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Comparison of four immunoassay analyzers for relationship between thyroid stimulating hormone (TSH) and free thyroxine (FT4)

[Dört immünolojik ölçüm cihazının tiroid stimüle edici hormon (TSH) ve serbest tiroksin (FT4) arasındaki ilişki yönünden karşılaştırılması]

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ABSTRACT

Objective: There is an inverse log/linear relationship between TSH and FT4 due to the negative feedback of these hormones on the pituitary. The objective of our study was to compare this relationship of TSH and FT4 between four different immunoassay analyzers.

Methods: In our study, four data sets obtained from the database of four different hospital laboratories each using only a single method of measurement was used to evaluate this relationship between TSH and FT4.These data sets with their assay methods include: 21.102 test results measured by Modular E170 Analyzer (Roche Diagnostics, Germany), 20.241 test results measured by Access DxI 800 Unicel (Beckman Coulter, USA), 22.444 test results measured by Architect i2000sr (Abbott Laboratories, Abbott Park, Illinois, U.S.A) and 20.200 test results measured by ADVIA Centaur XP (Siemens Diagnostics, Tarrytown, NY). Inverse logarithmic relationship were determined from each data sets and compared between analyzers.

Results: The correlation coefficients were -0.439 [95% CI, (-0.450)- (-0.428)], -0.488 [95% CI, (-0.498)- (-0.478)], -0.353 [95% CI, (-0.364)- (-0.342)], -0.430 [95% CI, (-0.441)- (-0.419)] for DxI 800 Unicel, Modular E 170, Architect i2000sr and ADVIA Centaur XP, respectively. In our study, all immunoassay analyzers showed poor correlation in a concentration range of TSH between 1.0 to 10.0 uIU/mL and the inverse log/linear relationship was not observed. Inverse relationship between TSH and FT4 is the result of negative thyroid pituitary hypothalamic feedback mechanism and this relationship is important especially in the diagnosis and treatment of hypo and hyperthyroidism. In data sets obtained from four different immunoassay analyzers, poor and statistically different correlation was observed between analyzers at TSH values ranged from 1.0 to 10.0 uIU/mL compared with FT4.

Conclusion: These variations between analyzers may affect the clinical decisions especially in the evaluation of subclinical hypothyroidism, clinicians and laboratory specialists should be aware of these situation.

Key Words: thyroid stimulating hormone (TSH), free thyroxine (FT4), Inverse log/linear relation, immunoassay, thyroid function tests

Conflict of Interest: Authors have no conflict of interest.

ÖZET

Amaç: TSH ve FT4 arasında, bu hormonların hipofiz bezi üzerindeki negatif feedback etkisine bağlı olarak, ters logaritmik lineer bir ilişki mevcuttur. Çalışmamızın amacı TSH ve FT4 arasındaki bu ilişkinin dört farklı immünolojik ölçüm cihazı arasında karşılaştırılmasıdır.

Metod: Çalışmamızda, TSH ve FT4 arasındaki bu ilişkinin değerlendirilmesi amacıyla, her biri yalnızca tek bir ölçüm metodunu kullanan hastane laboratuvarlarının veritabanından elde edilmiş veri serileri kullanılmıştır. Bu veri serileri ve ölçüm metotları, Modular E170 Analyzer (Roche Diagnostics, Germany) ile ölçülen 21.102, Access DxI 800 Unicel (Beckman Coulter, USA) ile ölçülen 20.241, Architect i2000sr (Abbott Laboratories, Abbott Park, Illinois, U.S.A) ile ölçülen 22.444, ADVIA Centaur XP (Siemens Diagnostics, Tarrytown, NY) ile ölçülen 20.200 test sonucundan oluşmaktadır. Ters logaritmik ilişki herbir veri serisinde belirlenmiş ve cihazlar arasında karşılaştırılmıştır.

Bulgular: Korelasyon katsayıları DxI 800 Unicel için -0.439 [95% CI, (-0.450)- (-0.428)], Modular E 170 için -0.488 [95% CI, (-0.498)- (-0.478)], Architect i2000sr için -0.353 [95% CI, (-0.364)- (-0.342)] ve ADVIA Centaur XP için -0.430 [95% CI, (-0.441)- (-0.419)] saptanmıştır. Çalışmamızda immunolojik ölçüm cihazlarının hepsinde 1.0-10 uIU/mL TSH değerleri için zayıf korelasyon bulunmuş ve ters logaritmik lineer ilişki gözlenmemiştir. TSH ve FT4 arasındaki ters ilişki negatif hipotalamo-hipofizo-tiroidal feedback mekanizmasının sonucu olup, bu ilişki özellikle hipo ve hipertirodizmin tanı ve tedavisinde önemlidir. Dört farklı immunolojik ölçüm cihazından elde edilen veri serilerinde özellikle 1-10 uIU/mL aralığındaki TSH değerleri FT4 ile karşılaştırıldığında cihazlar arasında farklı ve zayıf korelasyon görülmüştür.

Sonuç: Cihazlar arasındaki bu farklılıklar özellikle subklinik hipotoroidinin değerlendirilmesinde klinik kararları etkileyebileceğinden klinisyenler ve laboratuvar uzmanları bu durumun farkında olmalıdırlar.

Anahtar Kelimeler: Tiroid stimüle edici hormon (TSH), serbest tiroksin (FT4), ters logaritmik lineer ilişki, immünolojik ölçüm, tiroid fonksiyon testleri

Çıkar Çatışması: Yazarların çıkar çatışması yoktur.

Introduction

Thyroid disorders are important and a common problem for population. Laboratory testing is essential for diagnosis, treatment and management [1,2]. Thyroid stimulating hormone (TSH) and free thyroxin (FT4) are used as laboratory tests [3]. Serum TSH measurement is recommended for the initial screening. Thyroxine (T4) is secreted by the thyroid gland as the major thyroid hormone secreted and nearly all bound to specific plasma proteins. Only about 0.02% of T4 in the circulation is non-protein bound. The free thyroxine (FT4) is biologically active and therefore, mostly monitored in patients with thyroid disorders. There is an inverse log/linear relationship between TSH and FT4 due to the negative feedback of these hormones on the pituitary. As a result of this relationship even small changes in serum FT4 concentration will result a large response in TSH concentration [3]. This relationship is helpful to the clinician and laboratory specialists especially in the diagnosis of subclinical thyroid disease.

The objective of our study was to compare this relationship of TSH and FT4 between four different immunoassay analyzers.

Materials and Methods

Inverse log/linear relationship between FT4 and TSH was analyzed in four data sets of FT4 and TSH test results. The results of in-patients and out-patients , aged from 18 to 68 years, referred for thyroid testing, representing the whole range of thyroid functions from hypothyroidism to hyperthyroidism, was collected from the laboratory database of four different hospitals which used only one assay method for their FT4 and TSH measurements. These data sets with their assay methods include: 21.102 test results measured by Modular E170 Analyzer (Roche Diagnostics, Germany), 20.241 test results measured by Access DxI 800 Unicel (Beckman Coulter, USA), 22.444 test results measured by Architect i2000sr (Abbott Laboratories, Abbott Park, Illinois, U.S.A) and 20.200 test results measured by ADVIA Centaur XP (Siemens Diagnostics, Tarrytown, NY). Inverse logarithmic relationship between TSH and FT4 were determined for data sets and this relationship were compared among analyzers. Correlation coefficients (r) with their confidence intervals (CI) were calculated. Statistical calculations were performed by Microsoft Excell.

Results

The inverse relationship between TSH and FT4 were calculated for four immunoassay analyzers (Figure 1). The correlation coefficients were -0.439 [95% CI, (-0.450)-(-0.428)], -0.488 [95% CI, (-0.498)- (-0.478)], -0.353 [95% CI, (-0.364)- (-0.342)], -0.430 [95% CI, (-0.441)-(-0.419)] for DxI 800 Unicel, Modular E 170, Architect i2000sr and ADVIA Centaur XP, respectively. The inverse relationship between TSH and FT4 determined for each analyzer were significantly different.

After reviewing the test results in general, we divided the test results of each data sets according to their serum TSH concentrations and calculated the correlation coefficients for each group. TSH levels in these three groups ranged 0 to 1.0 uIU/mL, 1.0 to 10.0 uIU/mL and over 10.0 uIU/mL were shown in Figure 1. All of the immunoassay analyzers showed poor correlation for the TSH concentrations between 1.0 to 10.0 uIU/mL and the inverse relationship was not observed in this concentration range (Figure 1).

We also combined all four data sets together and calculated the inverse log/linear relationship. The correlation coefficient of combined four data sets was -0.340 [95% CI, (-0.346) –(-0.334)] (Figure 2).

Discussion

Patients with subclinical hypo- or hyperthyroidism have few or no symptoms or signs of thyroid dysfunction and thus subclinical thyroid disease is a laboratory diagnosis. In addition , this relationship provides a physiological rationale for assessing the validity of FT4 results in a clinical setting [1-3]. Although TSH measurement is commonly accepted as reliable, it is not well defined and there is no reference measurement procedure available. However FT4 assay methods include equilibrium dialysis, ultrafiltration and LC MS/MS [4]. Therefore, the routine measurements of FT4 and TSH have some limitations and assay methods have poor correlation. In one of our studies, we compared TSH and FT4 assay methods between three immunoassay analyzers. There were significant correlation between three analyzers for TSH. However, measurements of FT4 were different between analyzers. The regression coefficient of three analyzers for FT4 were ≤ 0.970. Comparison of three methods, analyzed by EP Evaluator, was statistically different for FT4 results. The differences between three analyzers were $p<0.001$ (Cronbach's Alpha, 0.989) and $p=0.430$ (Cronbach's Alpha, 0.994) for FT4 and TSH, respectively [5].

In this study, we found poor relationship between TSH and FT4, especially in patients with 1-10 mIU/mL of TSH levels. However, we found high correlation for the TSH concentrations between 0 to 1.0 uIU/mL and over 10 mIU/mL, between log TSH and T4 (Figure 1). Same results were published by Van Deventer HE et al [3]. Soldin et al. reported a poor correlation between FT4 and log TSH on a run of the Abbott Architect ci8200 immunoassay platform ($r=0.010$ for males and 0.050 for females) using a direct analog method for FT4 measurement [6]. In our study we also found the poorest correlation at Architect i2000sr analyzer.

Biological variation of thyroid hormones should be taken into account when evaluating the levels of TSH and thyroid hormones [7,8]. Erden at al. found that the intraindividual and interindividual biological variations for serum TSH and FT4 were 37.21/37.6% and 13.26/7.47%

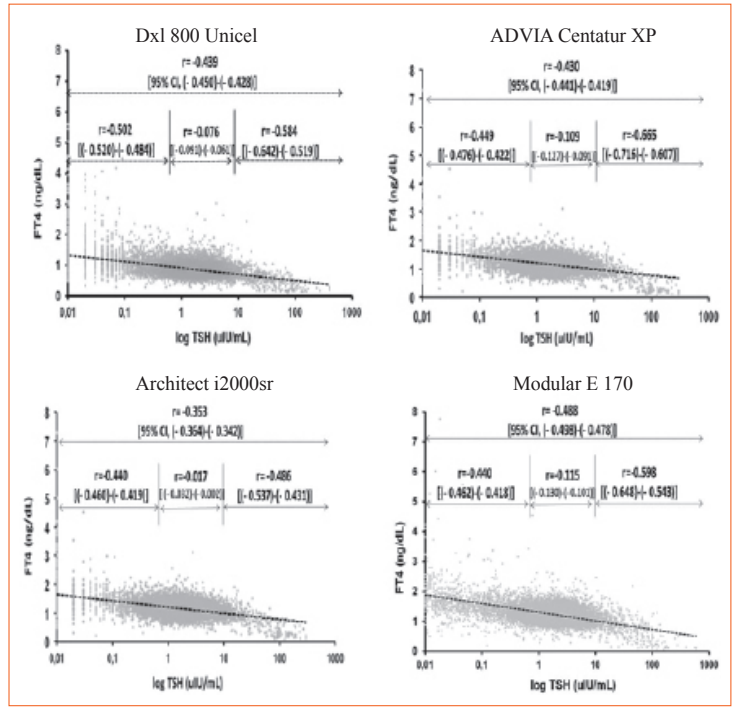


Figure 1. The correlation coefficients with their 95% confidence intervals at different (0-1, 1-10 and over 10 uIU/ml) and the overall TSH concentrations were depicted for DxI 800 Unicel, Modular E 170, Architect i2000sr and ADVIA Centaur XP. Conversion factor for FT4 (ng/dL→pmol/L):12.87.

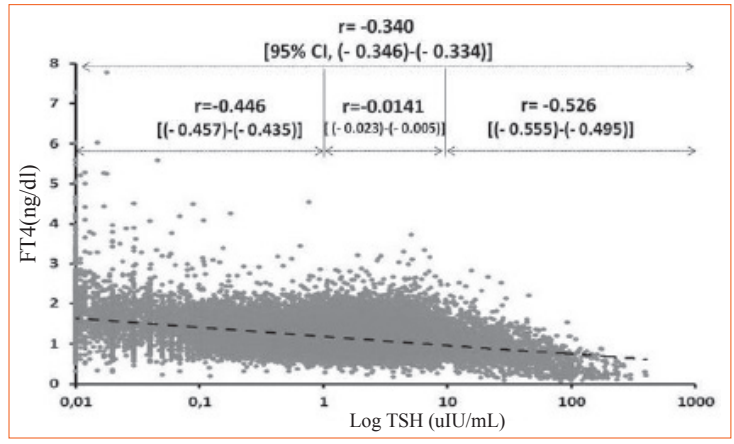


Figure 2. The correlation coefficients with their 95% confidence intervals at different (0-1, 1-10 and over 10 uIU/ml) and the overall TSH concentrations were depicted for combined four data sets. Conversion factor for FT4 (ng/dL→pmol/L):12.87.

respectively. The reference change values for TSH and FT4 were 104.04%, 38.87%, respectively [9]. The correlation of FT4 and TSH results measured by Access DxI 800 Unicel and Architect i2000sr especially are limited in patients with 1-10 uUI/mL of TSH values. Although these discrepancies may be insignificant for the evaluation of patients with manifested hypothyroidism and hyperthyroidism, it is critically important for patients with subclinical hypothyroidism.

Clinicians and laboratory specialists should be aware of such limitations to make interpretations of FT4 and TSH results. These limitations are important in conditions that affect binding protein concentration, such as acute illness, pregnancy, and hereditary variants in the structure of thyroid binding globulin, albumin and transthyretin [3,6].

Limitation of our study is that no clinical information about patient's history was available so patients taking thyroid medication or with illnesses other than thyroid disorders may be included in the study.

The poor correlation between FT4 and log TSH highlighted some of the limitations of current immunoassay methods for the measurement of FT4 and TSH. Thyroid Function Tests of IFCC working group are still proceeding [10]. Laboratory specialists should know the limitations of their current methods and they should share them with clinicians.

Conflict of Interest

There are no conflicts of interest among the authors.

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