



Changes in Thyroid Hormones and Free Triiodothyronine-to-Free Thyroxine Ratio in Euthyroid Patients with Obesity in Terms of Different Glucose Metabolism Statuses

Obezitesi Olan Ötiroid Hastalarda Farklı Glukoz Metabolizması Durumlarında Tiroid Hormonları ve Serbest Triiodotironin/Serbest Tiroksin Oranı

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Abstract

Objective: The variations of thyroid hormones within normal ranges are observed in different metabolic conditions. Considering available data, levels of thyroid hormones change in obesity and type 2 diabetes mellitus (DM) in opposite ways. This study aimed to evaluate thyroid hormone levels and free triiodothyronine-to-free thyroxine (FT3/FT4) ratios in different glucose metabolism statuses of euthyroid patients with obesity. **Material and Methods:** This retrospective study evaluated thyroid hormones and the FT3/FT4 ratio of 209 patients with obesity who were grouped according to their glucose metabolism statuses. **Results:** One hundred and thirty-one (62.7%) patients had normal glucose tolerance, 41 (19.6%) patients had prediabetes, and 37 (17.7%) patients had DM. Serum FT4 level was found to be higher in patients with DM compared to patients with normal glucose tolerance ($p=0.009$), although no difference was observed in serum thyroid-stimulating hormone and FT3 levels among groups. FT3/FT4 ratio was determined to be lower in patients with DM than patients with normal glucose tolerance ($p=0.012$). Hemoglobin A1c was independently and positively associated with FT4 ($\beta=0.345$, $r^2=0.119$, $p=0.003$) and negatively associated with FT3/FT4 ratio ($\beta=-0.371$, $r^2=0.138$, $p=0.001$). **Conclusion:** Serum FT4 level increased, and FT3/FT4 ratio decreased in patients with type 2 DM independent of the degree of obesity. The interaction of DM with thyroid hormones in our cohort seemed to overcome obesity-related changes in thyroid functions.

Keywords: Diabetes mellitus; FT3/FT4 ratio; obesity; prediabetes; thyroid hormones

Özet

Amaç: Farklı metabolik durumlarda tiroid hormon düzeylerinde normal referans aralıkta iken bile varyasyonlar görülebilmektedir. Mevcut veriler, obezite ve tip 2 diabetes mellitustaki (DM) tiroid hormon değişimlerinin farklı yönlerde olduğunu göstermektedir. Bu çalışmada, obezitesi olan ötiroid hastalarda farklı glukoz metabolizması durumlarında tiroid hormon düzeyleri ve serbest tiroksin/serbest triiodotironin (sT3/sT4) oranlarının değerlendirilmesi amaçlanmıştır. **Gereç ve Yöntemler:** Bu retrospektif çalışmada, glukoz metabolizması durumlarına göre gruplandırılmış obezitesi olan ötiroid 209 hastanın tiroid hormonları ve sT3/sT4 oranları değerlendirilmiştir. **Bulgular:** 131 (%62,7) hastada normal glukoz toleransı, 41 (%19,6) hastada prediyabet ve 37 (%17,7) hastada tip 2 DM mevcuttu. Serum sT4 düzeyleri DM'si olan hastalarda normal glukoz toleransı olanlara kıyasla artmış olarak bulunmuşken ($p=0,009$), gruplar arasında serum tiroid stimulan hormon ve sT3 düzeylerinde fark izlenmemiştir. ST3/sT4 oranı ise DM'li hastalarda normal glukoz toleransı olanlara kıyasla düşük idi ($p=0,012$). Hemoglobin A1c düzeyi sT4 ile bağımsız pozitif ilişkili iken ($\beta=0,345$, $r^2=0,119$, $p=0,003$), sT3/sT4 oranıyla bağımsız negatif ilişkiliydi ($\beta=-0,371$, $r^2=0,138$, $p=0,001$). **Sonuç:** Tip 2 DM'li ötiroid hastalarda obezite derecesinden bağımsız olarak serum sT4 düzeyleri artmış, sT3/sT4 oranı ise azalmış olarak bulunmuştur. Kohortumuzda DM'ye ait tiroid hormon değişimleri obeziteye bağlı tiroid fonksiyonlarındaki değişimlere üstün gelmiş görünmektedir.

Anahtar kelimeler: Diabetes mellitus; sT3/sT4 oranı; obezite; prediyabet; tiroid hormonları

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Introduction

Obesity and type 2 diabetes mellitus (DM) are closely related health problems that affect people at a rapidly increasing rate. Thyroid hormones are known to have a crucial role in the regulation of energy homeostasis, thermogenesis, and glucose metabolism (1). Thyroxine and a small amount of triiodothyronine are secreted from thyroid follicles. Thyroxine is converted into its bioactive form, triiodothyronine, by type 1 iodothyronine deiodinase in peripheral tissues. The free triiodothyronine-to-free thyroxine (fT3/fT4) ratio indicates the peripheral turnover of thyroid hormones. Thyroid dysfunction is associated with impairment in glucose metabolism and obesity. The hypothesis of thyroid hormone variations within the normal reference range influencing metabolic conditions continues to be investigated by researchers. Thyroid hormone profiles can alter in patients with obesity as a consequence of the adaptation process in resting energy expenditure (2). Some adipocyte-derived signals are responsible for the initiation of this adaptation. Obesity leads to a moderate increase in serum thyroid-stimulating hormone (TSH) with or without altering fT4 or serum fT3 levels. A linear association was also shown between weight gain and TSH increase (3). Previous studies have also revealed that serum fT3 level may be slightly increased in patients with obesity (4,5). Thyroid hormones also have significant effects on glucose metabolism through various mechanisms. They produce an enhanced expression of glucose transporters (GLUTs) and potentiate the action of several enzymes involved in gluconeogenesis (6). Hepatic glucose output increases as a result of increased production of GLUT-2 in the hepatocyte membrane, and therefore it leads to impaired glucose metabolism (7). Meanwhile, fT3 regulates pancreas beta-cell proliferation and insulin secretion (8). The positive association of the occurrence of type 2 DM with fT4 and negatively associated with fT3 and fT3/fT4 ratio have been established by several studies (9,10). Considering the above-mentioned results, thyroid hormone alteration in obesity and type 2 DM do not occur in the same manner. Changes in thyroid hormones in patients

having both obesity and impaired glycemic status have not been established yet. With the increasing interest in this topic, the current study aimed to evaluate thyroid hormones and fT3/fT4 ratio in different glucose metabolism statuses of euthyroid patients with obesity.

Material and Methods

This study was designed as a retrospective and approved by Clinical Research Ethics Committee (22.06.2021-90/01) of our institute following the principles of the Declaration of Helsinki.

Three hundred and four patients with obesity evaluated in the endocrinology outpatient clinic between January 2018 and January 2020 were assessed to be included in the study inclusion. Primary and secondary hypothyroidism, hyperthyroidism, history of trauma, surgery, or radiation exposure in the neck, drug use like lithium and amiodarone (which can affect thyroid hormones), severe hepatic or renal impairment, pregnancy, and type 1 DM were the exclusion criteria. Following the exclusion criteria, 209 patients (18-65 years old) with a body mass index (BMI) greater than 30 kg/m² were enrolled in the study.

The anthropometric measurements, including BMI and waist and hip circumferences, were acquired from clinical records. The patients were categorized according to glucose metabolism status as patients with normal glucose tolerance (NGT), DM, and prediabetes. Either patients with newly diagnosed or previously known DM were included in the study. The diagnosis criteria of type 2 DM and prediabetes were based on the American Diabetes Association (ADA) Diabetes Guideline (11). According to the ADA guideline, the patients having either fasting plasma glucose (FPG) ≥ 126 mg/dL or 2-h post-prandial glucose (PG) ≥ 200 mg/dL during oral glucose tolerance test (OGTT) or glycated hemoglobin A1c (HbA1c) $\geq 6.5\%$ are diagnosed with DM. Prediabetes is defined as the presence of either FPG 100-125 mg/dL or 2-h PG during 75 g OGTT 140-199 or HbA1c 5.7-6.4%. In this study, FPG, HbA1c, creatinine, alanine aminotransferase (ALT), total cholesterol, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, TSH, fT4, and fT3

levels of the groups were evaluated. Then FT3/FT4 ratios of the patients were calculated. Reference ranges of thyroid hormones were as follows: TSH, 0.38-5.33 mIU/L; FT4 0.58-1.6 ng/dL; and FT3 2.66-4.37 ng/dL.

Statistical Analysis

Statistical analysis was performed using the SPSS software version 21 (Chicago, IL). To detect if the variables are normally distributed, analytic (Kolmogorov-Smirnov/Shapiro-Wilk's test) and visual methods (histograms and probability plots) were used. To compare categorical variables among groups, the Chi-Square test was performed. The parameters among the groups were compared using the Kruskal-Wallis test. The significance of pairwise differences was determined through the Mann-Whitney U test. Multiple comparisons were adjusted using Bonferroni correction. Variables that

were not normally distributed were presented using the medians and interquartile ranges (IQRs) 25 and 75 percentiles. To determine a statistically significant difference, p values less than 0.05 were based on. An overall 5% type 1 error level was used to infer statistical significance. Estimation of both correlation coefficients and their significance in the investigation of correlations between thyroid parameters and other variables were performed through the Spearman's test. A multiple linear regression analysis was carried out to identify the independent factors for thyroid hormone parameters. Appropriate residual and goodness-of-fit statistics were used to assess a model fit.

Results

Three hundred and four patients with obesity were considered for the eligibility of inclusion. Figure 1 presents the flowchart of

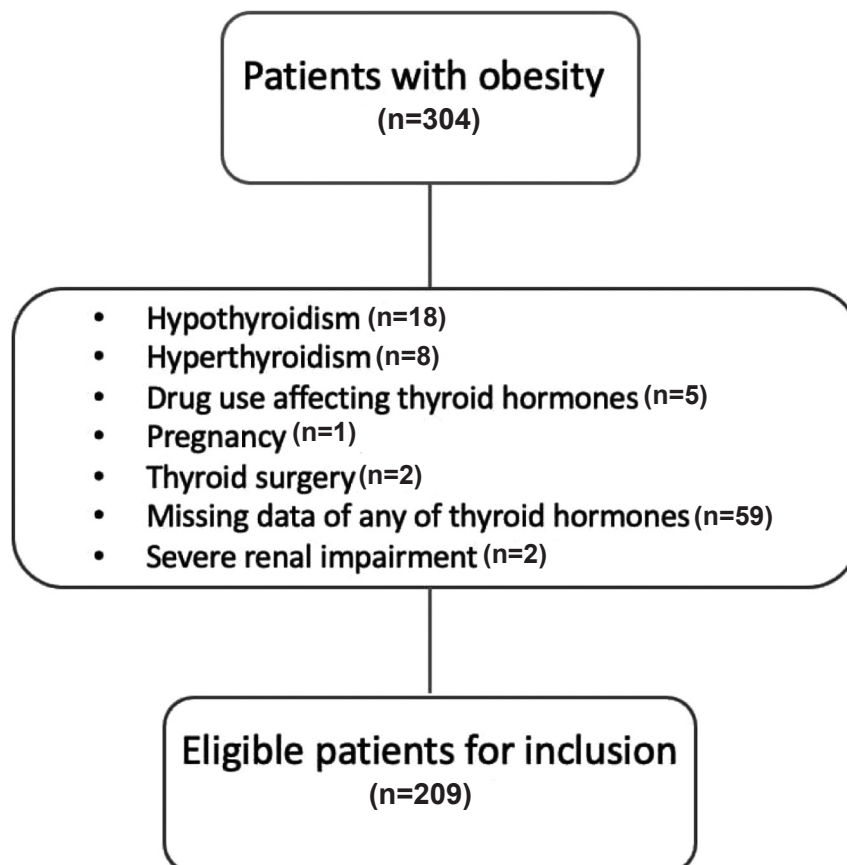


Figure 1. Flowchart of patient inclusion.

patient inclusion. Finally, 209 patients with obesity were grouped according to their glucose metabolism statuses.

One hundred and thirty-one (62.7%) patients had NGT, 41 (19.6%) had prediabetes, and 37 (17.7%) had DM. Among the patients with DM, 2 (4.9%) patients were newly diagnosed, and 35 (85.3%) of them were previously diagnosed with DM. BMI and waist/hip ratio were similar among the three groups ($p > 0.05$). Patients with DM were older than subjects with NGT and prediabetes ($p < 0.001$, $p = 0.005$, respectively). One hundred and five (80.2%), 26 (63.4%), and 36 (70.3%) patients in the NGT, prediabetes, and DM groups, respectively, were female. Gender composition was similar among groups.

A significant difference was observed in FPG and HbA1c levels among groups ($p < 0.001$ for each; on comparing patients with NGT and DM, NGT and prediabetes, and prediabetes and DM). Serum creatinine, ALT level, and serum lipid parameters out of triglyceride were also similar among the three groups ($p > 0.05$ for each parameter). No difference was detected in triglyceride levels on comparing NGT and prediabetes groups, and prediabetes and DM groups ($p > 0.05$ for each). But serum triglyceride was detected to be higher in euthyroid patients with DM compared to patients with NGT ($p < 0.001$).

In the thyroid hormone analysis, no difference was determined in serum TSH and ft3 levels among groups ($p > 0.05$ for each). Serum ft4 level was 0.87 ng/dL (IQR 25-75; 0.81-0.97) in the NGT group, 0.86 ng/dL (IQR 25-75; 0.81-0.96) in the prediabetes group, and 0.94 (0.89-1.1) in the DM group. Serum ft4 level was higher in patients with DM compared to that in patients with NGT and prediabetes ($p = 0.009$, $p = 0.018$, respectively). FT3/FT4 ratio was 4 (IQR 25-75; 3.5-4.4), 4 (IQR 25-75; 3.4-4.5), and 3.6 (IQR 25-75; 2.9-4.3), respectively, in patients with NGT, prediabetes, and DM. FT3/FT4 ratio was determined to be lower in euthyroid patients with DM than patients with NGT and prediabetes ($p = 0.012$, $p = 0.028$, respectively). After an adjustment following Bonferroni correction, the differences in serum ft4 level and FT3/FT4 ratio between patients with DM and

prediabetes were not statistically significant. Baseline characteristics, laboratory test results, thyroid hormones, and FT3/FT4 ratio of the subjects are presented in [Table 1](#).

In correlation analysis, ft3/ft4 ratio was found inversely correlated to HbA1c and age ($r = -0.157$, $p = 0.039$; $r = -0.293$, $p < 0.001$, respectively). While TSH and ft3 levels were negatively correlated with age ($r = -0.251$, $p < 0.001$; $r = -0.425$, $p < 0.001$, respectively), a weakly positive correlation was observed between ft4 level and HbA1c ($r = 0.161$, $p = 0.034$). We also observed a negative correlation between TSH level and waist/hip ratio ($r = -0.290$, $p = 0.005$).

Thereafter, we performed a multivariate regression analysis to identify independent parameters for TSH, ft3, ft4, and FT3/FT4 based on a model considering age, gender, BMI, waist/hip ratio, FPG, and HbA1c as independent variables. When ft3 was the dependent variable, age was a negative independent factor of ft3 ($\beta = -0.320$, $r^2 = 0.102$, $p = 0.006$). When ft4 was the dependent variable, ft4 was independently and positively associated with HbA1c ($\beta = 0.345$, $r^2 = 0.119$, $p = 0.003$). When FT3/FT4 was the dependent variable, only HbA1c was a negative independent factor for the FT3/FT4 ratio ($\beta = -0.371$, $r^2 = 0.138$, $p = 0.001$). No independent association was determined between TSH and other variables.

Discussion

The current study revealed that euthyroid patients with obesity and DM had higher serum ft4 levels and a lower FT3/FT4 ratio. HbA1c was determined to be positively associated with serum ft4 level and negatively associated with FT3/FT4 ratio irrespective of age, gender, and BMI of the included patients. Additionally, prediabetes did not considerably alter thyroid hormones in our study population.

Thyroid hormones have an essential role in many metabolic pathways, including energy homeostasis, thermogenesis, and lipid and glucose metabolism (1). While thyroid dysfunctions are determined to be associated with obesity and the impairment of glucose metabolism, some considerable changes have been observed in thyroid hormones of

Table 1. Baseline characteristics, laboratory parameters, and thyroid hormones of the subjects.

	Patients with NGT	Patients with prediabetes	Patients with DM	p value NGT vs. DM	p value NGT vs. prediabetes	p value Prediabetes vs. DM
Number, n	131	41	37			
Baseline characteristics						
Age, years	34 (27-44)	39 (31-46)	48 (38-53)	<0.001	0.045*	0.005
Gender, female, n (%)	105 (80.2)	26 (63.4)	26 (70.3)	0.202	0.029*	0.524
BMI, kg/m ²	40 (34-44)	40.4 (33-47)	41.2 (32-49)	0.869	0.676	0.886
Waist/hip ratio	0.86 (0.8-0.93)	0.92 (0.81-0.95)	0.85 (0.8-0.99)	0.752	0.339	0.815
Laboratory parameters						
FPG, mg/dL	89 (79-95)	104 (98-112)	136 (120-148)	<0.001	<0.001	<0.001
HbA1c, %	5.6 (5.4-5.6)	6.2 (6-6.3)	7.3 (6.8-8.2)	<0.001	<0.001	<0.001
Creatinine, mg/dL	0.8 (0.74-0.88)	0.82 (0.75-0.95)	0.79 (0.69-0.85)	0.137	0.273	0.069
ALT, mg/dL	23 (17-34)	22 (17-37)	24 (18-41)	0.469	0.929	0.574
Total cholesterol, mg/dL	192 (173-212)	197 (167-218)	197 (168-224)	0.496	0.578	0.913
Triglyceride, mg/dL	144 (111-200)	149 (110-223)	195 (146-265)	<0.001	0.317	0.053
LDL-C, mg/dL	132 (112-154)	141 (118-155)	135 (117-164)	0.525	0.515	0.956
HDL-C, mg/dL	44 (38-50)	44 (39-52)	41 (38-49)	0.67	0.676	0.439
Thyroid hormones						
TSH, mIU/L (RR: 0.38-5.33)	2 (1.3-3.1)	2.2 (1.2-3.4)	1.75 (1.3-2.9)	0.398	0.826	0.722
FT4, ng/dL (RR: 0.58-1.6)	0.87 (0.81-0.97)	0.86 (0.81-0.96)	0.94 (0.89-1.1)	0.009	0.769	0.018*
FT3, ng/dL (RR: 2.66-4.37)	3.5 (3.1-3.9)	3.4 (3.2-3.6)	3.4 (3-3.7)	0.054	0.446	0.344
FT3/FT4 ratio	4 (3.5-4.4)	4 (3.4-4.5)	3.6 (2.9-4.3)	0.012	0.967	0.028*

*The p value did not maintain significantly after adjusting according to Bonferroni correction; Categorical data were demonstrated with numbers and percentages (%); Other variables were presented as medians (interquartile ranges 25-75); NGT: Normal glucose tolerance; DM: Diabetes mellitus; BMI: Body mass index; FPG: Fasting plasma glucose; HbA1c: Hemoglobin A1c; ALT: Alanine aminotransferase; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; TSH: Thyroid-stimulating hormone; FT4: Free thyroxine; FT3: Free triiodothyronine.

patients with obesity or type 2 DM, even in euthyroid status (10,12,13). According to the results of previous studies, the levels of thyroid hormones change in obesity and type 2 DM in opposite ways.

Thyroid hormone levels are compensatory elevated in patients with obesity to increase the resting energy expenditure (2). Obesity is associated with an increase in fat mass accumulation and an alteration in adipokine distribution (14). Experimental studies on animals have supported the data that increased levels of leptin, a very well-established altered adipokine in obesity, activates the ft4 to ft3 transformation (15). Leptin has also been found positively associated with increased TSH levels in obese patients (16). type 1 iodothyronine deiodinase activity has also been shown enhanced in white adipose tissue in obesity (17). In several studies, weight gain was determined to be positively correlated to serum TSH levels (3,18). Some studies have also revealed a positive association between serum leptin and TSH levels (19). A recent prospective study stated that increased levels of ft3 and ft3/ft4 ratio are related to both metabolically healthy and unhealthy obesity in a euthyroid population (5). Accordingly, Nie et al. have presented that subcutaneous fat accumulation is related to increased ft3/ft4 ratio and ft3 level in euthyroid subjects with obesity (20).

In a study excluding DM, progressive central fat accumulation was determined to be positively related to serum TSH and ft3 levels independent of insulin resistance (21). Consequently, the vast majority of the studies have concluded that obesity affects thyroid hormones by increasing the circulating TSH and ft3 levels.

Glucose metabolism is regulated by several factors, including thyroid hormones. Studies in animals have revealed that thyroid hormones activate many enzymes in the gluconeogenesis pathway (6). Thyroid hormones per se increase the synthesis of glucose and its utilization by peripheral tissues. T3, in addition to insulin, has been found to regulate glucose transport of insulin-sensitive tissues by increasing the expressions of GLUTs, especially GLUT-4 (22,23). At the molecular level, T3 potentiates the beta-

adrenergic system by stimulating cyclic adenosine monophosphate and leads to increased uptake of glucose (24). Experimental studies in rats have revealed that T3 has a mitogenic effect on pancreatic beta cells (25). In contrast to the proliferative effect of T3, some other animal studies have shown that high doses of T4 treatment decrease the pancreas insulin reserve and secretion (26). Additionally, an increase in levels of serum ft3 and ft4 lead to increased absorption of glucose from the gastrointestinal system (27). Considering the interaction between thyroid hormones and glucose homeostasis, thyroid hormone-mediated alterations in insulin resistance and DM have also been investigated. A study conducted on two populations from Germany and Denmark has demonstrated that thyroid hormones are positively associated with the incidence of prevalent type 2 DM (27). The researchers of this study also commented that hyperthyroxinemia may contribute to the pathogenesis of type 2 DM. A recent study revealed a higher ft4 level and lower ft3/ft4 ratio, in patients having untreated type 2 DM compared to the general population (9). This interesting study also addressed that ft4 level is independently and negatively associated with the function of pancreatic beta-cells in euthyroid subjects. Our results indicate that the ft4 is independently and positively associated with HbA1c and thus support these findings. Likewise, another study from China has also demonstrated a significant increase in ft4/ft3 ratios of patients with type 2 DM, especially in previously diagnosed ones (28). The minority of the reports about this topic have presented contrary results to this study. A higher T3 level and T3/T4 ratio were found to be positively associated with FPG and HbA1c in a study population consisting of patients with metabolic syndrome (29). Higher levels of both ft3 and ft4 within normal limits were found linked to insulin resistance and the initiation of type 2 DM, according to a study (30). The findings of change in TSH levels in patients with DM are conflicting; while some studies have found the association of suppressed or elevated TSH levels with DM, some of them are not (28,31,32). In the

current study, we did not observe any change in serum TSH levels among the groups analyzed. The authors have explained these discrepancies in thyroid hormone alteration with differences in the study population and confounding factors of the participants. Consequently, the findings of the current study are concurrent with those of the previous studies evaluating thyroid hormones of patients with DM. However, limited data is available on the thyroid hormone alterations in prediabetes. The results of a cross-sectional study have concluded that insulin resistance is associated with a high fT4 and low fT3/fT4 ratio in prediabetic patients (33). Likewise, higher levels of fT3 and fT3/fT4 ratio were found related to impaired fasting glucose, although higher fT4 level was associated with impaired glucose tolerance (34). Low serum fT4 levels in the euthyroid range have also been found to be a risk factor in male patients (35). In our study, no difference was observed in thyroid hormones in patients with prediabetes conditions when compared to those with NGT or type 2 DM.

Study Limitations

The smaller scale of subgroups was one of the limitations of this study. Next, owing to the retrospective design, some of the patients had to be excluded for missing data on thyroid hormones. Additionally, the results of this study reflect data of only Turkish patients evaluated at a single center and should be corroborated with further studies based on a different population.

Conclusion

Serum fT4 level increased, and fT3/fT4 ratio decreased in euthyroid patients with type 2 DM independent of the degree of obesity. In our cohort, the interaction of DM with thyroid hormones seemed to overcome obesity-related changes in the thyroid functions.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces med-

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Sema Hepşen, Pınar Akhanlı, Muhammed Kızılgül, Muhammed Erkam Sencar; Design: Sema Hepşen, Pınar Akhanlı, Muhammed Kızılgül, Muhammed Erkam Sencar, İsmail Emre Arslan; Control/Supervision: Erman Çakal; Data Collection and/or Processing: Sema Hepşen, Pınar Akhanlı, Hakan Düger, Hayri Bostan, Muhammed Erkam Sencar, İsmail Emre Arslan; Analysis and/or Interpretation: Sema Hepşen, Muhammed Kızılgül, Erman Çakal, İsmail Emre Arslan; Literature Review: Sema Hepşen, Hakan Düger, Hayri Bostan; Writing the Article: Sema Hepşen; Critical Review: Sema Hepşen; References and Fundings: Erman Çakal; Materials: Sema Hepşen, Pınar Akhanlı, Muhammed Erkam Sencar.

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