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Utilization of the Bioresonance Metatron System for the Early Detection of Subclinical Hypothyroidism

Evaluating Biophysical Markers and their Correlation with Routine Diagnostic Methods

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Abstract: Hypothyroidism is a prevalent condition that can progress from subclinical to overt forms. Early detection of subclinical hypothyroidism is essential for effective and cost-efficient treatment, as well as for identifying risk factors that may prevent disease progression. While TSH is the standard first-line screening test, its levels can be misleading due to various factors, and thyroid ultrasonography, though useful, has limitations. This article explores the use of 3D-NLS bio-resonance feedback diagnostics for the early detection of subclinical hypothyroidism, focusing on biophysical markers such as Fleindler's Index (FI), Entropy Index, and Noise/Information Index (NII). The study compares these markers with ultrasound criteria and biochemical parameters, including serum levels of T3, T4, TSH, and anti-TPO. Results indicate that the NLS-3D bio-feedback system effectively evaluates biophysical spectral-entropy parameters, revealing significant differences between the groups studied. The analysis demonstrates that Spectral Entropy Analysis (SEA) parameters are valuable for the early detection of thyroid-related disorders and can be utilized in screening asymptomatic patients.

Keywords: *Sub-hypothyroidism, Screening, TSH, Ultrasound, 3D-NLS Bio Resonance Feed- Back Diagnostic, Spectral-Entropy-Analysis, Biophysical Markers.*

Abbreviation: SCH- subclinical hypothyroidism., US – ultrasonography., 3D NLS BR- 3D-Nonlinear Bio feedback bioresoance system., SEA - spectral-entropy analysis

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I. INTRODUCTION

Hypothyroidism is characterized by a decreased function of the thyroid gland and is one of the most common chronic diseases, representing the leading disorder caused by hormone deficiency. This condition can have significant and lasting effects on an individual's health throughout their lifetime. Accurate diagnosis and effective management are crucial for reducing these impacts and enhancing the quality of life for those affected [1-2].

Hypothyroidism can be classified according to several criteria: by the time of onset into congenital and acquired forms; by the level of endocrine dysfunction into primary and secondary (or central); and by severity into severe (clinical) and mild (subclinical) hypothyroidism (SCH). It is a commonly encountered condition. The most prevalent cause of primary hypothyroidism is thyroiditis due to antithyroid antibodies, which leads to insufficient secretion of thyroid hormone, a condition known as "Hashimoto's thyroiditis." In contrast, secondary hypothyroidism results from a deficiency in the production of thyroid-stimulating hormone (TSH) from the pituitary gland [3-4].

The distinction between subclinical and clinical hypothyroidism is of significant importance. In clinical hypothyroidism, symptoms are more severe and can even lead to coma, whereas in subclinical hypothyroidism, symptoms

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are generally milder and may be absent altogether. Subclinical hypothyroidism has the potential to progress to overt hypothyroidism, especially when antithyroid antibodies are present. Additionally, it has been associated with various adverse effects, including metabolic, cardiovascular, reproductive, maternal-fetal, neuromuscular, and cognitive abnormalities, as well as a lower quality of life [5-7]. Subclinical thyroid dysfunction, particularly subclinical hypothyroidism, is associated with increased body mass index (BMI) and obesity. Research indicates that even mild thyroid dysfunction can lead to significant metabolic changes, contributing to weight gain and obesity-related complications [8].

Subclinical hypothyroidism can negatively affect pregnancy and conception, leading to increased risks of infertility, miscarriage, and adverse pregnancy outcomes. Treatment may improve pregnancy rates and reduce complications, highlighting the importance of monitoring thyroid function in women trying to conceive. Some observational studies have indicated the presence of adverse outcomes [9]. In a large prospective study, pregnant women with SCH were at a higher risk for placental abruption and preterm delivery compared with euthyroid women and also, their offspring were more likely to be admitted in the neonatal intensive care unit and have respiratory distress syndrome [10].

Overt hypothyroidism during pregnancy is associated with different adverse outcomes, including miscarriage, pre-eclampsia, placental abruption, preterm birth, low birth weight and reduced IQ in offspring [11-13].

Hypothyroidism is classified as a chronic disease, characterized by a prolonged and often variable preclinical phase. This preclinical phase refers to the period in the disease's natural history during which the condition may be detectable through medical evaluation, yet remains unrecognized or asymptomatic. Understanding this phase is crucial, as early detection and intervention can significantly improve management and outcomes for individuals with hypothyroidism. Lead time refers to the interval between the detection of a disease through screening and the recognition of the disease in the absence of screening. The lead time generated by a screening program for an individual is influenced by the timing of the screening in relation to the preclinical phase of the disease, as well as the sensitivity of the screening test used. Screening involves the application of a test to identify a condition in individuals who do not exhibit any known signs or symptoms of the disease. Effective screening can facilitate earlier detection, potentially leading to improved outcomes and more timely interventions [14-15].

While most serum thyroid markers are generally straightforward to interpret and can confirm the clinical diagnosis of thyroid disorders such as euthyroidism, hypothyroidism, or hyperthyroidism, there exists a significant subgroup of patients for whom the results may be ambiguous. In these cases, the serum thyroid markers may be discordant with the clinical presentation or may not align with one another. For example, a patient may exhibit elevated thyroid hormones (TH) alongside non-suppressed thyrotropin (TSH), or present with elevated TSH while having normal TH levels. Such discrepancies can complicate the diagnosis and management of thyroid conditions, necessitating a more nuanced approach to interpretation and further investigation [16].

The serum thyroid-stimulating hormone (TSH) level is considered the most sensitive test for assessing thyroid dysfunction. However, TSH measurements can yield misleading results in individuals with fluctuating levels of thyroid hormones. In such cases, the TSH level may not accurately reflect the thyroid's functional status, leading to potential misdiagnosis or inappropriate management. Non-thyroidal disorder, in field of acute and chronic inflammation process, can modify hypothalamic/pituitary function and thyroid hormone metabolism and consequently lead to thyroid test abnormalities, including both decreased and increased serum TSH levels. Among individuals with serious, acute illness, the serum TSH is less specific for thyroid disease because a serious illness alone can depress TSH secretion. The prevalence of both low and high serum TSH levels (with normal serum free T4 results) is increased in elderly subjects compared with younger people [17-20].

TSH levels exhibit diurnal variation, typically reaching their lowest values in the late afternoon and peaking between midnight and 4 AM. As a result, fluctuations in serum TSH values within the normal range—up to 50%—do not necessarily indicate a change in thyroid status. This variability underscores the importance of considering the timing of TSH measurements and the potential impact of circadian rhythms when interpreting thyroid function tests [21].

Recent studies have highlighted the significant role of the immune system in regulating thyroid hormone activity and TSH production, particularly through interactions between immune cells and thyroid hormones. This crosstalk indicates that immune cells can influence thyroid function in ways that extend beyond the traditional regulation by the pituitary gland [22].

Estrogen therapy increases serum thyroxine-binding globulin (TBG) levels, which raises the total thyroxine (T4) concentration while lowering the free T4 fraction. This may necessitate adjustments in T4 dosage for individuals undergoing thyroid hormone replacement therapy [23-24].

Recently, it was reported that thyroid hormone receptors (TRs) are also present in human ovarian surface epithelium and act on ovarian follicles and show some slight localization in granulosa cells of ovarian follicles([25].

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Hypothyroidism is prevalent in chronic kidney disease (CKD) patients, often characterized by elevated TSH levels and altered thyroid hormone dynamics. Research indicates that kidney dysfunction can affect thyroid hormone levels, with some patients exhibiting elevated T3 and T4 levels despite hypothyroidism, highlighting the complex interplay between these systems [26-28].

Drugs can lead to thyroid dysfunction and abnormality in serum level of thyroid hormones with different mechanisms. Various drugs can significantly impact thyroid hormone metabolism and absorption, leading to alterations in thyroid function. Some medications, such as carbamazepine, hydantoins, phenobarbital, and rifampin, can impair the absorption of thyroxine, potentially resulting in hypothyroidism. Additionally, these drugs may increase the hepatic metabolism of thyroid hormones, which can lead to decreased secretion of thyroid hormones and necessitate higher doses of thyroxine for effective management. Medications like aminoglutethimide, amiodarone, iodide-containing agents, lithium, methimazole, propylthiouracil, sulfonamides, and tolbutamide can decrease thyroid hormone secretion, further increasing thyroxine requirements. Furthermore, certain drugs, including amiodarone, beta-adrenergic antagonists, glucocorticoids, and propylthiouracil, can reduce the activity of T4 5'-deiodinase, which is crucial for converting T4 to the more active T3 form. Some medications can also alter serum thyroxine-binding globulin (TBG) levels; for instance, estrogen, clofibrate, heroin/methadone, and tamoxifen can elevate TBG levels, while androgens/anabolic steroids, glucocorticoids, nicotinic acid, and asparaginase may decrease TBG concentrations. Additionally, certain drugs, including furosemide, heparin, hydantoins, and nonsteroidal anti-inflammatory drugs (NSAIDs) like fenamates, phenylbutazone, and salicylates, can displace thyroid hormones from their protein-binding sites, potentially leading to increased free hormone levels [29-32].

Thyroid ultrasonography (US) has established itself as a common and valuable tool in the evaluation and management of thyroid disorders. Ultrasound scanning is non-invasive, widely available, less expensive, and does not use any ionizing radiation [33]. Several studies demonstrated an association between hypoechogenicity at thyroid US and higher levels of serum TSH even in subjects without overt thyroid disease, suggesting decreased echogenicity as an early sign of thyroid dysfunction [34-36].

- *Limitations of Sonography are the Following:*

The primary limitation of ultrasound in thyroid imaging is its inability to assess thyroid function, meaning it cannot determine whether the thyroid gland is hypoactive, hyperactive, or functioning normally. Additionally, ultrasound is an observer-dependent technique, which can introduce variability in the interpretation of results [33]. An important source of error in ultrasonography depends on the technical skill of the operator. A diagnostic procedure performed by a poorly trained ultrasound technician or a well-trained technician making an error can produce inconsistent and incorrect results. Emergency US is particularly susceptible to errors, more than any other diagnostic imaging technique; in fact, the misinterpretation of sonographic images should be considered as a serious risk in US-based diagnosis [37].

Technical limits of thyroid US are represented by thyroid nodules spreading into substernal, retroclavicular, intrathoracic or retrotracheal locations that may not be easily imaged with US. Sonography can be effective in detection of retrosternal goiter when it is in the upper mediastinum, however, location of the goiter below the bifurcation of the trachea limits the possibility of US [38].

High-resolution ultrasound can detect thyroid lesions as small as 1-2 mm, including both fluid and solid nodules. However, nodules less than 10 mm are often too small for accurate assessment in clinical practice [39].

Another disadvantage of ultrasound technology is its dependence on the patient's body size. Visualization issues can occur when the target area is located deep within the body, as increased adipose tissue or other anatomical factors can hinder the clarity and quality of the ultrasound images. The presence of gas also affects the visual quality of ultrasound images, as gas induces poor quality image output [40]. When performing thyroid US, proper compression is essential: insufficient force may lead to imaging artifacts. Failure to apply adequate pressure results in deeper lesions appearing more indistinct because of ultrasound attenuation.

Sonography procedure is generally safe, but may lead to the non-thermal, mechanical and thermal effect at the cellular and molecular levels. Non-thermal effects of ultrasound include acoustic cavitation, by acceleration and movement of particles in liquid and the sudden release of energy, which can be sufficiently intense to disrupt molecular bonds. In molecular level, according to the frequency resonance hypothesis, ultrasound's non-thermal action affects enzyme activity and possibly gene regulation in tissues through two different mechanisms. First, absorption of mechanical energy by a protein may produce a transient conformational shift in the 3-dimensional structure and alter the protein's functional activity. Second, the resonance properties of the wave may dissociate a multi-molecular complex, thereby disrupting the complex's function [41].

Human body can be considered as an open, non-isolated superorganism. Thyroid diseases are multifactorial and complex disorders. As with other chronic diseases, there is a multifactorial etiology with a complex interaction of environmental and physiological factors in development of thyroid disease [42-43].

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Probably, any physiological and pathological phenomena basically cannot be explained on separated factors and mechanism alone, without the consideration of other aspect of life. Reduction of life phenomena to separated biological levels of organization of living organisms means almost totally refusing consideration of such typical features living systems as nonlinearity, networking, stochasticity, emergence and others aspects of complex systems [44]. In the recent decade the use of informative-wave technologies has been widely applied into practical medicine. The 3D-Nonlinear Bio Resonance Feed-back Diagnostics Systems (3D NLS BR) have been extensively used recently and are gaining ever growing popularity. Non-linear (NLS) diagnostic approaches are based on a new physics of quantum-entropic interactions or Quantum-entropic logic theory, that was previously described [43,45-46].

To our knowledge, to date, no studies have been published regarding using 3D-NLS BR Systems in screening of thyroid glands.

The purpose of this study was to test individuals with no dominant clinical symptoms with spectral-entropy analysis (SEA) parameters using 3D-NLS BR diagnostic method. This study was carried out in the medical scientific center of bioelectric and bio-feedback technologies in cooperation with Institute of Practical Psychophysics (IPP).

II. PARTICIPANTS AND METHODS

This experimental study was evaluated and approved by our Institutional Review Board, and was carried out from 2016 till 2018. The study was conducted on 1,200 adults (aged from 18 to 60 years old), who annually underwent thyroid hormone measurement with normal results and did not have any history of thyroid disease or other systemic diseases in their past medical history.

A. Inclusion and Exclusion Criteria:

In this study, our team initially used biophysical markers for evaluation of thyroid dysfunction. For confirmation or exclusion of an underlying thyroid disorder, the NLS-3D BR system was used for evaluation 3 biophysical spectral-entropy parameters:

- Fleindler's 12-point polychrome scale (FI).,
- Entropy level (EI) and
- Noise/information index (NII).

The NLS-bioresonance diagnostic is carried out using the hardware-software complex Metatron device registration no FSNO 022a2005/222105 using the Spectral Entropy Analysis (SEA) parameters, which were described in the previous article [43].

Individuals who showed FI- from 1 to 3, EI- from 1-4 and NII- less than 1, were classified as the Control Group (with this range indexes, it was expected the thyroid function and structure to be normal. Individuals, who showed FI= 4 or more than 4., EI= 5 and more than 5, and NII equal 1 or more than 1, were classified as the Case Group (with this range indexes, it was expected the thyroid function and structure to be abnormal (see Table1).

Tablet 1: Classification of Participants According to Spectral-Entropy Parameters

Groups	Fleindler's index(FI)	Entropy index(EI)	Noise/information index(NII)
Control=normal	3	Up to 4	Less than 1
Case	4 and more	5 and more	Equal 1 and more

After that, according to greatness of biophysical parameters, the Case Group was subdivided into two subgroups, namely A and B. All cases with the FI=4, EI=5 and NII=1 were assigned to Case Group A, and those with FI=5 or more than 5., EI=6-7 and NII- more than 1 were assigned to case group B (cases B, were expected to show worse thyroid structural and functional abnormality than Cases A) (see Table2).

Tablet 2: Classification of Case Group Based on the Magnitude of Spectral-Entropy Parameters

Cases	Fleindler's index(FI)	Entropy index	Noise/information index(NII)
Case A	4	5	Equal 1
Case B	5 or more	6 -7	more than1

According to the inclusion and exclusion criteria, after scanning with 3D NLS-BR system, participants were subdivided into two groups namely case group and control group. Case group consisted of 400 individuals, 300 of them were women (75%) and 100 of them were men (25%) (average age 42±28 years). Control group consisted of 800 individuals. 562 of them were women (70.25%) and 238 of them were men (29.85%). (average age 43±34 years). All participants were from Tehran city, Iran.

B. Ultra-Sound Screening of Thyroid Gland:

After evaluation with NLS-bioresonance diagnostic method, the blood sampling was sent to reference lab for TSH, T3, T4 and anti-TPO testing. In addition, ultrasound

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examinations were performed on both Control and Case groups. Thyroid ultrasound (US) was performed using the HDI 5000 or IU 22 (Philips medical system, Best, the Netherlands) with a 7.5 MHz linear probe. A reference radiologic center with 15 years of experience in thyroid US interpreted the US results in consensus. The Case Group and Control Group were classified into three groups based on the US results: group A (patients who had normal US) and group B (patients who were hypoechoic relative to the submandibular gland, but hyperechoic relative to strap muscle), and finally group C (It defined when the US showed multiple scattered small hypoechoic nodules in the whole thyroid parenchyma).

Decreased echogenicity was defined when more than two-thirds of the whole thyroid parenchyma showed lower echogenicity than that of the individual patient's submandibular gland by visual assessment. When the echogenicity of submandibular gland was abnormal due to sialoadenitis or connective tissue disease, the echogenicity of parotid gland was considered as standard.

C. Laboratory Procedures

Thyroid status was evaluated from blood samples by laboratory serum markers. Laboratory tests for thyroid function (serum levels of T3, T4, and TSH) and serum thyroid anti-thyroid peroxidase autoantibody [anti-TPO) were evaluated in these subjects.

Total T3 and T4 and TSH were determined by standard Electro-chemiluminescence (ECL) technique, supplied by Architect-Abott. Reference ranges(micg/dl) for total thyroxine (T4) were as follows: In 1-3 days (11.8-22.6), 4-14 day (9.8-16.6)., 15 day-4 months (7.2-14.4)., 5-12 month (7.8-16.5)., 13 month-5 years (7.3-15)., 6-10 year (6.4-13.3 and more than 11 years (5.1-14.1).

Reference ranges (ng/ml) for total thyroxine (T3) were as follows: In 1-3 days (1-7.4), 4 day- 5 years (1.05-2.69)., 6-10year (0.94-2.41)., 11-15year (0.83-2.13)., and more than 16 years (0.58-1.59).

For TSH value: between 4.7 and 10 mU/L is considered subclinical hypothyroidism., over 10 mU/L is overt (symptomatic) hypothyroidism., between 1.5 and 2.0 mU/L is suggestive of thyroid dysfunction., between 0.1 and 0.5 mU/L is considered subclinical hyperthyroidism and less than 0.1 mU/L is overt hyperthyroidism.Anti-TPO (IU/ml) was determined by Elisa technique, supplied by Tecan-sunrise: less than 50 IU/ml –negative., 50-75 borderline and more 75 considered as positive.

III. STATISTICAL ANALYSIS

Data analyses were conducted in SPSS (version 25) using Mann-Whitney U test (this nonparametric test was employed in this study, because the data were classified as nominal scales) to confirm whether the differences occurred between groups.

IV. RESULTS

Table 3 shows the biochemical and ultra-sound outcome in the case group and the control group.

In the Control Group, all 800 (100%) individuals had normal levels of TSH and T4 hormones, and 784 individuals (98%) had normal and 16(2%) showed the positive level of anti-TPO.

In the Case Group, out of 400 cases (A+B), 362 (90%) had normal levels of TSH and 38(10%) cases had borderline levels of TSH. 396 (99%) had normal levels of T4 and 4(1%) had the abnormal levels of T4. For Anti-TPO marker, 230(57.5%) at the normal (42.5%levels, normal and abnormal level, respectively (see Table 3).

Tablet 3: Biochemical and Ultrasound Outcomes in the Case and Control Groups

Groups	group		Biochemical						Ultrasono			
			TSH micIU/ml		T4 micg/dl		Anti TPO IU/ml		Hypo/echo		nodule	
			0.4-4.6	4.7-10	5-14	≥14.2	≤50	≥51	yes	NUS	yes	no
Case	A+ B= 400	N	362	38	396	4	230	170	389	11	116	284
		%	90	10	99	1	57.5	42.5	97	3	29	71
Control	C= 800	N	800	0	800	0	784	16	800	0	800	0
		%	100	0%	100	0%	98%	2%	0%	100%	0%	100

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Serum level of T3 hormone in all participants was normal. Sonography of 800 participants in the Control group showed 100% had normal pattern, compared to the Case group, in which, 394 (97%) had decreased echogenicity and 116 (29%) had nodular pattern of thyroid gland.

Mann Whitney U test showed a difference between Case group and Control group in biochemical and sonography at the significance level of .05. (Table 4).

Table 4. Descriptive statistics of biochemical parameters

Case Group (n=400)				Control Group (n=800)			
Min	**Max**	**M**	**SD**	**Min**	**Max**	**M**	**SD**
1.00	2.00	1.10	0.29	1.00	1.00	1.00	0.00
1.00	2.00	1.91	0.29	1.00	2.00	2.00	0.00
1.00	2.00	1.01	0.10	2.00	1.00	1.00	0.00
1.00	2.00	1.99	0.10	1.00	2.00	2.00	0.00
1.00	2.00	1.43	0.49	2.00	2.00	1.02	0.14
1.00	2.00	1.58	0.49	1.00	2.00	1.98	0.14
1.00	2.00	1.97	0.16	1.00	2.00	1.00	0.04
1.00	2.00	1.03	0.16	1.00	2.00	2.00	0.00
1.00	2.00	1.71	0.45	2.00	2.00	2.00	0.00

Note: Mann Whitney U test showed a difference between group case group and control group in biochemical and sonography at the significance level of .05

On the other hand, as shown in Table 2, when all cases were divided into two groups, data were collected from a total of 400 cases (A + B), with 280 classified as group A and 120 as group B. In group A, all 280 participants (100%) had normal levels of TSH and T4 thyroid hormones. For the Anti-TPO marker, 181 participants (64%) tested negative, 32 (12%) were borderline, and 67 (24%) had positive serum levels.

In group B, 82 participants (68%) had normal TSH levels, while 38 (32%) had borderline levels. For T4 serum levels, 116 participants (97%) had normal levels, and 4 (3%) had abnormal levels. Regarding the Anti-TPO marker, 49 participants (41%) tested negative, none were borderline, and 71 (59%) had positive serum levels. In the control group, all 800 individuals (100%) had normal levels of TSH and T4 hormones, with 784 (98%) showing normal Anti-TPO levels and 16 (2%) testing positive (see Table 5).

In the sonography findings for the Case A group, 269 participants (96%) exhibited decreased echogenicity, while 11 participants (4%) had a normal echogenic thyroid pattern. Additionally, 59 participants (21%) presented with a nodular pattern of the thyroid gland, while 221 participants (79%) did not. In the Case B group, all 120 participants (100%) showed decreased echogenicity, with 57 participants (48%) displaying a nodular pattern. Among the 800 controls, all participants (100%) exhibited a normal thyroid gland pattern (see Table 5).

A Mann-Whitney U test was conducted to assess significant differences in biochemical markers between the case and control groups. It assesses whether the distributions of the two groups are significantly different from each other. As shown in Table 4, significant differences were observed in all biochemical markers between the two groups.

Tablet 5: Biochemical and Ultrasound Outcomes in the Cases group (A, B) and Control Groups

Groups	group		biochemical							Ultrasono			
			TSH micIU/ml		T4 micg/dl		Anti TPO IU/ml			Hypo/echo		Nodule	
			0.4-4.6	4.7-10	5-14	≥14.2	Ng	Bl	Po	yes	NUS	yes	no
Case	A=280	N	280	0	280	0	181	32	67	269	11	59	221
		%	100	0	100%	0%	64%	12%	24%	96%	4%	21%	79%
		N	82	38	116	4	49	0	71	120	0	57	63

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	B=120												
		%	68%	32%	97%	3%	41%	100	59	100%	0%	48%	52%
Control	C=800	N	800	0	800	0	784	7	9	800	0	800	0
		%	100	0%	100%	0%	98%	0.8%	1.2%	0%	100%	0%	100

Mann Whitney U test showed a difference between group A and group B in biochemical and sonography at the significance level of .05 (Table6).

Table 6. Mean and standard deviation values of biochemical and sonography for two sub-scales of A and B groups.

Biophysical Index			TSH[1]	TSH[2]	T4[3]	T4[4]	AntiTPO≤ 50	AntiTPO ≥50	NUS[5]	HHPE P[6]	Nodule
Fleindler's index	Case A (n=280)	Mean	1.00	2.00	1.00	2.00	1.35	1.65	1.96	1.04	1.79
		SD	0.00	0.00	0.00	0.00	0.48	0.48	0.19	0.19	0.41
	Case B (n=120)	Mean	1.32	1.68	1.03	1.97	1.59	1.41	2.00	1.00	1.53
		SD	0.47	0.47	0.18	0.18	0.49	0.49	0.00	0.00	0.50
Entropy index	Case A (n=280)	Mean	1.00	2.00	1.00	2.00	1.35	1.65	1.96	1.04	1.79
		SD	0.00	0.00	0.00	0.00	0.48	0.48	0.19	0.19	0.41
	Case B (n=120)	Mean	1.32	1.68	1.03	1.97	1.59	1.41	2.00	1.00	1.53
		SD	0.47	0.47	0.18	0.18	0.49	0.49	0.00	0.00	0.50
Noise/ information index	Case A (n=253)	Mean	1.00	2.00	1.00	2.00	1.29	1.71	1.96	1.04	1.87
		SD	0.00	0.00	0.00	0.00	0.45	0.45	0.20	0.20	0.34
	Case B (n=147)	Mean	1.26	1.74	1.03	1.97	1.66	1.34	2.00	1.00	1.44
		SD	0.44	0.44	0.16	0.16	0.48	0.48	0.00	0.00	0.50

Note: Mann Whitney U test showed a difference between group A and group B in biochemical and sonography at the significance level of .05

1= TSH (normal range: 0.4-4.6 micIU/ml), 2=(more than 4.7 to 10 -subclinical hypothyroidism), 3= T4 micg/dl (5-14 normal range), 4=(more than 14.2 abnormal range), 5= normal sonography, 6= Heterogeneous and Hypoechoic Parenchymal Echo Pattern

A Mann-Whitney U test was run to determine if there were significant differences between group A and group B in biochemical markers and sonography. As shown in Table 5, there were significant differences in all biochemical markers and sonography between group A and group B.

V. DISCUSSION

This experimental study provides evidence for the effective application of the 3D-NLS BR system in screening for thyroid dysfunction. To the best of the authors' knowledge, this is the first study to explore this topic, highlighting the potential of this technology in enhancing the detection and assessment of thyroid-related conditions. Subclinical hypothyroidism (SH), also referred to as isolated hyperthyrotropinemia, is frequently linked to various adverse health risks, including cardiovascular disorders, elevated cholesterol levels, hypertension, endothelial dysfunction, and atherosclerosis. These ischemic abnormalities are likely associated with the long-term effects of a gradually progressing hypothyroid state. The chronic nature of SH may contribute to the development of these conditions, emphasizing the importance of monitoring and managing thyroid function to mitigate potential health risks [47- 49].

The most useful marker for assessing thyroid hormone action is the TSH level, which is characterized by an elevated TSH level while free T4 and T3 levels remain within the normal reference range. However, the secretion and action of TSH can be influenced by various factors, including non-thyroidal disorders, disturbances in the immune system, infections, different medications, and aging. These factors can

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complicate the interpretation of TSH levels and may lead to misdiagnosis or inappropriate management of thyroid conditions. The key role of the clinical laboratory is to provide accurate results for the diagnosis of diseases. While this goal has largely been achieved for routine biochemical tests, it remains a challenge for immunoassays. Immunoassays can sometimes lack adequate specificity and accuracy, making them susceptible to interference from endogenous immunoglobulin antibodies. This interference can lead to false and clinically misleading results, which may complicate diagnosis and management [50- 52]. Interference in immunoassay is one factor that contributes to the uncertainty of medical testing. In recent years, it has become evident that a consensus on the exact limits for cut-off between normal and subclinically hypothyroid individuals is not currently possible. Reference populations used as the basis for a normal range are highly different in relations of genetics and epigenetics background, and environmental factors such as iodine intake, age, gender and presence of thyroid autoantibodies and should not be confused with cut-off limits [53].

Then, although, the TSH level is a useful marker for the assessment of peripheral thyroid hormone action, but the values should be interpreted carefully, and TSH level alone could not be used to assess the thyroid hormone action in vivo.

Thyroid ultrasonography (US) is an essential tool in the diagnosis of thyroid-related diseases. For optimal examination of the thyroid gland, the use of a high-frequency linear transducer, typically in the range of 10-15 MHz, is recommended. This frequency allows for improved resolution and detail, enabling the detection of small nodules, cysts, and other abnormalities within the thyroid tissue. High-resolution ultrasound can also assist in characterizing lesions, guiding fine-needle aspiration biopsies, and monitoring changes over time, making it a valuable component of thyroid assessment and management [54-55]. Ultrasound can produce both thermal and non-thermal biological effects in body tissues. All ultrasound waves carry energy and momentum, which can lead to various interactions with biological tissues. Acoustic radiation force, radiation torque, acoustic streaming, shock waves and cavitation are considered non-thermal effects of the ultrasound. Acoustic radiation force is a physical phenomenon resulting from the interaction of an acoustic wave with an obstacle placed along its path. Cavitation is described as the formation and oscillation of a gas bubble and is recognized as a major cause of ultrasound-induced mechanical and thermal effects. Tissues naturally containing gas bodies, such as the lung and intestine, are more sensitive to the bio-effects of ultrasound exposure because of the presence of gas. Cavitation-related bio-effects are more dependent on frequency [56].

Several animal studies observed hemorrhage in lung tissues after ultrasound exposure (at 1.2 MHz, 3-min exposure) in mice, rabbit and pigs [57-59]. Acoustic cavitation can be generated in a wide variety of intestinal environments, as this part of body contain gas bodies located in a fluid-like medium [60].

Ultrasound contrast agents, particularly microbubbles, can induce blood cell destruction through mechanisms like fragmentation and targeted microbubble destruction. These processes can facilitate drug delivery and enhance imaging by creating microvessel ruptures, leading to localized effects in tissues [61]. Fetal red blood cells are more susceptible to lysis from exposure to ultrasound in the presence of contrast agents in vitro [62].

Cells and tissues can be damaged when exposed to ultrasound pulses, particularly if they are located near a region of gas already present within the tissue. The shear forces generated at the tissue/gas interface can be sufficient to cause cellular damage. However, it is generally accepted that diagnostic ultrasound does not produce serious side effects in organisms when used appropriately. Despite this, there are limitations to consider, such as the potential for non-thermal effects and the need for careful application to minimize any risks. Compared with traditional ultrasound, 3D NLS (Non-Linear System) systems offer several advantages, including reduced observer dependency. This technology allows for a more objective assessment of the thyroid gland, minimizing variability in interpretation that can occur with ultrasound imaging. Additionally, 3D NLS systems provide the capability to evaluate both the functional status and the structural characteristics of the thyroid gland simultaneously. This comprehensive approach enhances diagnostic accuracy and can facilitate better clinical decision-making in the management of thyroid-related conditions.

Data analysis from the 3D NLS bioresonance feedback system has demonstrated that Spectral Entropy Analysis (SEA) parameters serve as valuable markers for the early detection of thyroid-related disorders. These parameters can be particularly useful in screening asymptomatic patients, allowing for the identification of potential thyroid issues before they manifest as clinical symptoms. This capability highlights the potential of SEA in enhancing early diagnosis and improving patient outcomes in thyroid health management.

In general, screening serves two primary objectives. The first is the early detection of disease—before symptoms develop—at a stage when treatment is more effective and less costly. The second objective is to identify risk factors that place an individual at a higher risk of developing a disease, with the aim of modifying these risk factors to prevent or reduce the incidence of the disease [63-66]. While neither serum TSH levels nor ultrasound methods can fully meet both criteria for effective screening, the 3D NLS bioresonance (BR)

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system offers a holistic characterization that can address both objectives. This innovative approach allows for early detection and the identification of risk factors, thereby enhancing the overall effectiveness of screening efforts.

VI. CONCLUSION

Based on the findings of this study, the 3D NLS bioresonance feedback system is clinically effective for screening hypothyroidism. This system is not intended to replace traditional medicine; rather, it offers significant support in many cases. It is a holistic and non-invasive method suitable for medical practice.

Conflict of Interest: Authors have no conflict of interest.

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