil hekimlerine, başka bir seçenek olarak 4-6 mg intravenöz deksametazon vermeyi önermektedir. ACTH ve serum kortizolü deksametazondan etkilenemeyeceği için bu durumda testler daha sonra da yapılabilir.
2010 yılında yayınlanan bir kılavuzda Alman hematoloji onkoloji derneği nötropenik hastalardaki sepsiste steroid kullanmayı önermediklerini, orta derecede aleyhte kanıta dayandırarak söylemişlerdir (27).
Sepsis konusunda en kapsamlı ve yeni kılavuz Şubat 2013'te yayınlanmıştır. Bu kılavuz sıvı ve inotropik ajanlara yanıtı olmayan septik şok hastasında hidrokortizonun düşünülmesini önermektedir. Öneri 2 ^{0}C düzeyinde yani düşük düzeyde kanıta dayalı zayıf bir öneridir (21) Önerilen doz 200 mg/gün hidrokortizondur. Yazarlar, sepsis hastalarında her hangi bir zaman yapılacak kortizol ölçümünün doğru sonuç vermeyeceğini ve ACTH uyarı testinin de gereksiz olduğunu söylemektedirler. Vazopressör ihtiyacı ortadan kalktıktan sonra steroid tedavisi azaltılarak kesilebilir.

Sonuç

Sepsis birçok sistemin etkilendiği ve farklı yanıt mekanizmalarının dâhil olduğu karmaşık bir süreçtir. Septik bir hastada steroidler, hem HPA aksında hem de hücre içinde, sağlıklı bir kişide olduğundan çok farklıdır. Bu nedenle sepsiste steroidin yeterli olup olmadığını saptayacak güvenilir bir test yoktur. Klinik çalışmalar ise steroidin sepsis mortalitesine olan etkisi konusunda çelişkili bilgiler vermektedir. Güncel kılavuzlar ışığında, steroid tedavisinin, uygun vazopressör ve sıvı desteğini aldığı halde hipotansiyonu düzelmeyen sepsis hastalarında verilebileceği düşünülmektedir. Bu önerinin kesinlik kazanması için randomize kontrollü çalışmalardan elde edilmiş daha güçlü kanıtlara ihtiyaç vardır.

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Panhypopituitarism Due to Hemochromatosis

Hemokromatozise Bağlı Panhipopituitarizm

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Abstract

Hemochromatosis is an iron storage disease. Panhypopituitarism is a clinical condition in which the anterior pituitary hormones are deficient. Herein, we report a rare case of panhypopituitarism due to hemochromatosis. *Turk Jem 2013; 17: 125-6*

Key words: Hemochromatosis, hypopituitarism, liver cirrhosis

Özet

Hemokromatozis bir demir depo hastalığıdır. Panhipopituitarizm ise ön pituiter bez hormonlarının yetersiz olduğu klinik durumdur. Bu yazıda hemokromatozise bağlı panhipopituitarizmli nadir bir olgu bildirilmiştir. *Turk Jem 2013; 17: 125-6*

Anahtar kelimeler: Hemokromatozis, hipopituitarizm, karaciğer sirozu

Introduction

Hemochromatosis is an iron storage disease characterized by iron deposition in parenchymal cells due to increased intestinal iron absorption. Iron overload leads to tissue damage and dysfunction particularly in the liver, pancreas, heart, joints, and pituitary gland. Panhypopituitarism is a clinical condition in which the anterior pituitary hormones are deficient. Herein, we report a rare case of hemochromatosis.

Case Report

A sixty-two-year-old woman was admitted to our hospital with the complaints of weakness, body swelling and confusion. On admission, her general condition was poor; regarding her state of consciousness, she had a tendency to sleep, and she had an apathetic face and bronze-colored skin. Past medical history included hepatitis C, esophageal varices and a liver biopsy performed 1.5 years ago which revealed the presence of micronodular cirrhosis with accumulation of hemosiderin. Laboratory values on admission are shown on Table 1. Abdominal ultrasonography showed chronic parenchymal liver disease, splenomegaly (15.5 cm) and cholelitiasis. She was hospitalized in the intensive care unit with the diagnosis of chronic parenchymal liver disease and hepatic encephalopathy. We performed pituitary hormone tests for the possibility of pituitary involvement due to hemochromatosis. The values were: LH: 1.12 [14.2-52.3] IU/ml, FSH: 2.77 [19.3-100.6] IU/ml, GH: <0.05 ng/ml, prolactin: 0.657 [3-23] ng/ml, cortisol: 3.54 [5-23] µg/dl. An ACTH stimulation test was done for pituitary insufficiency (Synacthen 1 mg IM). At 0th minute, the cortisol level was 3.54 µg/dl, 30th minute - 20 µg/dl and at 1st hour, it was 10 µg/dl. Therefore, primary adrenal insufficiency was excluded. Contrast-enhanced computed tomography of the pituitary was normal. Thus, the patient was diagnosed as having panhypopituitarism. Methylprednisolone 40 mg IV initially and levothyroxine on the fifth day were administered. She recovered with this therapy and discharged with prednisolone 7.5 mg/day and levothyroxine 0.1 mg/day.

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Table 1. Laboratory values

	Patient's values	Normal values		Patient's values	Normal values
AST (U/L)	39	[13-40]	AFP (IU/ml)	5.4	[0.5-5.5]
ALT (U/L)	28	[7-45]	Hb (g/dl)	10.5	[12-18]
GGT (IU/L)	21	[3-96]	Fe (mcg/dl)	127	[50-175]
ALP (IU/L)	85	[32-213]	Ferritin (ng/ml)	581	[10-250]
T. BIL (mg/dl)	5.3	[0.3-1.2]	IBC (mcg/dl)		
D. BIL (mg/dl)			fT3 (pg/ml)	120	[250-450]
PT (sec)	4.3	[0-0.2]	fT4 (pg/ml)		
Alb (g/dl)			TSH (IU/ml)	0.39	[1.8-5.2]
	36.7	[11-16]		< 1	[0.8-2.7]
	2.5	[3.5-5.5]		0.79	[0.4-4.2]

AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma-glutamyl transferase, ALP: alkaline phospatase, T.BIL: total bilirubin, D.BIL: Direct bilirubin, PT: Prothrombin time, Alb: Albumine, AFP: Alpha-fetoprotein, Hb: haemoglobin, Fe: serum iron level, IBC: iron binding capacity, fT3: free triiodothyronine, fT4: free tetraiodothyronine, TSH: tiroid stimulating hormone

Discussion

Hereditary hemochromatosis is an autosomal recessive disorder caused by mutations in the HFE gene on chromosome 6 (1). The outcome of this genetic mutation is excessive absorption of dietary iron leading to parenchymal iron overload and subsequent tissue damage. It typically presents in the 4th and 5th decades, and while phenotypic expression is variable; iron overload in the liver and skin predominate. Hemochromatosis causes hypopituitarism by deposition of iron in the anterior pituitary. After diabetes, hypogonadotrophic hypogonadism is the most common endocrinopathy in hemochromatosis. Recently, an Irish study reported a prevalence of hypogonadism of only 6.4% in its male hemochromatosis patients (2). Transferrin saturation (calculated from the ratio of serum iron concentration to total iron-binding capacity expressed as a percentage) is regarded as the best screening test for hereditary hemochromatosis (3). Liver biopsy is not required for diagnosis in all patients but is obviously useful in assessing disease progression (3,4).

In conclusion, hemochromatosis may rarely cause panhypopituitarism by accumulation of hemosiderin. The clinician should consider pituitary involvement if the state of the consciousness diminishes in patients with cirrhosis due to hemochromatosis. Hepatic encephalopathy might be confused with panhypopituitarism. Additionally, panhypopituitarism may lead to a change in consciousness in the presence of secondary hypothyroidism. Hyponatremia, which may accompany hypothyroidism, may also cause confusion and lethargy. Imaging is usually normal and patients are often wrongly labeled as having idiopathic hypopituitarism. The differential diagnosis should be made; otherwise the treatment might be delayed. Therefore, in consistent with Lewis et al., we recommend that iron studies are performed in all patients who present with hypopituitarism and normal pituitary imaging (5).

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Tiroglossal Kanal Kisti Papiller Karsinomu ve Tiroid Papiller Mikrokarsinom Birlikteliği

Coexistence of Thyroglossal Duct Papillary Carcinoma and Thyroid Papillary Microcarcinoma

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Özet

Tiroglossal kanal kistinde karsinom gelişimi oldukça nadirdir. Malign patolojilerin çoğu tiroidin papiller karsinomudur. Tanı, genellikle cerrahi sonrası çıkarılan dokunun histopatolojik incelemesi sonucunda konur. Boyun orta hatta kitlesi olan 41 yaşında erkek hasta başlangıçta tiroglossal duk¬tus kisti tanısıyla Sistrunk ameliyatı oldu, histopatolojik inceleme sonucunda tiroglossal duktus kisti içinde tiroid papiller karsinomu tespit edildi. Tiroid Ultrasonografi ve Elastografi yapıldı. Elastosonografi ile sert , B-mode 'da tamamen mavi görülen 3 milimetre boyutunda hipervasküler tiroid nodülü tespit ettik. Sonrasında hastaya total tiroidektomi, bilateral boyun diseksiyonu yapıldı. Patolojisi, servikal lenf nodu metastazı olmaksızın, tiroid papiller mikrokarsinomu olarak rapor edildi. Tiroglossal kanal kistine yönelik yapılan Sistrunk ameliyatı sonrası histopatolojik inceleme sonucu, malignite olarak tespit edildiğinde, tiroid bezi radyolojik yöntemlerle dikkatle değerlendirilmelidir. *Turk Jem 2013; 17: 127-8*

Anahtar kelimeler: Tiroglossal kanal kisti, tiroid papiller kanser, hipervasküler nodül

Abstract

Malignant lesion of a thyroglossal duct cyst (TGDC) is an extremely rare entity. Papillary carcinoma is the most common malignancy of the endocrine system. Diagnosis is commonly made after pathological examination of the surgical specimen. A 41-year-old male patient with a midline neck mass was initially diagnosed with a thyroglossal duct cyst and underwent a Sistrunks procedure. Histopathologic examination revealed a papillary thyroid car¬cinoma within the thyroglossal duct cyst. Ultrasound elastography of the thyroid gland was performed. We have detected a hypoechoic hypervascular thyroid nodule measuring 3 mm in diameter that appeared completely blue in B-mode ultrasonography, and hard tissue was visualized by elastosonography (ES). The patient then underwent total thyroidectomy and bilateral neck dissection. The final pathological finding showed papillary microcarcinoma of the thyroid gland without cervical lymph node metastasis. When a thyroglossal duct cyst is excised using Sistrunk's procedure and when the definitive hystological analysis depicts malignancy, the thyroid gland must be studied carefully with radiological examinations. *Turk Jem 2013; 17: 127-8*

Key words: Thyroglossal duct cyst, thyroid papillary carcinoma, hypervascular nodule

Giriş

Tiroglossal kanal kisti, tiroglossal kanal artıklarından gelişen konjenital bir anomalidir ve genç erişkin popülasyonda %7 oranında görülür (1). Tiroglossal kanal kistinde karsinom gelişimi oldukça nadirdir ve olguların %1'inden azında gözlenir (2,3). En sık görülen malign patoloji tiroidin papiller karsinomudur (4). Tanı genellikle cerrahi sonrası çıkarılan dokunun patolojik incelemesi sonucunda konur. Biz, tiroglossal kanal kisti tanısıyla opere olan ve histopatolojisi papiller karsinom olarak raporlandıktan sonra yaptığımız incelemelerde, tiroidin mikropapiller kanseri tespit ettiğimiz bir vakamızı sunmayı planladık.

Olgu

Kırk bir yaşında erkek hasta, 3 ay önce fark ettiği, boyunda ele gelen ağrısız şişlik şikâyetiyle, kulak burun boğaz polikliniğine başvurmuş, yapılan fizik muayenede; boyun orta hatta, tiroid

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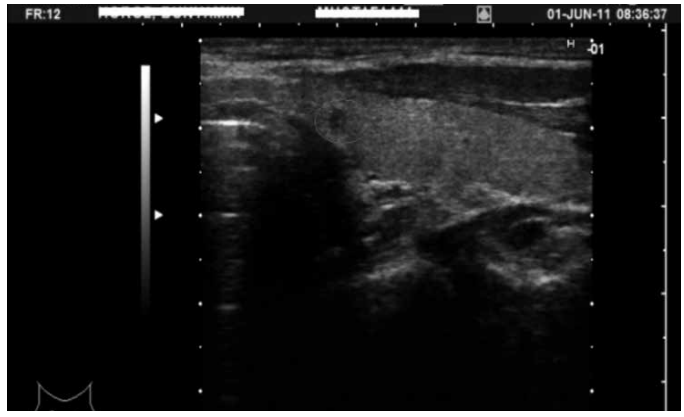
kartilaj ve hyoid kemik arasında yaklaşık 2x2cm kitle palpe edilmiş. Boyuna radyasyon öyküsü olmayan hasta, klinik olarak ötroid idi. Radyoloji bölümünce yapılan boyun ultrasonografisinde (USG); hyoid kemik superior sağ lateral komşuluğunda 20x15 mm düzensiz solid komponent içeren kistik kitle lezyonu izlenmiş. Tiroid glandı boyutları normal, konturları düzgün, eko paterni homojen izlenmiş ve gland içerisinde eko farkı oluşturan bir lezyon tespit edilmemiş. Kitle eksizyonu planlanan hastanın ameliyat öncesi çekilen bilgisayarlı boyun tomografisi incelemesinde de benzer şekilde hyoid kemik anterosuperiorunda 19x13 mm lobüle konturlu hipodens kitle izlenmiş, patolojik boyut ve görünümde lenf nodu izlenmemiş, tiroid glandında yer kaplayan lezyon tanımlanmamış. Yapılan Tc-99m tiroid sintigrafisi normal bulunmuş. Hastaya kulak burun boğaz kliniği tarafından Sistrunk operasyonu yapılmış ve histopatolojik inceleme tiroglossal kanaldan kaynaklanan papiller karsinom olarak rapor edilmesi üzerine hasta, ileri inceleme amacı ile Endokrinoloji polikliniğine yönlendirilmiş. Hastaya kliniğimizde yapılan tiroid USG'de sağ lob istmus komşuluğunda 2x3x3mm hipoekoik lezyon tespit edildi (Şekil 1). Bu lezyonun elastografi skoru=4, strain indeksi=2,67 olarak ölçüldü (Şekil 2). Lezyondan yaptığımız ince iğne aspirasyonu sonucu 'papiller karsinom' olarak raporlandı. Hastaya total tiroidektomi ve anterior boyun diseksiyonu yapıldı. Histopatolojik değerlendirmede; 4 mm ve 2 mm çapında 2 odak halinde papiller karsinom tespit edildi. Değerlendirilen 20 adet lenf nodu ve tiroglossal remnantta tümör rapor edilmedi.

Tartışma

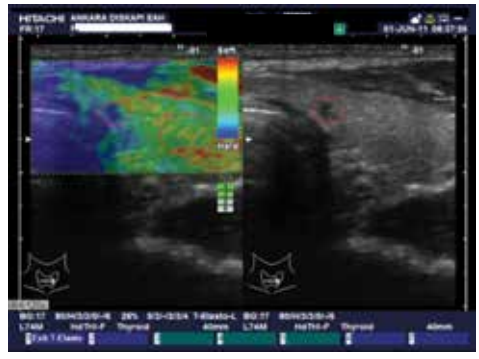
Boyunda kitle, sık karşılaşılan bir klinik bulgudur ve ayırıcı tanı çok sayıda nedene bağlı olabilir. Kitlelerin çoğu, benign nedenlere bağlı olmakla birlikte, malign hastalıklar göz ardı edilmemelidir. Bu nedenle boyunda kitle ile başvuran bir hastaya, sistematik bir yaklaşım geliştirmek önemlidir.

Benign tiroglossal kanal kistleri, genellikle, asemptomatik, yumuşak ve büyümeye meyilli olmayan ön boyun kitleleri olarak tespit edilebilirler. Tiroglossal kanal kistinde karsinom gelişimi, oldukça nadirdir ve olguların %1 inden azında gözlenir (2,3). Nadir görülmesi nedeniyle cerrahi eksizyondan önce maligniteden kuşkulanılmaz. Ancak, bizim vakamızda da olduğu gibi, fikse ve boyutu hızla artış gösteren bir kitle varlığında maligniteden kuşkulanılabilir. İleri yaştaki hastalar, kadın hastalar ve lezyonun hızlı büyüme gösterdiği hastalar malignite yönünden daha fazla risk altındadır (5).

Tiroglossal kanal kistinden kaynaklanan karsinomlarda 2 tip histolojik odak tariflenmiştir. Birincisi ve sıklıkla görüleni, tiroid elemanlarından, ikincisi ise yassı hücreli epitelden gelişen karsinomlardır. Karsinom rastlanan tiroglossal kistlerde en sık kanser bizim olgumuzda da olduğu gibi papiller karsinomdur (%85). Tiroglossal kanal kistinden karsinom gelişimi çok nadir olması nedeniyle klinisyenler genellikle, cerrahi öncesi onkolojik tanıdan şüphelenmezler ve sonuçta tiroglossal kanal kisti karsinomu tanısı, cerrahi sonrası örneklerin histopatolojik incelemesi ile konmaktadır. Bu güçlüğün üstesinden gelebilmek için, tiroglossal kanal kisti tespit edilen hastalarda tiroid glandının ve boyun lenf nodlarının ayrıntılı incelenmesi gerekmektedir. Bizim vakamızda, operasyon öncesi radyoloji tarafından tiroid glandı değerlendirmesi yapılmış ancak 3 mm hipoekoik nodül gerek ultrasonografik gerekse sintigrafik incelemelerde tespit edilememişti. Elastosonografi (ES)'nin tiroid nodüllerine tanısal yaklaşımda kullanımı son yıllarda yaygınlaşmaya başlamıştır. ES ile belirlenmiş SI değerleri, nodülün ultrasonografik özellikleri ile birlikte kullanılarak tiroid nodüllerinin ayırıcı tanısında non invaziv bir metod olarak avantaj sağlamaktadır (8).



Şekil 1. Tiroid Ultrasonografi görüntüsü



Şekil 2. Nodülün elastosonografi görüntüsü

Literatürde, boyunda patolojik lenf nodu yok iken, tiroid glandında papiller kanser ile birlikte tiroglossal kanal kisti papiller karsinomu tespit edilen 2 vaka raporu daha mevcuttur (6,7). Dolayısıyla tiroglossal kanal kisti saptanan olgularda, çok az malignite riski olsa dahi, tiroid glandında papiller mikrokarsinom ile birliktelik ihtimali göz önüne alınmalıdır. Bu durumun, tiroid mikrokarsinomunun tiroglossal kanala metastazı ya da aynı mutasyonun iki ayrı bölgede multifokalite benzeri papiller tiroid karsinomuna yol açtığını düşünmekteyiz. Ayrıca tiroid glandı ve lenf nodlarına yapılacak ayrıntılı değerlendirme, hastaya yapılacak olan operasyonun tipinin belirlenmesi açısından da önem arz etmektedir.

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Dengue Preceding Diabetic Ketoacidosis

Tirotoksikozda Mavimsi Renk Değişikliği

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Dear Editor;

Diabetic ketoacidosis (DKA) is an important hyperglycemic complication of diabetes mellitus. Infection is confirmed as an important underlying etiology of DKA. Here, the author presents an interesting case of dengue preceding DKA. The case is a 61-year-old female presenting to the physician with the complaint of high fever without relief by self-prescription of acetaminophen. She had an underlying disease, diabetes mellitus (DM). Her body temperature was 39.4 degrees Celsius and her complete blood count showed an important finding: thrombocytopenia (platelet count = 85.000). The serological test was done and the diagnosis of dengue hemorrhagic fever was finally confirmed. This case was treated by standard fluid replacement therapy (normal saline regimen). On day 3, the patient developed new symptoms, frequent urination (more than 3 times in an hour, abdominal pain, nausea, vomiting and rapid breathing). Complete blood count was done but platelet count was within normal limit at this time. However, the urinalysis showed many positive findings, sugar 4+ and ketone 3+. Her additional blood chemistry results showed a blood glucose level of 454 mg/dL and positive serum ketone. The patient was finally diagnosed to have DKA and endocrinologists were consulted for the management. Of interest, this is a simple case of DKA but the interesting issue is the underlying condition leading to DKA in this patient. Although there are many reports confirming that infection can induce DKA, this is the first reported case of dengue preceding DKA. Indeed, there is a previous report from Thailand on a female patient presented to the physician with concurrent DKA and dengue infection (1). However, DM had not previously been diagnosed in the present case. The dengue infection is common in the tropical world and DM is also the important emerging health problem in this area. Some reports note that DM can be an aggravating factor in the development of dengue shock (2,3). There is an interesting report stating that patients suffering from dengue fever should be cautioned for development of diabetes in future (4)". However, dengue has rarely been mentioned as a risk factor in the development of DKA. Based on the present situation that DM is a very common problem, testing blood glucose during the management of dengue infection is useful (4). The concern on the diabetic complications such as DKA should also be kept in mind in the treatment of patients suffering from dengue. Moreover, it should be noted that not only bacterial but also viral infections (such as dengue, herpes, etc.) can induce DKA (1,5). The good example is a previous report on herpes simplex virus infection inducing DKA (5).

Key words: Dengue, diabetic ketoacidosis

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