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Scintigraphy has the potential to replace thyroid stimulating hormone and ultrasonography in hyperthyroidism diagnosis

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ABSTRACT

The value of thyroid scintigraphy in hyperthyroidism diagnosis has long been the subject of debate. Unresolved issue is whether scintigraphy should be performed routinely, selectively, or for all hyperthyroidism patients. So, this study is concerned with the evaluation of thyroid scintigraphy for identifying hyperthyroidism in comparison with thyroid stimulating hormone (TSH) and ultrasound. This is cross sectional study including convenient patients sample (n = 50, 15 males and 35 females) aged (20–50 years) with primary hyperthyroidism and were attending endocrine clinics at King Faisal Specialist Hospital and Research Centre. All patients performed clinical investigations (TSH, ultrasound and thyroid scintigraphy). Among these patients, 96%, 48/50, had positive findings for hyperthyroidism with thyroid SC (95% CI; 96.0–99.5%); 84%, 42/50, had positive findings for hyperthyroidism by US (95% CI; 70.9–92.8%); and 56%, 28/50, had positive findings for hyperthyroidism by TSH measurement (95% CI; 41.3.0–70.0%). There was very good agreement between scintigraphy diagnosis and ultrasonography (kappa score = 0.812 ($P < 0.0001$), 95% CI (0.77–0.85). In many cases, scintigraphy provides considerably more functioning and anatomic details than ultrasound. In conclusion, these findings bring forth practical aspects of thyroid scintigraphy utilization for hyperthyroidism. By combining functional and anatomical information in one step, scintigraphy provides non-invasive, simple, fast and cost effective hyperthyroidism diagnostic method and has the potential to replace TSH and ultrasonography in hyperthyroidism investigation.

1. Introduction

Inappropriately high thyroid hormone (TH) synthesis and secretion by the thyroid is the cause of hyperthyroidism. TH elevates the basal metabolic rate and tissue thermogenesis, and decreases systemic vascular resistance and cholesterol serum levels (Kahaly et al., 2018). Thus, complications related to untreated hyperthyroidism include cardiovascular dysfunction, embolic events, atrial fibrillation, fragility fractures, osteoporosis and weight loss (Bartalena, 2013; Biondi and Kahaly, 2010). Hyperthyroidism prevalence is 0.2–1.6% overt and 0.7–1.0% subclinical (Kahaly et al., 2018; Taylor et al., 2018). Among Saudi adults, prevalence of hyperthyroidisms in both sexes was 2.8%, the highest prevalence was in females (Ali and Altahir, 2016).

Normal thyroid gland and anatomic variants can be routinely imaged by diagnostic imaging modalities including ultrasound (US), magnetic resonance imaging (MRI), computed tomography (CT) and scintigraphy (SC) (Kobylecka et al., 2017). Although, ultrasound has advantages of lack of radiation and easy availability, it is limited by operator dependency (Garberoglio and Testori, 2016). Also, in addition to morphological information obtained by US, thyroid SC visualizes active thyroid tissue distribution. Thus, SC general indications are indeed wide and include both single thyroid nodule, and multinodular goitre. When US is not able to visualize thyroid gland lower pole, SC is used to evaluate retrosternal goitre extent and in suspected ectopic thyroid (Czepczynski, 2012).

Now, it is well know that thyroid gland iodine uptake is attributed to sodium-iodide symporter (Kaminsky et al., 1993). Concerning thyroid function evaluation, thyroid cells iodine uptake is

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remains widely used by means of thyroid SC and radioiodine uptake test (Hindie et al., 2015; Niececki et al., 2015). Thyroid SC practice and value in hyperthyroidism diagnosis is unsettled (Okosieme et al., 2010). Diagnostic regimens using different imaging methods as well as their specificity and sensitivity vary depending on protocols used, physicians experience and patient's population (Kobylecka et al., 2017). The aim of the present research was to determine the usefulness of thyroid SC in comparison with TSH and US in patients diagnosed for hyperthyroidism.

2. Material and methods

2.1. Study design

This cross sectional study was registered in King Faisal Specialist Hospital and Research Centre (KFSH and RC), Riyadh, Saudi Arabia. It was conducted over 15 months period from September 2017 to December 2018.

2.2. Patient's inclusion and exclusion criteria

This study included convenient patients sample (n = 50, 15 males and 35 females) including patients with any age (20–50 years) diagnosed primary as hyperthyroidism and were attending endocrine clinics at KFSH and RC. All cases have three clinical investigations (lab analysis, US and nuclear medicine examination). Exclusion criteria are previous radioactive iodine treatment, treatment with immunomodulatory drugs, major co-morbidity, ongoing anti-thyroid drug treatment for >2 months, complete/partial thyroidectomy and pregnancy or breast-feeding.

2.3. Ethical statement

This work was approved by the ethics committee of KFSH and RC and the institute review board of each participant. All patients were provided by questionnaire that explained study aims and importance and a written consent was attained from each participant.

2.4. Examinations

All patients had clinical history suggestive of hyperthyroidism.

2.4.1. Ultrasonography

Neck US was performed for all patients using high-resolution US apparatus (HDI 5000 or iU 22; Philips Medical Systems, Bothell, WA, USA) with high frequency (7–15 MHz) linear-array transducer in supine position with hyperextended neck. It provides adequate penetration and high resolution image. Scanning is done both in transverse and longitudinal planes.

2.4.2. Thyroid scintigraphy

Two weeks prior to their thyroid investigation, all patients were placed on a low iodine diet (e.g. Iodine-containing vitamins and food supplements, whole eggs or yolks, sea-foods). Immediately before scanning, patients ingested water abundantly to clear any esophageal activity. Based on dose calculation, patients were given ^{123}I dose of (0.2–0.5 mCi) for scan and ^{131}I dose of 10 mCi for uptake. Also, patients were given ^{99m}Tc dose of about 3–5 mCi. Scintillation camera (Philips Medical Systems, Andover, MA, USA) equipped with high-resolution, medium/high energy and parallel-hole collimator was used for determining sodium iodide (NaI) crystal uptake. Thyroid scintigraphy and uptake were performed 24 h after radioiodine, and 15–20 min after ^{99m}TC injection.

2.4.3. Biochemical analysis

Thyroid stimulating hormone (TSH) serum levels were measured using fully automated Enzyme-Linked Immunosorbent Assay (ELISA) analyser using commercial ELISA Kits (Abcam, UK) with reference values of 0.5–6.5 m IU/l.

2.5. Statistical analysis

All statistical analysis was performed using SPSS (SPSS Inc., Chicago, IL, USA, version 17). The comparison between the three tests was based on the Proportion Correctly Classified (PCC) which reflects the total proportion of individuals that are correctly classified as having hyperthyroidism (Vickers et al., 2013). Agreement between post-scintigraphy diagnosis and US findings was examined using the kappa statistics. Interpretation of Kappa values was as follows: poor agreement (0–0.2), regular agreement (0.21–0.4), moderate agreement (0.41–0.6), good agreement (0.61–0.8) and very good agreement (0.81–1.0) (Landis and Koch, 1977).

3. Results

All patients (n = 50) included in this study had a clinical history suggestive of hyperthyroidism. In this study, all 50 patients underwent thyroid SC diagnosis, US diagnosis and laboratory test (TSH) measurement for diagnosis of hyperthyroidism.

US findings for 50 patients with hyperthyroidism were classified as multinodular goiter (MNG) with thyroid gland enlargement, normal gland (in shape and size), gland enlargement with no nodularity, Graves' disease, Solitary nodule, right and/or left lobes large nodules (>1 cm each) and micronodularity with thyroiditis. The analysis was based on the PCC mentioned above. Among these patients, 96%, 48/50, had positive findings for hyperthyroidism with thyroid SC (95% CI; 96.0–99.5%); 84%, 42/50, had positive findings for hyperthyroidism by US (95% CI; 70.9–92.8%); and 56%, 28/50, had positive findings for hyperthyroidism by TSH measurement (95% CI; 41.3.0–70.0%) (Table 1). Thyroid scintigraphy was superior to US and TSH test and provided valuable information regarding both thyroid physiology and anatomy and thus can play an integral role in hyperthyroidism diagnosis.

Thyroid scintigraphy was correctly matched to US in 42 cases (84%) and mismatched in 8 patients (16%). There was very good overall agreement between thyroid scintigraphy diagnosis and US with a kappa score of 0·812 (P < 0·0001), 95% CI (0·77–0·85). Also, in many cases scintigraphy provides considerably more functioning and anatomic details than ultrasound.

Table 1
Nuclear medicine versus ultrasound and biochemical findings in patients with hyperthyroidism.

	Hyperthyroidism present	Hyperthyroidism absent	Total
Test results for thyroid SC diagnosis			
Test positive	48	0	48
Test negative	2	0	2
Total	50	0	0
Test results for US			
Test positive	42	0	42
Test negative	8	0	8
Total	50	0	0
Test results for laboratory TSH measurement			
Test positive	28	0	28
Test negative	22	0	22
Total	50	0	0

4. Discussion

Usually, hyperthyroidism diagnosis is straightforward and typically include the combination of laboratory evaluation, physical findings and historical symptoms (Sharma et al., 2011). Thyroid function evaluation guidelines recommend measuring TSH first (Schneider et al., 2018). Also in hyperthyroidism patients, recent studies reemphasized the need for US as an essential part of the evaluation as thyroid gland morphology could be variable and nodules in these glands would need to be investigated. This consequently would significantly affect follow-up management plan and decision-making (Varadhan et al., 2016).

Current role of nuclear scintigraphy using ^{99m}Tc-pertechnetate or $^{123/131}$I is adjunctive rather than as first-line diagnostic method (Ramos et al., 2002). However, it gives valuable information regarding not only thyroid anatomy, but also it gives excellent functional information about the gland. This is in contrast to ultrasound, which provides information on gross morphology or biopsy that provides histological information. Therefore, thyroid scintigraphy can play integral role in hyperthyroidism diagnosis (Broome, 2006). But, only few studies have specifically discussed this issue and thyroid scintigraphy value in hyperthyroidism diagnosis and management has long been the subject of debate (Lacey et al., 2001; Okosieme et al., 2010). Thus, this study aimed to evaluate the utility of scintigraphy in differential hyperthyroidism diagnosis in comparison to TSH testing and US.

In this study, TSH low serum levels detected in only 56% of patients with hyperthyroidism. In contrast, radioactive iodine uptake scans successfully evaluates thyroid gland function in 48/50 (96%) of hyperthyroidism patients even patients with normal TSH serum levels. Thyroid scintigraphy permits direct visualization of functional adenomatous thyroid tissue responsible for hyperthyroidism development. So, it will allow hyperthyroidism diagnosis before laboratory tests are consistently abnormal (Broome, 2006).

The American and European thyroid associations guidelines recommend radionuclide scanning in patients with thyroid nodules only if serum TSH level is low (Gharib et al., 2010; Haugen et al., 2016). But, this motive comes from expert opinions (Meier and Kaplan, 2001) or small clinical studies (McHenry et al., 1998). In patients with thyroid nodule and normal TSH level in the absence of thyroid scintigraphy, there is a risk of performing fine needle aspiration cytology (FNAC) in unsuspected autonomously functioning thyroid nodules (AFTN) (Moreno-Reyes et al., 2016). A study demonstrated that more than 70% of patients with an AFTN referred to the hospital had normal TSH level (Chami et al., 2014).

Main thyroid scintiscanning uses includes the diagnosis of hyperthyroidism cause and the identification of normal and ectopic thyroid tissue (Meier and Kaplan, 2001). In this study, thyroid scintigraphy was superior to US (90% *vs.* 84%) in identification of hyperthyroidism autecology. There was very good overall agreement between thyroid scintigraphy diagnosis and US ($\kappa = 0.812$, $P < 0.0001$). Also, in many cases scintigraphy provides considerably more functioning and anatomic details than ultrasound.

In addition to the morphological information obtained from US, thyroid SC visualizes active thyroid tissue distribution [5]. Thus, SC general indications are quite wide and include both thyroid single nodule and multinodular goiter. Also, SC is used in evaluation suspected ectopic thyroid. When US is not able to visualize thyroid gland lower pole, scintigraphy is also used to evaluate retrosternal goiter extent (Dhingra, 2017). Many studies recommended that scintigraphy may be indicated in Graves' disease differentiation from toxic nodular goitre and in thyroiditis diagnosis (Meier and Kaplan, 2001; Okosieme et al., 2010). Although these studies found that scintigraphy in most cases given additional information over the diagnosis obtained from immunological and standard clinical data, they did not justify the routine use of scintigraphy in clinical practice (Okosieme et al., 2010). Also, they assured that thyroid uptake scan has undoubtedly role in some clinical scenarios like factitious hyperthyroidism and acute thyroiditis (Okosieme et al., 2010). Thyroid SC is non-invasive, simple, fast and cost effective method for hyperthyroidism evaluation (Dhingra, 2017).

Some limitations of this study should be noted; it was a single-center study and external validity is required to support widespread changes in practice. Also, the small sample size may affect statistical power of the study.

In conclusion, by combining functional and anatomical information in one step, thyroid SC has the potential to provide superior information regarding hyperthyroidism and the potential to replace thyroid profile and US in hyperthyroidism investigation.

Declaration of Competing Interest

None.

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