Multiple Sclerosis is a Risk Factor for Hyperthyroidism and Interferon Beta Action on Thyroid Hormones via Novel Immuno-neuro-enzymological Mechanisms

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Abstract:

Objective : Multiple sclerosis (MS) is a common neurological disease deeply linked with the immune-inflammatory disorders whereas the term (multiple) mostly refers to the multi-focal zones of Inflammation caused by lymphocytes and macrophages infiltration besides oligodendrocytes death. Accordingly , the dysfunctional immune system able to damage myelin (a pivotal component of the central nervous system) which responsible for communication among neurons. The aim of the present study is to innovate a biochemical relationship between MS and thyroid hormones (THs) by highlighting immunological responses and also to examine the action of Interferon beta (IFNβ) drug on thyroid hormone (THs) and thyroid stimulation hormone (TSH). Materials and methods: Sixty (60) Iraqi women in the age ranged (36-43) years were enrolled in the present study, (30) of them were MS patients and the other (30) were healthy. Anyway, the protocol of the study involved four groups: G1 is a healthy control group, G2 involved untreated MS patients, G3 included the MS patients treated with IFNβ for (6) weeks and G4 composed of the same patients treated with IFNβ for (12) weeks. THs (T4 and T3) and TSH levels were determined in sera of all groups. Results: Data of the present study have reported that T4 level was highly significant increase in sera of G2 compared with G1 while it was significant and highly significant decreased in G3 and G4 respectively compared with G2, the difference between G4 and G1 and also between G4 and G3 was significant. T3 level was highly significant increase in sera of G2 compared with G1 but it was highly significant decreased in G3 and G4 compared with G2, the difference between G4 and G1 was non-significant while the difference between G4 and G3 was significant. Conversely, TSH level was highly significant decreased in G2 compared with G1 but it was highly significant increase in G3 and G4 compared with G2, the difference between G4 and G1 and also between G4 and G3 was highly significant. Conclusions : Interestingly , the present study is the first in Iraq reporting that MS may be a key risk factor for hyperthyroidism and also the first suggesting that IFNβ regulates THs biosynthesis via novel immuno-neuro-enzymological mechanisms regarding thyroid peroxidase (TPO) and iodothyronine deiodinase 1 (D1), meanwhile the present study indicates that IFNβ has an indirect antioxidant activity. Moreover, the present study provides a definite clarification for the changed NF kappa B level in MS. Remarkably, the present study reveals that IFNβ is more potent on T3 than T4 while it has less action on TSH.

Key words: Multiple sclerosis. T4. T3

التصلب اللويحي المتعدد عامل خطورة لإفراط إفراز الغدة الدرقية و تأثير الإنترفيرون بيتا على هرمونات الدرقية عن طريق ميكانيكية إنزيمية-عصبية-مناعية جديدة

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الخلاصة:
التصلب اللويحي المتعدد هو احد الأمراض العصبية الشائعة المرتبطة بقوة مع الإضطرابات المناعية الإلتهابية حيث أن كلمة (متعدد) غالبا تعود إلى مناطق موضعية محددة من الإلتهاب بسبب تسريب و تأثير الخلايا اللمفية و الخلايا البلعمية فضلا عن موت الخلايا العصبية المناعية المتعددة و على هذا الأساس فإن إختلال وظيفة الجهاز المناعي له القدرة على تدمير المايلين (المكون الحيوي الأساسي للجهاز العصبي المركزي) المسؤول عن الإتصال مابين الأعصاب. إن هدف الدراسة الحالية هو إبتكار علاقة كيموحيوية بين التصلب اللويحي المتعدد و هرمونات الغدة الدرقية عن طريق تسليط الضوء على الإستجابات المناعية و أيضا إختبار تأثير عقار الإنترفيرون بيتا على هرمونات الدرقية و الهرمون المحفز للدرقية. تم إشتراك ٦٠ إمرأة عراقية في الدراسة الحالية ضمن المرحلة العمرية (٣٦ إلى ٤٢) سنة ، ٣٠ إمرأة مصابة بالتصلب اللويحي المتعدد و الثلاثون الأخريات غير مصابات بأي مرض مزمن (كمجموعة ضابطة) . إن بروتوكول الدراسة تضمن أربع مجاميع : المجموعة الأولى كمجموعة ضابطة للنساء غير المصابات بينما المجموعة الثانية تضمنت النساء المصابات بالتصلب اللويحي المتعدد قبل العلاج ، المجموعة الثالثة تضمنت نفس النساء المريضات و لكن بعد خضوعهن للعلاج بالإنترفيرون بيتا لمدة ستة أسابيع و المجموعة الرابعة أيضا نفس النساء بعد إثنا عشر إسبوعا من نفس العلاج. تم تقدير مستوى كل من هرمونات الغدة الدرقية (الثايروكسين و الثلاثي أيودو ثايرونين) و الهرمون المحفز للدرقية في أمصال دم جميع المجاميع. إن نتائج هذه الدراسة أثبتت أن مستوى الثايروكسين إرتفع بشكل معنوي عالي في أمصال المجموعة الثانية مقارنة مع المجموعة الأولى بينما إنخفض بشكل معنوي و معنوي عالي في المجموعة الثالثة و الرابعة على التوالي مقارنة مع المجموعة الثانية. أما الإختلاف مابين المجموعة الرابعة و الأولى ، و الرابعة و الثالثة فكان معنويا. بالمقابل فإن مستوى ثلاثي أيودو ثايرونين إرتفع بشكل معنوي عالي في أمصال المجموعة الثانية مقارنة مع الأولى بينما إنخفض بشكل معنوي عالي في المجموعتين الثالثة و الرابعة مقارنة مع الثانية ، أما الإختلاف مابين المجموعة الرابعة و الأولى فكان غير معنوي بينما الإختلاف مابين الرابعة و الثالثة فكان معنويا. و على العكس فإن مستوى الهرمون المحفز للدرقية إنخفض بشكل معنوي عالي في المجموعة الثانية مقارنة مع الأولى ، و لكنه إرتفع بشكل معنوي عالي في كل من الثالثة و الرابعة مقارنة مع الثانية ، أيضا كان الإختلاف مابين الرابعة و الأولى ومابين الرابعة و الثالثة فكان أيضا معنوي عالي. في مايخص الإستنتاجات فإن الدراسة الحالية كانت الأولى في العراق التي بينت أن التصلب اللويحي المتعدد هو عامل خطورة رئيسي لإفراط إفراز الدرقية و أيضا الأولى التي أشارت إلى أن الإنترفيرون بيتا ينظم التخليق الحيوي لهرمونات الغدة الدرقية و عن طريق ميكانيكيات إنزيمية عصبية مناعية غير مطروقة تتعلق بكل من إنزيمي الثايرويد بيروكسيديز و الأيودو ثايرونين ديأيودينيز ١ ، و كذلك أكدت الدراسة الحالية أن الإنترفيرون بيتا له فعالية مضادة للأكسدة غير مباشرة ، فضلا عن ذلك فإن الدراسة الحالية قدمت تفسيرا واضحا لتغيير مستوى العامل النووي المعزز لسلسلة كابا B. و من الجدير بالملاحظة أن الدراسة الحالية أشارت إلى أن الإنترفيرون بيتا يكون الأقوى فعالية على الثلاثي أيودو ثايرونين مقارنة مع الثايروكسين بينما تأثيره يكون الأقل فعالية على الهرمون المحفز للدرقية.

الكلمات المفتاحية: التصلب اللويحي المتعدد . الثايروكسين . ثلاثي أيودو ثايرونين

Introduction
Multiple sclerosis (MS) is a complex chronic auto-immune inflammatory disease [1,2,3] characterized by repeated demyelination of the central nervous system [4,5,6] Demyelination is a pathophysiological condition including localized destruction of myelin [7,8] Moreover , its pathophysiology involves oligodendrocytes death and axonal degeneration.[8] Lesions or plaques composed of inflammatory and demyelinating cells cross with the correct transmission of nerve impulses and cause neuronal dysfunction mainly autonomic and sensorimotor defects , difficulties in thinking and fatigue. [9] Broadly, MS is diagnosed by magnetic resonance imaging (MRI). [10,11] Thyroxine (T_4) and triiodothyronine (T_3) are the mostly hormones linked with metabolism, they are secreted by the thyroid gland, [12] under stimulation of thyroid stimulating hormone (TSH) which secreted by pituitary gland. [13] Moreover, thyroid hormones (THs) T_4 and T_3 controls a different essential biophysiology processes involving brain development, body growth, skeleton maturation, oxygen consumption, reproduction, heat production and heart contractility. [14] Thyroid stimulating hormone (TSH) is a major sensitive biochemical hormone reflecting thyroid function [15] because its secretion is being

under negative feedback control depending on THs. [16] Interferons (IFNs) are cytokines with protein structure, play a central role in the immunological responses. There are three types of IFNs used as drugs: IFNα, IFNβ and IFNγ. IFN is commonly used for MS treatment. [17] Accordingly, exogenous IFN (used as drugs) interacts with endogenous (natural) IFN by immune-modulations pathways. [18]

Materials and methods

- Basics of research:

Honestly, at the beginning of the present study, the first intention was to measure some biochemical parameters in MS patients rather than THs and TSH, but during blood samples collections in both of MS clinic of medical city / Baghdad and private laboratories I noted some features related to thyroid gland disorder in MS patients. Accordingly , this interested circumstance provoke a motive for me to change the direction of the research towards studying the relationship between untreated MS patients and thyroid gland disorders by determination THs and TSH , and in the same time examination the action of the drug given commonly to MS patients in Iraq (IFNβ).

- Subjects:

Sixty (60) Iraqi female with age in range (36-43) years were enrolled in this study, (30) of them were untreated MS diagnosed by magnetic radiation image (MRI), the other (30) were healthy (enrolled as a control group). Patients were treated with IFNβ injection (250 µgm/mL) one injection / two days for (12) weeks. The protocol of the present study involved four groups: G_1: healthy control group (30 member). G_2: untreated MS patients (30 patient). G_3: MS patients treatedwith IFNβ for (6) weeks (30 patient). G_4: MS patients treated with IFNβ for (12) weeks (30 patient). Practically, T_4, T_3 and TSH were determined in sera of each group.

- Blood samples and biochemical parameters determination:

Five milliliters (5mL) of venous blood were collected from all subjects in this study, placed into plain tubes, when coagulation was happened, serum was isolated by centrifugation (4000 round per minute) subsequently, sera were kept frozen until biochemical determination. THs (T_4 and T_3) were determined by competitive ELISA method, T_4 contained in serum (the native antigen) competes with T_4 horseradish peroxidase conjugate for binding with monoclonal antibody coated on the microplate. Also a competition reaction occurred between the native antigen of T_3 and horseradish peroxidase conjugate to bind with a limited number of biotinylated antibody (Anti-T_3 labeled with biotin) In both of T_4 and T_3 determination , the enzyme activity in the antibody bound fraction is measured by a reaction with a substrate and producing a color its intensity is inversely proportional with T_4 and T_3 concentrations. On the other hand , TSH is determined by sandwich ELISA method , high affinity and specific antibodies (enzyme and immobilized) were used and the native antigen is included within serum , a reaction happened between TSH antibodies and the native TSH in the microwell without a competition forming a soluble sandwich method , the complex is deposited to the well through the high affinity reaction of streptavidin and biotinylated antibody . After equilibrium was attained, the antibody – bound fraction was separated from unbound antigen by decantation, enzyme activity in the antibody bound fraction is directly proportional to the native antigen concentration. Similarly, the enzyme activity presenting on the surface of the well was determined by a reaction with a substrate and producing a color its intensity proportional with TSH concentration

- Statistical Analysis:

Data of the present study were represented as mean ± S.D (S.D : standard

deviation) , student t- test was applied for estimation the degree of significance among groups by calculating probability value (p) , ($p< 0.001$) , ($p<0.05$) and ($p\geq0.05$) were assumed statistically highly significant , significant and non-significant respectively as will be reported in results divisions

Results

Table (1): T_4 level in sera of MS patients and control subjects.

Groups	T_4 level (nmol/L)	
	Mean	S. D
G_1	85.2	10.63
G_2	194	16.78
G_3	110	9.23
G_4	99.8	8.12
P G_2/G_1: H.S (1.16969E-17) P G_3/G_2: S (0.00154) P G_4/G_2: H.S (3.08629E-18) P G_4/G_1: S (0.0036) PG_4/G_3: S (0.00163)		

Table (2): T_3 level in sera of MS patients and control subjects.

Groups	T_3 level (nmol/L)	
	Mean	S. D
G_1	1.82	0.39
G_2	3.42	0.75
G_3	2.33	0.58
G_4	1.90	0.47
P G_2/G_1: H.S (2.92538E-18) PG_3/G_2: H.S (6.74439E-23) PG_4/G_2: H.S (7.30241E-26) P G_4/G_1: N.S (0.0648) PG_4/G_3: S (0.0019)		

Table (3): TSH level in sera of MS patients and control subjects.

Groups	TSH level (µU/mL)	
	Mean	S. D
G_1	2.10	0.12
G_2	0.13	0.01
G_3	0.5	0.04
G_4	1.04	0.07
P G_2/G_1: H.S (8.88031E-21) PG_3/G_2: H.S (1.09045E-12) P G_4/G_2: H.S (5.67248E-17) P G_4/G_1: H. S (1.35922E-09) PG_4/G_3: H.S (1.23867E-08)		

Results of table (1) have reported that T_4 level was highly significant increase in sera of G_2 (194±16.78) nmol/L compared with G_1 (85.2±10.63) nmol/L, conversely , it was significant and highly significant decreased in sera of G_3 (110± 9.23) nmol/L and G_4 (99.8±8.12) nmol/L respectively compared with G_2(194±16.78) nmol/L while the difference between G_4 (99.8±8.12) nmol/L and G_1 (85.2±10.63) nmol/L was significant and the difference between G_4 (99.8±8.12) nmol/L and G_3(110± 9.23) nmol/L was significant. Also , results of table (2) have suggested that T_3 level was highly significant increase in sera of G_2 (3.42±0.75) nmol/L compared with G_1 (1.82±0.39) nmol/L but it was highly significant decreased in sera of G_3 (2.33±0.58) nmol/L and G_4 (1.90±0.47) nmol/L compared with G_2 (3.42±0.75) nmol/L , remarkably the difference between G_4 (1.90±0.47) nmol/L and G_1 (1.82±0.39) nmol/L was non-significant while the difference between G_4 (1.90±0.47) nmol/L and G_3 (2.33±0.58) nmol/L was significant . Nevertheless , results of table (3) have shown that TSH level was highly significant decreased in sera of G_2 (0.13±0.01) µU/mL compared with G_1 (2.10±0.12)) µU/mL , interestingly it was highly significant increase in sera of G_3 (0.5±0.04) µU/mL and G_4 (1.04± 0.07) µU/mL compared with G_2(0.13±0.01) µU/mL but the difference between G_4 (1.04± 0.07) µU/mL and G_1 (2.10±0.12) µU/mL was highly significant. Moreover, the difference between G4 (1.04± 0.07) µU/mL and G3 (0.5±0.04) µU/mL was highly significant.

Discussion

Thyroid peroxidase (TPO) is the key enzyme responsible for the biosynthesis of T_4 and T_3. [19] which are secreted by the thyroid gland, [20] In particular, this enzyme catalyzes covalent incorporation of oxidized iodine into tyrosine in thyroglobulin and coupling of iodinated tyrosine to form T_4 and T_3. [21] thyroglobulin regulates development and function of the central nervous system. [22] According to multiple sclerosis which is characterized by inflammatory auto-immunological demyelinating conditions, [23] a recent study has revealed that tissue damage in MS resulted from a complex and dynamic interplay among immune cells, (myelin-making oligodendrocytes) and neurons. [10] In this regard, a recent study has suggested that oligodendrocytes are the major cause of demyelination in MS patients. [24] Also a second recent one has reported that B cells and T cells mostly contribute to the physiology of demyelinating disorders. [1] Moreover, a previous study has shown that demyelination may be mediated by a direct attack of macrophages. [25] Interestingly, a recent review has mentioned that myelin debris activates nuclear factor kappa B (NF-kB) in neural and glial cells mediating neuro-inflammation and neuro-degeneration, [26] NF-kB constitutes a major component in many immunological responses. [27] Consequently, the present study provides a definite pathway for the high expression and activity of NF-kB in MS patients by highlighting immunological factors that lead to demyelination. Although the recent study [2] suggested that NF-kB pathway is changed in MS, but the mechanism was partially understood. Since NF-kB is expressed primarily in the brain , [28] it plays a crucial role in the nervous system , [29] In accordance with thyroid hormones , NF-kB acts as a regulatory element in TPO expression , it has been suggested by [21] TPO promoter has a conserved binding site for NF-kB. Consequently, the over-expression of NF-kB resulting from demyelination in MS up-regulates TPO and subsequently induces T_4 and T_3 biosynthesis over the normal range (The major features of hyperthyroidism). On the other hand, reactive oxygen species (ROS) are so active in MS. [1] because those neuro-toxic molecules (produced by inflammatory cells) are present at an active demyelination site. [24, 30] Increased levels of ROS and their intermediates induce cellular damage and trigger chronic inflammation. [25, 31] Interestingly, Hydrogen peroxide H_2O_2 binds with thyroglobulin tyrosine to form iodothyronine in the first step of THs biosynthesis. [32 ,33] As a result, the present study submits a neuro-immuno mechanism emphasizing the data related to the highly significant increase of T_4 table (1) and T_3 table (2) in G_2 (untreated patients) compared with G_1 (healthy control subjects). This mechanism divided into two pathways: The first by up-regulation of TPO via over expression of NF-kB and the second by activation of TPO via higher level of H_2O_2, both of the two pathways linked with demyelination. In other words, the present study is the first reporting that MS may be a key risk factor for hyperthyroidism via novel immuno-neuro enzymological pathways, fig (1) Remarkably, T_4 and T_3 levels were depressed under treatment with IFNβ as shown in table (1) and table (2). However, the significant and highly significant decrease of T_4 in G_3 and G_4 compared with

G_2 besides the highly significant decrease of T_3 in G_3 and G_4 compared with G_2 revealed that their biosynthesis was down regulated by IFNβ. Hence, immunological factors lead to demyelination (macrophages, lymphocytes) and oligodendrocytes in fig (1) must be highlighted. Broadly, endogenous IFNβ, is released by macrophages and activates the immunological responses through type I IFN signaling pathway, [34] exogenous IFNβ acts as indirect inhibitor for endogenous IFNβ signaling by overcoming the inhibition and rescuing infected macrophages. [35] Accordingly, a recent study has revealed that macrophages play a potential role in demyelination and remyelination. Hence, depletion of macrophages plays a pivotal role in decreasing the severity of demyelination. [24] Furthermore, IFNβ interacts with the immune system at multiple levels by modulationg the function of T cells and B cells in the adaptive immune system. Also, IFNβ help maintaining the number of type I interferon secreting plasmacyloid dendrocytes. [3] Consequently, when macrophages, lymphocytes and dendrocytes changed to the balance by the superior drug IFNβ, demyelination will be inhibited, subsequently NF-kB expression will be controlled, and TPO shifted towards its normal activity, in other words T_4 and T_3 biosynthesis will be down-regulated. Therefore, this study is the first reporting that IFNβ is an indirect regulator for THs in Iraqi patients with MS via its reactive effect on demyelination, fig (2). Moreover, IFNβ has an indirect antioxidant property caused by inhibition of demyelination and consequently restrict the sites of H_2O_2. However, the significant decrease of T_4 table (1) and T_3 table (2) in G_4 compared with G_3 suggesting that the duration of treatment with IFNβ has a positive action. The difference between G_4 and G_1 in T_3 table (2) was non-significant while it was significant in T_4 table (1) revealing that T_3 approximately reached its normal levels under treatment with IFNβ. In accordance with T_3, iodothyronine deiodinase plays a central role in maintaining normal serum T_3. [36] Remarkably, a relationship between IFNβ and iodothyronine deiodinase may be possible. Anyway, 20% of T_3 is directly released by the thyroid gland under normal bio-physilogical circumstances, [21] and predominantly 80% of T_3 derived from T_4 metabolism by iodothyronine deiodinase. [14] Besides TPO, T_3 levels and its biosynthesis is controlled by iodothyronine deiodinase, [37] there are three types of iodothyronine deiodinase: iodothyronine deiodinase 1 (D_1), iodothyronine deiodinase 2 (D_2) and iodothyronine deiodinase 3 (D_3), they catalyze the production and degradation of T_3 respectively via the outer and inner deiodination. [38] Interestingly, D_1 is expressed not only in thyroid and other organs linked with metabolism, [39] but also in lymphocytes (B cells and T cells) as mentioned by the recent study [37], that also has suggested a correlation between D_1 and inflammation. Moreover, the study [37] linked between neurological disorders (brain and depressive disorders) and high expression of D_1. Consequently, D_1 is highly expressed in MS patients where the immune system is destroyed and neurological disorders are possible, fig (2). On the other hand, IFNβ modulates inflammatory – immunological responses related to B cells and T cells and depress pro-inflammatory cytokines (although exogenous IFNβ is also a cytokine but it acts as anti-inflammatory cytokine). [40,

41, 42] As a result, D_1 is down-regulated by IFNβ towards the balance and T_3 will be approximately reached the normal balance in G_4 table (3). Collectively, IFNβ could be considered as indirect down-regulator for D_1 in MS, fig (3). Lastly , according to table (3) , the highly significant decrease of TSH in G_2 compared with G_1 indicate that untreated MS suffering from hyperthyroidism (besides higher level of T_4 and T_3) cited above , this significant decrease of TSH in G_2 compared with G_1 and the highly significant increase in G_3 and G_4 compared with G_2 are explained based on T_4 and T_3 level in the context of pituitary thyroid feedback regulation. [43, 44] When T_4 and T_3 biosynthesis is overactive, TSH releasing will be suppressed by the negative feedback inhibition. In turn, when T_4 and T_3 levels in blood decreased, the pituitary release more TSH. [45, 46] Another recent study emphasizes the last explanation related to TSH by reporting that lower level of TSH mostly refers to the over-activity of thyroid gland (hyperthyroidism). [47] The highly significant difference between G_4 and G_1 suggested that IFNβ has a less action on TSH in comparison with T_4 and T_3 whereas the highly significant difference between G_4 and G_3 emphasizes the role of treatment duration.

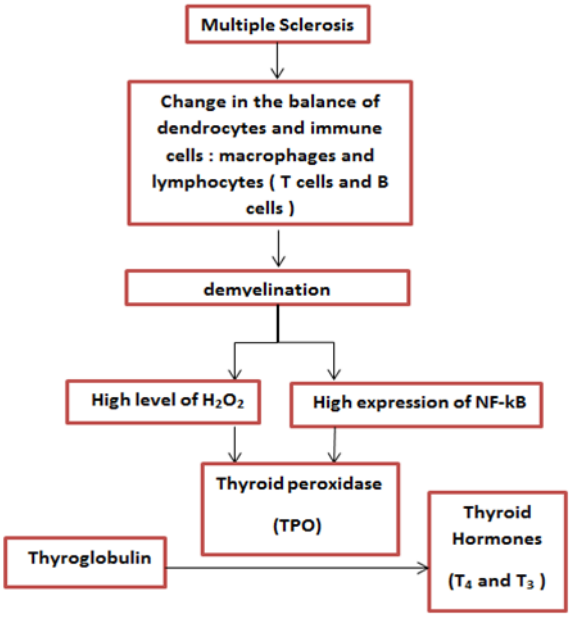

Figure (1) : The suggested mechanism for MS as a risk factor for hyperthyroidism via the up-regulation of TPO

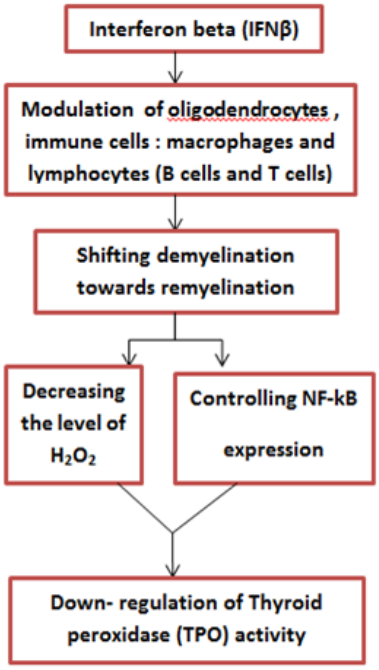

Figure (2): The indirect action of IFNβ as a down-regulator for TPO.

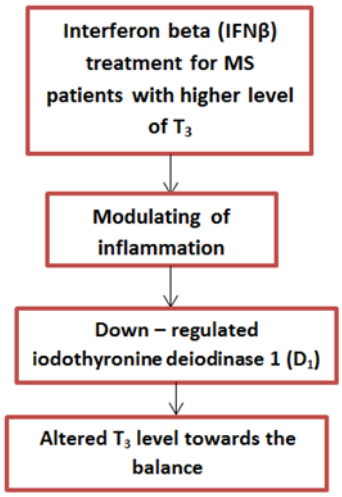

Figure (3) : IFNβ action on D_1.

Conclusions

This study is the first in Iraq reporting:1) Untreated MS may be a key risk factor for hyperthyroidism via novel immuno– neuro –enzymological mechanism regarding TPO dividing into two pathways : the first including the over-expression of NF-kB as an up-regulator for TPO and the second dealing with higher levels of H_2O_2 as a cofactor for TPO. 2) A definite clarification for the changed level of NF-kB in untreated Iraqi MS patients based on immuno-neuro changes. 3) A novel immuno–neuro- enzymological mechanism by which IFNβ modulates THs biosynthesis in Iraqi MS patients via the indirect down regulation of TPO. 4) An immuno – neuro relationship between untreated Iraqi MS and high expression of D_1. 5) An indirect mechanism by which IFNβ down-regulate D_1 activity and shifting T_3 towards the balance in Iraqi patients with MS.

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