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Applying a systems approach to thyroid physiology: Looking at the whole with a mitochondrial perspective instead of judging single TSH values or why we should know more about mitochondria to understand metabolism

Roy Moncayo*, Helga Moncayo

WOMED, Karl-Kapferer-Strasse 5, AT-6020 Innsbruck, Austria

ABSTRACT

Classical thinking in endocrine physiology squeezes our diagnostic handling into a simple negative feedback mechanism with a controller and a controlled variable. In the case of the thyroid this is reduced to TSH and fT3 and fT4, respectively. The setting of this tight notion has no free space for any additions. In this paper we want to challenge this model of limited application by proposing a construct based on a systems approach departing from two basic considerations. In first place since the majority of cases of thyroid disease develop and appear during life it has to be considered as an acquired condition. In the second place, our experience with the reversibility of morphological changes makes the autoimmune theory inconsistent.

While medical complexity can expand into the era of OMICS as well as into one where manipulations with the use of knock-outs and -ins are common in science, we have preferred to maintain a simple and practical approach. We will describe the interactions of iron, magnesium, zinc, selenium and coenzyme Q10 with the thyroid axis. The discourse will be then brought into the context of ovarian function, i.e. steroid hormone production. Finally the same elemental players will be presented in relation to the basic mitochondrial machinery that supports the endocrine.

We propose that an intact mitochondrial function can guard the normal endocrine function of both the thyroid as well as of the ovarian axis. The basic elements required for this function appear to be magnesium and iron. In the case of the thyroid, magnesium-ATP acts in iodine uptake and the heme protein peroxidase in thyroid hormone synthesis. A similar biochemical process is found in steroid synthesis with cholesterol uptake being the initial energy-dependent step and later the heme protein ferredoxin 1 which is required for steroid synthesis. Magnesium plays a central role in determining the clinical picture associated with thyroid disease and is also involved in maintaining fertility. With the aid of 3D sonography patients needing selenium and/or coenzyme Q10 can be easily identified. By this we firmly believe that physicians should know more about basic biochemistry and the way it fits into mitochondrial function in order to understand metabolism. Contemplating only TSH is highly reductionistic.

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* Corresponding author.
  E-mail address: r.moncayo@chello.at (R. Moncayo).

1. Author's profiles, motivation and contribution for this evaluation

We have been involved in clinical practice dealing with endocrinology since many years, in fact decades, i.e. RM since 1976 and HM since 1986. Our individual areas of work have been thyroid disease and reproductive medicine including assisted reproduction techniques, respectively. In 1995 we made a short joint excursion into the field of ovarian autoimmunity [1]. Our initial publications were derived from academic medical and scientific work at the University of Ulm, Germany, and later at the Medical School of the University of Innsbruck, Austria. Since 2002 we have continued to do research in both fields on the basis of private academic initiative. Our daily work is currently done by including additional techniques such as principles of locomotion biomechanics, Applied Kinesiology, TCM, acupuncture, herbal therapy, manual medicine, and natural medicine from the Shuar people of Ecuador.

In times of advancement of science the simple world of ligand and receptor interaction [2,3] has evolved into an age of OMICS [4]. This information has widened our horizon but at the same times it can overwhelm our perception and simple facts might disappear. With this in mind, we will attempt here to link modern biochemical knowledge into basic thyroid and ovarian physiology and present it in a simple way according to the thesis of elementological biology of Nishimuta, i.e. the interactions between chemistry and biology [5].

2. The philosophical alternatives in science and medicine

The philosophical views that drive medical work have been discussed recently by Andrew C. Ahn as either relying on reductionism or on systems approach [6,7]. The first one is disease driven and aims at normalcy, i.e. finding a normal range. The second one is individualized, multidimensional, time and space sensitive and synergistic. At a meeting dedicated to the topic of complex systems these characteristics were described as: "complex, because they exhibit global properties not made obvious from the properties of the individual components, and they are "systems," because they are composed of interconnected parts" (page 1017 in [8]). The basic statements from Ahn are given on Table 1.

The reductionism found in Evidence Based Medicine (EBM) has been criticized as lacking realism. In order to overcome this, different perspectives should work additively to include practical choice options [9], i.e. connecting the parts. In the words of Henry H.Q. Heng [10]: "Clinical therapies must be individualized, balancing the parts of the system and the response of the patient as a whole". Whatever approach is taken the researcher and the clinician has to be aware of possible falsification of data or of concepts as has been described by Popper [11].

Looking back at the development of evidence based medicine one can consider it to be a direct consequence of the condition that affected Archibald Cochrane personally. He had to go through a tortuous path of medical examinations in order to have a diagnosis and cure of his own illness [12,13]. It is therefore not surprising that Cochrane discussed the general scientific problem of testing a hypothesis as to whether a certain treatment alters the natural history of a disease for the better (page 20 in [14]). This was stated in his monograph entitled: "Effec-

tiveness and Efficiency. Random Reflections on Health Services" [14].

In the following sections we will review data related to clinical work in the field of thyroid diseases. We will then proceed to develop a systems approach based on the concepts contained in the WOMED model of benign thyroid disease [15,16]. Finally we will attempt to integrate the functions of single elements such as iron, magnesium, coenzyme Q10 (CoQ10), selenium and zinc into a frame for mitochondrial function.

3. Reductionism in thyroid disease studies

In 2002 and 2003 two studies based purely on epidemiological laboratory examinations of serum TSH values were published. The final intention was to consider TSH as the master parameter that could describe thyroid function as a reductionist entity. Their results were not similar. We will look at the circumstances surrounding these studies.

The first publication by Hollowel et al. [17] reported the 95% reference limits for this analyte as being 4.12 (3.94–4.45) mIU/l. Hollowel's publication was based on the data collection of the NHANES III investigation which was conducted at the end of the past century (between 1988 and 1994) [17]. The NHANES study included 17,353 persons after a selection process called oversampling [18]. Oversampling was declared as the driving method (references 12 and 13 in [17]). Current documentation to oversampling states: "NHANES typically samples larger numbers of certain subgroups who are of particular public health interest. Oversampling is done to increase the reliability and precision of estimates of health status indicators for these population subgroups". (http://www.cdc.gov/nchs/tutorials/nhanes/FAQs.htm). Thus, in plain terms one can understand that oversampling is similar to counting the same data more than once. Hollowel, however, failed to explain or identify the subgroups that were created by oversampling. The potential bias produced by such an artificial - perhaps obscure – approach has never been discussed. In general terms allocation bias will distort the image of any study population [19]. The second publication on TSH values was made by Baloch and co-workers and had the title: "Laboratory medicine practice guidelines". They suggested a theoretical upper reference value for TSH of 2.5 mIU/l [20]. We have recently commented on the aftermath of the suggestions made by Baloch and also by Abalovich [21] and shown that they are invalid [22]. In other words, lowering the upper reference value for TSH to 2.5 mIU/l was no panacea.

4. The entry into complexity: the involvement of the musculoskeletal system

In 2007 we described changes in the musculoskeletal system in patients with thyroid associated ophthalmopathy [23]. The main findings were a deviation of the body axis occurring frequently after an ankle sprain. The physiological negative correlation between calcium and magnesium was altered. Using radionuclide imaging techniques Hartman Kainz et al. demonstrated accumulation of a ^{99m}Tc-labelled octreotide tracer in the musculoskeletal system of these patients [24]. Putting both pieces of evidence together we proposed that these patients had a process of low level inflammation in the muscles. A common denominator in these patients was an altered

Table 1
Reductionism vs. systems approach.

The limits of reductionism in medicine: could systems biology offer an alternative? [6]	The clinical applications of a systems approach [7]
Since Descartes and the Renaissance, science, including medicine, has taken a distinct path in its analytical evaluation of the natural world. This approach can be described as one of "divide and conquer," and it is rooted in the assumption that complex problems are solvable by dividing them into smaller, simpler, and thus more tractable units.	Reductionism, as a guiding principle, is tremendously helpful and useful. The problem with reductionism stems not from its use but from the wrongful assumption that it is the only solution. Reductionism becomes less effective when the act of dividing a problem into its parts leads to loss of important information about the whole.

circular rotation of the ankle. This situation appeared to be a consequence of a supination flexion lesion which has happened many years before. Additional changes in the musculoskeletal system include stiffness of the shank muscles and idiopathic moving toes, i.e. involuntary movement of the toes while the contralateral foot is rotating [23]. Biochemical evaluations showed that these alterations are primarily related to lower magnesium levels in blood. Patients with thyroid disease also presented selenium [25] and CoQ10 deficiencies [16].

An important tool in the examination of these patients has been ultrasound. Adapting an existing quantitative 3D power Doppler ultrasound methodology form the field of obstetrics [26] we have examined the feature of hyper-perfusion in thyroid disease [27]. Using a quantitative evaluation software (VOCAL© on a Voluson 730 ultrasound machine, GE Healthcare Austria GmbH & Co, Zipf, Austria) it is possible to distinguish specific features of perfusion. The first characteristic was that of increased vascularization-flow index (VFI) seen in connection with low levels of magnesium, and the second one was increased vascularization index (VI) which corresponded to low levels of CoQ10. Visually, magnesium deficiency is associated with "fine granular" perfusion, while CoQ10 deficiency can be recognized in the 3D image as thickened vessels [16]. Signs of fibrosis in the thyroid are suggestive of selenium deficiency [28]. This visual information obtained from 3D power Doppler sonography is crucial for planning an individual supplementation plan. Fig. 1 shows some characteristic findings in a case of newly diagnosed hyperthyroidism with combined magnesium, selenium and CoQ10 deficiencies. The vascular structure is clearly recognized in the 3D mode.

Fig. 2. Magnetic resonance Imaging of the right knee of a healthy subject. The arrow on a round marker shows the location of acupoint stomach 36 or Zu San Li. Technical details of the imaging procedure have been described before [34,35].
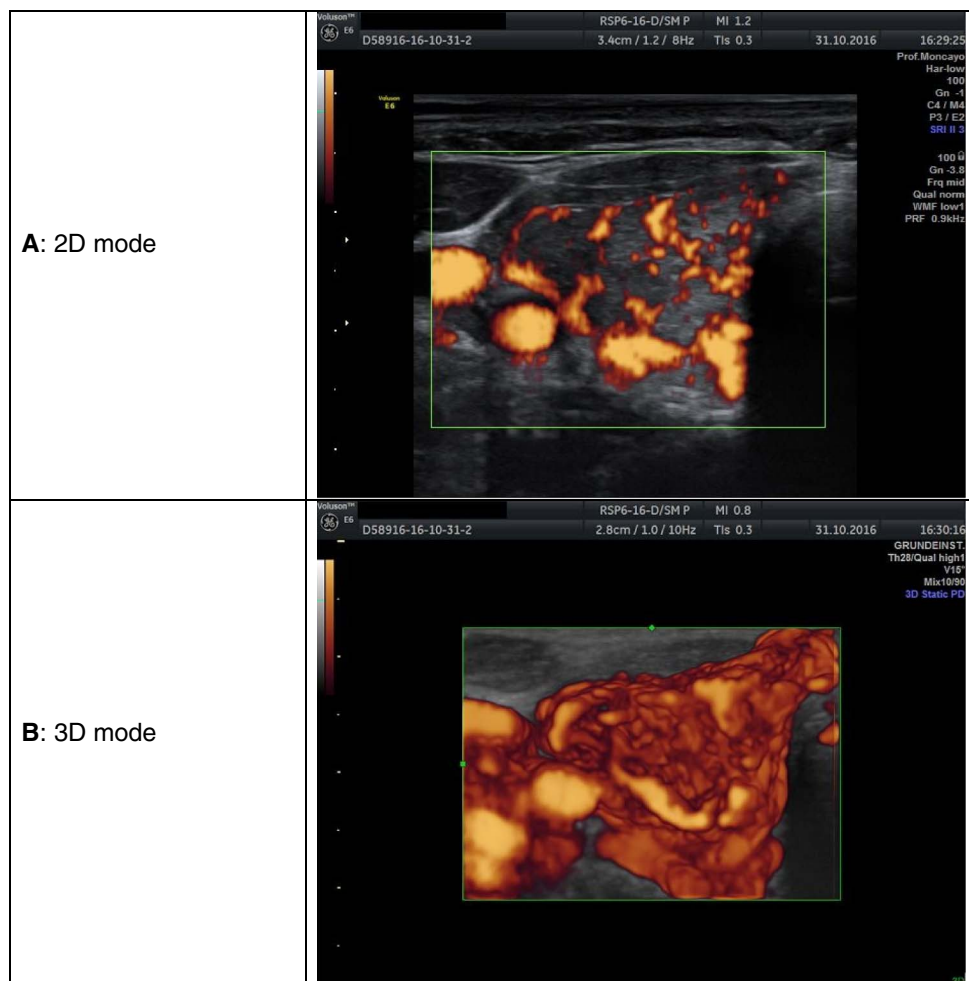

Fig. 1. Imaging of the thyroid in power Doppler mode in a case of newly diagnosed hyperthyroidism. The 2D image allows the examiner to recognize dispersed areas that correspond to vessels. The 3D image shows the complex continuous structure of vessels. This picture is associated with low CoQ10 values.

5. Integrating East and West: teachings from Chinese Medicine and evidence based medicine (EBM)

The inclusion, examination and treatment of the musculoskeletal system in our WOMED model of thyroid disease were influenced by teachings of Chinese Medicine relative on the extraordinary meridians [29–33]. The extraordinary meridians connect the feet and the head. Western medicine has no equivalent system. At an early stage of the development of our model we carried out magnetic resonance imaging (MRI) (Fig. 2) studies of specific acupuncture points which allowed us to identify the underlying muscle groups [34,35]. Besides the extra-ordinary meridians, our clinical, empirical work was centered on the acupuncture point Stomach 36 (ST36) or Zu San Li [36]. The region surrounding ST36 feels hardened on palpation and tension increases during rotation of the ankle. In Chinese Medicine this acupoint is directly connected to energy. Ellis, Wiseman and Boss recall that oral tradition in China said that stimulation of this point was thought to relieve fatigue sufficient to allow one to journey further [36]. In 2014 Wu presented data on ST36 showing that it contains an abundant expression of the transient receptor potential vanilloid receptor 1 or TRPV1 [37]. Since TRPV1 is a mechanosensor one can propose that our findings, which were gained through clinical examination, correspond to the function of this receptor, i.e. showing the condition of increased tension. Ahn has pointed out a mechanical link between the skin and muscle [38] thus complementing nicely the function of TRPV1. A second characteristic around ST36 is that of reduced skin sliding in this area. Skin sliding is a feature that depends on the connective tissue of the subcutis [39]. A hardening of the skin will neither allow pinching nor lifting [40]. This feature can be evaluated during acupuncture since the practitioner can feel the resistance or hardening at the ST36 point. Looking into the literature we found a report that described the presence of thyroid system components (Fig. 3) such as TSH and the TSH receptor in the skin [41]. Having such a repertoire of thyroid function related elements then thyroid-like active processes could be occurring via the skin. This idea has not been investigated. In our current practice we have empirically adapted a treatment using a skin care cream, i.e. Ultrabas or Ultrasicc or a mixture there off (Bayer©, Austria). The cream has to be applied to the whole surface of the lateral portion of the shank corresponding to ST36 downwards towards the ankle. Therapy success can be evaluated by simple manual examination which shows that the hardening has diminished.

How can these concepts fit into the RCT-driven cosmos of evidence based medicine? One proposal has been presented by Ana Fernandez [42]: "EBM needs to move forward and perceive health and healthcare as a complex interaction, i.e. an interconnected, non-linear phenomen-on that may be better analyzed using a variety of complexity science techniques". The use of manual medicine or acupuncture has not been included in existing guidelines for thyroid diseases. However, when treating the individual patient the clinical manual examination allows us to choose an adequate approach with manual therapy and acupunc-ture. Sizer et al. [43], when talking about orthopedic manual physical therapy point out the following: "… the clinician–patient team can make appropriate care decisions that may or may not match what the 'best evidence' may recommend" (page 117 in [43]). The authors concluded their article with the following statement: "Moreover, while a chosen alternative may not be fully supported by presently available evidence and could be considered an outlier, that outlier of today may be the basis for developing future evidence. Thus, choosing that alternative based on sound clinical reasoning places the clinicians in a position to navigate future clinical science discoveries" (page 118 in [43]). Mazzocchi has discussed the topic on how to be holistic, i.e. how to reach a concept of systems biology [44]. Even looking at practice guidelines, the inclusion of personal experience is not a disregarded issue [45]. Personal experience is the foundation of observational studies.

6. Can a mathematical model represent complexity seen in the daily thyroid practice?

The journal "Frontiers in Endocrinology" includes a Research Topic section dealing with regulatory aspects of thyroid function. The original statement about this section described its aim as: "a comprehensive overview on state-of-the-art methodology and recent results from the emerging new world of thyroidology, which tries to rationalize a scenario of previously unknown complexity." The first article of this section by Hoermann et al. presented a mathematical model that claimed to describe the homeostatic relationship between TSH and thyroid hormones [46]. This mathematical model of thyroid function was original developed by J.W. Dietrich [47] and has been published with slight variations in several Journals dedicated to Endocrinology [46,48–53]. Unfortunately the graphical depiction of the model suffers from a severe omission by leaving out any consideration of iodine metabolism which is the basic component of thyroid hormones (Fig. 1 in [47]). Another important omission is that of leaving out components of the deiodinase system such as selenium [54,55] and flavoproteins [56–58]. This same fundamental omission, however, can also be found in another model of thyroid function [59]. As a result, only the measurable hormone variables, i.e. TSH and thyroid hormones, have been used for a limited reductionist approach. Although Hoermann et al. emphasize the fact that: "a disturbingly high proportion of patients remains unsatisfied with the treatment they receive"(page 2 in [52]) the authors reached a conclusion that states: "Possible long-term consequences of the observed biochemical alterations such as the altered FT3–FT4 ratio are also presently unknown "(page 8 in [52]). This conclusion does not differ greatly from the general statement made by James E.A. McIntosh and Rosalind P. McIntosh in 1980 in their chapter on Concepts of Feedback when talking about mathematical models: "Therefore it may be difficult to identify and include in a model all relevant components and interactions, stimuli and responses, or even to know what stimuli are appropriate to the activation of a feedback system" [60].

7. How effective is thyroxine treatment? Also known as resolving the situation of residual symptoms in treated patients with thyroid disease

In spite of all laboratory work trying to define normalcy on the basis of a single TSH level, it often fails to tell that patients are free of complaints. Many publications refer to this situation of "residual symptoms" in apparently well treated hypothyroid patients. This situation is of relevance for each patient.

7.1. A short account of the situation or residual symptoms

In 2001 the results of the Basel Thyroid Study carried at the end of the 1990s were published [61]. The authors reported an improvement of clinical symptoms as measured by 2 scoring systems, i.e. Billewicz [62] and Zulewski [63]. In a later paper the same authors described the lack of association between TSH levels and the degree of clinical symptoms found in hypothyroidism [64]. The authors stated that TSH is a poor measure in the evaluation of the severity of thyroid failure and as such it should not be taken as the indicator for starting a therapy with thyroxine. Recently Winther et al. demonstrated that tiredness remained as the cardinal impairment in hypothyroidism in spite of therapy [65]. An Editorial in "Thyroid" written by Peter Andreas Kopp in 2014 [66], pointed out the important drawback found in the situation of residual complaints, i.e. patients remain symptomatic despite having normal thyroid hormone levels. Similar to the opinion of Kopp, Mary H. Samuels recently stated the following: "It is a common clinical observation that some otherwise healthy patients with hy-pothyroidism continue to complain of fatigue, poor mood, inability to concentrate, and vague cognitive difficulties (often described as "brain
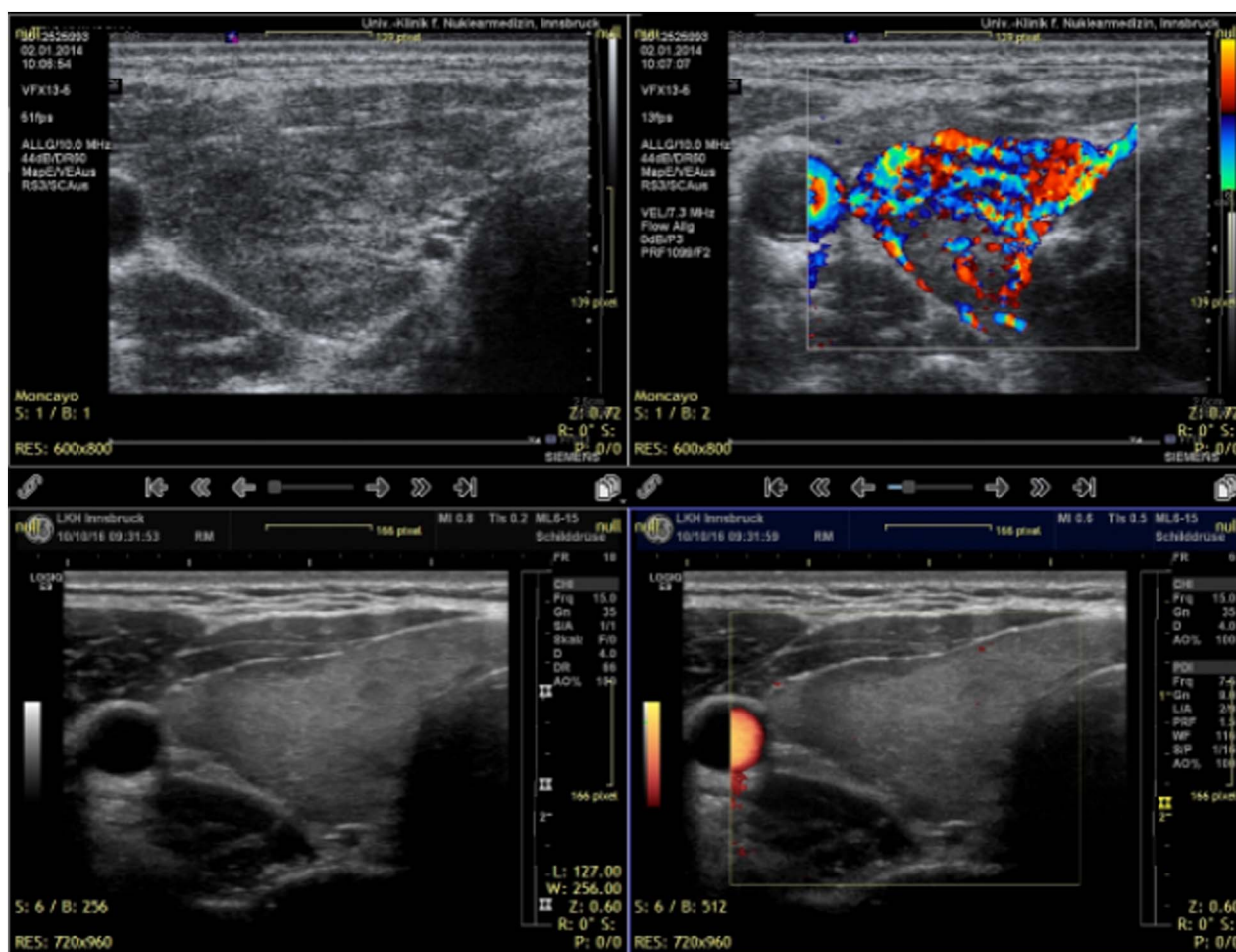
Fig. 3. Two years of follow up in a case of hyperthyroidism. The initial images are on the top row. They show markedly diminished echogenicity together with hyperperfusion. The lower row shows the current images with recovered echogenicity and normal perfusion. Two different machines were used in this evaluation, Siemens Antares (upper row) and GE Logiq E9 (lower row).

fog") despite normal TSH levels" [67]. Similar comments have been made by other authors in the past [68,69]. The condition of well-being has been also matter of investigation in relation to treatment with thyroid hormones. Walsh et al. [70] presented an evaluation of changing thyroxine dosage in the treatment of women with primary hypothyroidism. They found no significant treatment effects on their instruments aiming at measuring well-being and symptoms. They concluded that the target TSH range should not differ from the general laboratory range. Unfortunately none of the previous publications has provided an explanation for the condition.

A different therapeutic modality to be used in primary overt hypothyroidism called biopsychosocial approach, which was based on the use of a neuro-emotional-technique, was proposed in 2010 by Benjamin T. Brown [71]. They argued that this biopsychosocial model would be superior to the usual biomedical management of thyroid disease. In 2015 the study was finished and the final conclusion was that there was no clinical benefit using this approach [72]. Again a solution to resolve residual symptoms was not successful.

7.2. Our own experience

The initial motivation for our investigations was the complaint from many patients that they were unhappy with their treatment either for hypo- or for hyperthyroidism. Some patients who had had a total thyroidectomy still talked about the thyroid being responsible for their condition. The most common symptom we have observed was fatigue. The next most common ones were exhaustibility, muscle cramps,

muscle aches, irregular heartbeat, nervousness, perspiration, irritability, depressive mood, poor concentration, and poor memory, vertigo sensation and cephalea. This complex clinical picture could be misinterpreted as a psychosomatic disease. Dwelling deeper into this clinical situation we were able to identify a common denominator behind the "so-called" thyroid disease complex of symptoms, namely magnesium deficiency [15]. We have found that magnesium deficiency was related to psychological stressors, to physical stressors due to alterations in the musculoskeletal system, to muscular injuries, to infection, to the post-partum period [16] and physiologically to early pregnancy after IVF [73].

If we consider some of these situations to represent a stress condition it is important to point out that that anxiety and hypothalamic-pituitary-adrenal (HPA) axis dysregulation are the consequence of primary magnesium deficiency as has been shown in mice [74]. Some studies have shown a relation between psychosocial stress and lower levels of magnesium in humans [75,76]. Recently Harbeck and coworkers described that on biochemical terms TSH can be taken as an early and sensitive predictor of stress while at the same time there were no changes seen in cortisol, glucose or norepinephrine levels [77]. These data prompted us to reconsider the original stress model published by Hans Selye in 1936 where he described the effect of acute nocuous agents under experimental situations [78]. In a second letter in 1938 he postulated that adaptation of an organism depends upon a "special hitherto unrecognized type of energy" [79]. Looking back at his own research Selye spoke then of "adaptation energy" in 1950 [80]. This short account shows the connections of stress to energy, a

connection which we will address in the following sections.

7.3. The therapeutic approach

Our definition of low magnesium levels was based on the comparison with serum values found in control subjects who did not present any physical or psychological stressors. In a previous investigation we have shown how these stressors relate to low magnesium levels [15]. The blood levels of magnesium in these subjects had a mean level 0.95 ± 0.08 mmol/l. In cases of physical or psychological stress these levels are lower. Subjects with magnesium deficiency can be supplemented with pure magnesium citrate. The preparation we use contains 1.4 mmol of elemental magnesium per capsule. The initial dose is 1.4 mmol 3 to 4 times per day during 3 months. If this dose is not effective it can be increased to 6 capsules per day, i.e. 8.4 mmol of elemental magnesium. In pregnant women we use an initial dose of 6 times 1.4 mmol. Ideally blood controls should document an increase of magnesium levels to a level of at least 0.9 mmol/l.

In cases of CoQ10 deficiency, supplementation with 30 mg daily can be carried out [16]. If the selenium concentration in blood is < 80 μg/l, selenomethionin 200 μ/day, 3 times per week, is added to the supplementation. Follow up of supplementation can be supported by sonography with the power Doppler mode. Besides correcting deficiency conditions, the changes found in the musculoskeletal system require an individual manual and acupuncture therapy in order to recover body alignment.

Our emphasis on magnesium as being the vulnerable variable in the system is based on the following considerations. Stress situations are related to magnesium deficiency [74]; intra-cellular selenium is related to magnesium levels (Fig. 2 in [16]); selenium and CoQ10 levels are correlated [81] and CoQ10 levels are diminished in selenium deficiency [82]. We consider a magnesium level of 0.9 mmol/l as adequate to meet physiological needs [16]. The following ultrasound images will demonstrate the beneficial effect of our combined therapeutic approach for thyroid affections.

In situations where fibrosis of the thyroid is not found in the ultrasound examination, the changes in morphology and perfusion are reversible under this tailored treatment, i.e. the thyroid gland can regain a normal appearance [83]. Our experience shows that an age < 35 years is a biological turning point for achieving these results. This fact contradicts the dogmatic model of autoimmunity. We have replaced this belief with a model of an acquired deficiency of mitochondrial function affecting Complex V of the oxidative phosphorylation and being primarily induced by magnesium deficiency [16]. Using the outlined supplementation strategy, changes in thyroid morphology and perfusion will revert to normal.

The therapeutic approach outlined here (Fig. 4) eliminates the burden of unresolved complaints, and in special of fatigue, in the majority of cases. Although we have no confirmatory data, we hypothesize that the correction of these deficiency states allows a normal mitochondrial function and as a consequence, a normal supply of energy substrates. This postulate is our conceptual and practical answer to Selye's concept of an unknown adaptation energy [80].

Single cases that still present symptoms like anxiety and fear require sometimes special acupuncture techniques that help to resolve previous stressing situations [84]. The importance of psychological stress has to be considered and treated in all cases of thyroid disease.

Sequential controls of patients can show some relation between influencing situations and the course of thyroid function. Fig. 5 shows the biochemical data of a female patient with hyperthyroidism. The figure is divided into time points of the sequential follow-up. Anti-thyroid drugs were stopped at time point 2 and the patient continued to take only 4.2 mmol magnesium citrate daily. At time point 8, hyperthyroidism reappeared while at the same time magnesium levels fell. Between time points 7 and 8 had had a stressful situation at work and at the same time a viral infection. Anti-thyroid medication was started

again and the magnesium dose was doubled to 8.4 mmol/d. Thyroid function returned to normal within 2 weeks.

8. Minerals and elements at the metabolic crossroads between thyroid and mitochondria

In this section we will discuss individual elements that contribute to thyroid function from the standpoint of mitochondrial biochemistry (Fig. 6). We will consider iron, zinc, magnesium, selenium and also CoQ10. The complementary relationship between thyroid hormones and mitochondrial biogenesis especially within the frame of cardiac function has been described by others [85–88]. We will also mention some situations where the same elements have an influence on gonadal function and fertility.

8.1. Iron

The 2015 Global Burden of Disease Study revealed that iron deficiency is at place 4 among the top eight causes of chronic diseases affecting > 10% of the population [89]. Experimental data has shown that iron deficiency reduces the activity of thyroid peroxidase [90]. The kinetics of thyroid hormones [91] can also be impaired in iron deficiency. On the other hand iron supplementation can lead to reduction of goiter size [92]. Iron deficiency in fetal and neonatal periods can reduce the levels of thyroid hormone-responsive genes mRNA in the hippocampus and cerebral cortex of the neonatal rat [93]. Furthermore iron deficiency in pregnant rats can produce hypothyroxinemia [94].

Beard has studied the relation between iron deficiency and thermogenesis in 10 women [95]. Their experiments were able to show that thermogenesis upon cold exposure was impaired and that at the same time the levels of thyroid hormones were lower (Fig. 7). Iron supplementation corrected these alterations. In humans anemia can be related to intolerance to thyroxine therapy [96]. Positive effects of iron supplementation on the levels of thyroid hormones in two college female athletes have been described [97]. Iron deficiency has been seen to be associated with isolated hypothyroxinemia in women [98]. The impact of iron deficiency on thyroid function, i.e. high serum TSH and lower fT4 has been found to be quite frequent during early phases of pregnancy [99]. Finally iron deficiency has a predictive value in regard to a poor status of maternal thyroid function during pregnancy [100]. Iron deficiency can also affect cognitive function in young women [101]. It should be kept in mind that iron is connected to the development of the brain and influences processes such as learning and memory [102]. Iron deficiency can down regulate brain-derived neurotrophic factor (BDNF) expression in the hippocampus [103]. Correcting iron deficiency reactivates IGF signaling in the hippocampus [104].

The central role that iron has in thyroid economy can be explained by one good reason: thyroid peroxidase is a hemeprotein. Heme is produced in mitochondria and the path into these organelles requires a coordinated action between intestinal uptake or iron, iron transport and entry into the cytoplasm and into the mitochondria [105]. Besides iron other nutritional requirements for heme synthesis include: vitamin B6, riboflavin, biotin, copper and zinc. Starting from succinyl-CoA porphyrins are synthetized to be converted to heme [106]. Thyroid can also influence iron metabolism by modulating the interaction between the ferritin mRNA iron responsive element and iron regulatory proteins [107].

Besides heme, mitochondria also synthetize iron-sulfur proteins [108] which are related to iron sensing and intracellular iron delivery [109]. Hemes are integral components of the respiratory complexes II, III, and IV that perform multi-electron transport and catalysis [110]. One group of these iron-sulfur proteins is mammalian adrenodoxin or ferredoxin 1 (Fdx1) which is essential for steroid hormone synthesis. A second ferroxin, Fdx2, participates in the synthesis of heme A and of
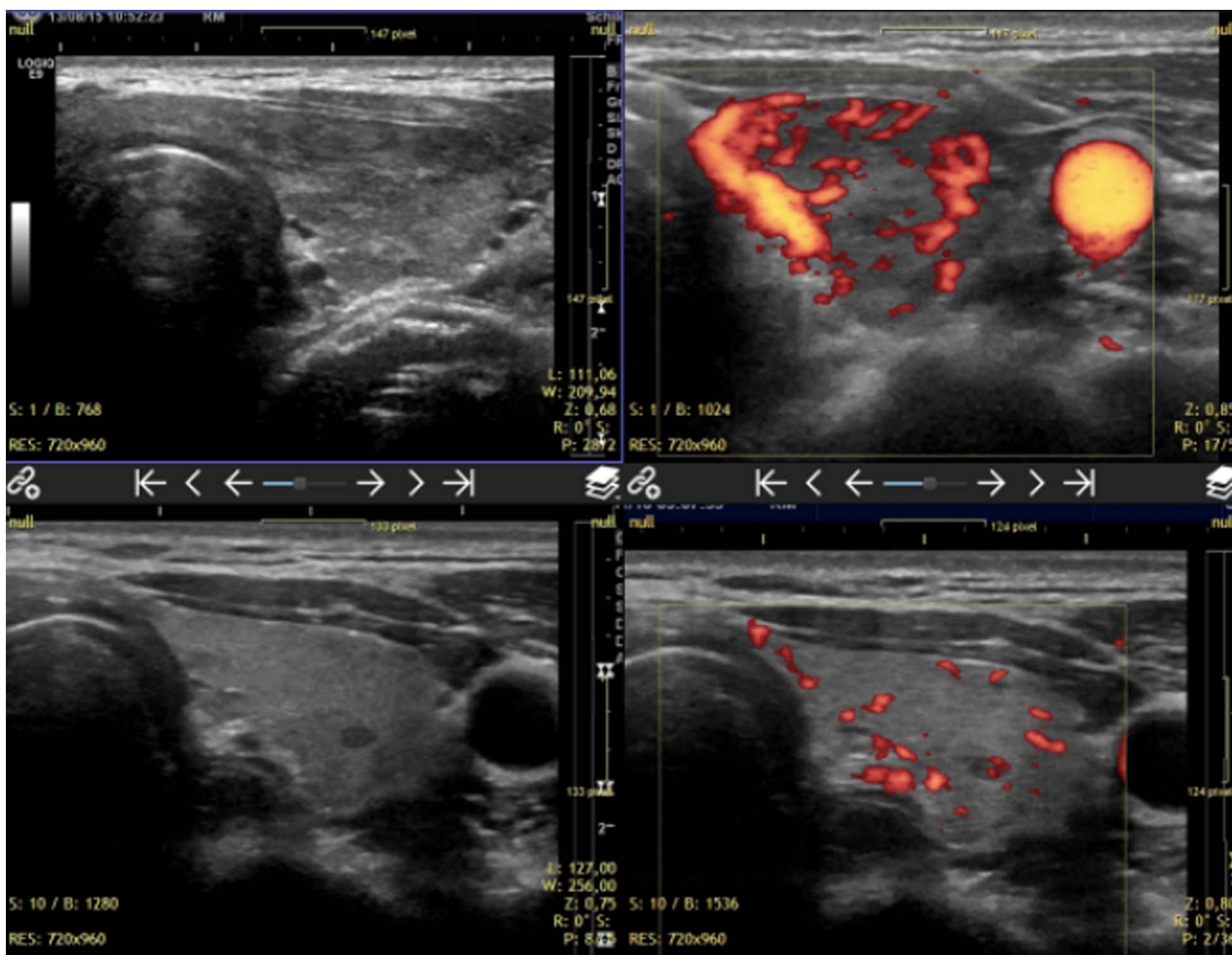
Fig. 4. Two years of follow up in a case of hyperthyroidism. Vascular structures are depicted using 2D power Doppler mode. The improvement of thyroid texture and perfusion can be seen by comparing the upper and the lower row of images. All images were done using a GE LOGIQ E9 ultrasound machine in power Doppler modus.
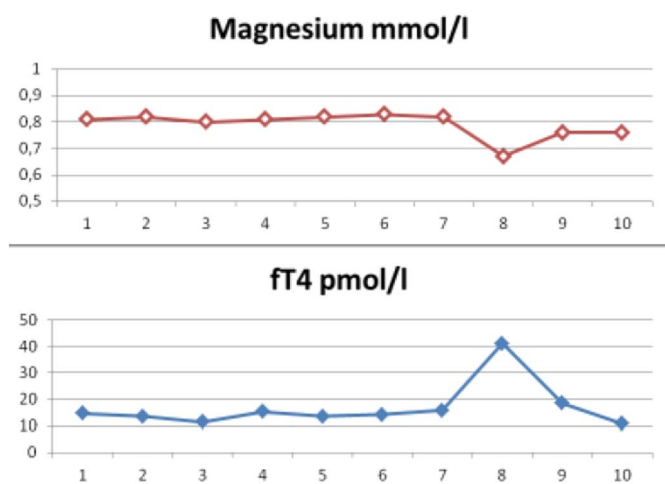

Fig. 5. Time relation between fT4 and magnesium levels observed during 10 follow-up time points. At time point 7 increased stress at work and an infection preceded a relapse of hyperthyroidism. At this time magnesium levels showed a concomitant drop from 0.82 to 0.67 mmol/l. Following supplementation with 8.4 mmol elemental magnesium fT4 normalized and magnesium rose to 0.76 mmol/l.

iron-sulfur proteins [111]. Cellular iron is also a regulator of mitochondrial biogenesis [112]. On the other hand the biogenesis of iron-sulfur clusters requires GTP, NAD and ATP [113].

In a direct tissue analysis study Melenovsky et al. [114] have shown that heart failure appears to be related to myocardial iron deficiency which in turn affects aconitase and citrate synthase [114]. Oxidative damage can also affect the aconitase Fe-S cluster [115]. The inactive form of aconitase has a 3Fe-4S cluster and one more iron atom is needed to produce the activated form leading to a 4Fe-4S cluster. This occurs via iron regulatory proteins [116,117]. More information on the homeodynamics of iron in relation to ROS stress and aconitase has been presented by Bresgen and Eckl [118]. These observations appear relevant to thyroid disease because in both organs H_2O_2 constitutes the source of oxidative challenge. This noxious situation requires regulation through glutathione peroxidase, a selenoprotein [119–121].

Looking beyond iron itself, Semba et al. found an association between low selenium levels with anemia in older women [122]. In addition, Christensen et al. [123] described the role of selenium in regulating the expression of genes for proteins related to iron metabolism in rat liver cells. Iron deficiency leads to decreased expression of the selenoprotein glutathione peroxidase [124] by which thyroid function can be compromised. Iron has an indirect effect on OXPHOS by increasing respiration and downregulating glucose utilization. The opposite occurs in iron depletion [117].

Localization of iron in ovarian cells has been documented in the intercellular space of enlarged cells [125]. Iron seems to be relevant in the process of steroidogenesis as it is part of frataxin [126] which is related to ferredoxins. Transferrin has been found in granulosa cells [127]. Using a proteomics approach, Wu et al. [128] have documented an increase in transferrin following controlled ovarian hyper-stimulation. Chavarro et al. [129] described a positive effect of iron consumption on fertility. Angelucci et al. have found an inflammation-like profile in human follicular fluid following assisted reproductive tech-

Fig. 6. Shows a simple example of B mode sonography of the thyroid during follow up. The initial diffuse hypoechogenic pattern disappeared after 3 years of specific supplementation.
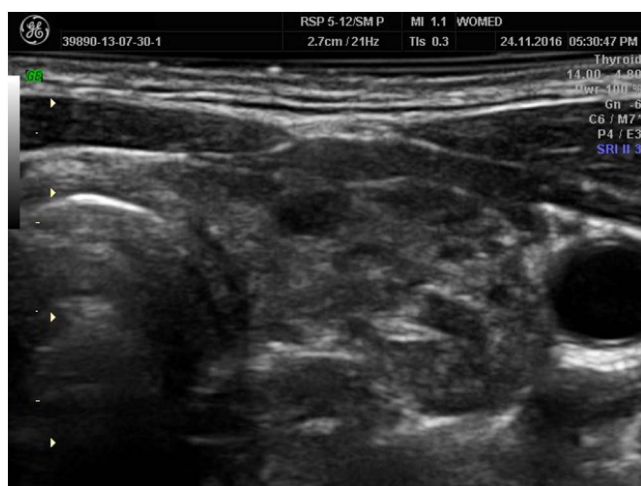

Fig. 7. Shows fibrotic changes of the thyroid. In this condition recovery of thyroid morphology is not achievable.

nology intervention which included a high concentration of transferrin [130]. A similar finding has been reported for studies done with follicular fluid of mares [131]. On the other hand, low levels of transferrin can be found in older women [132].

8.2. Zinc (Zn)

There are only few clinical accounts relating Zn to thyroid function. In 1979 Hartoma et al. described the association between low levels of zinc and decreased biochemical indices of metabolism including low levels of thyroid hormones [133]. Low basal metabolic rate and lower levels of thyroid hormones were also described by Wada and King [134]. An epidemiological study in Germany in 1997 showed no correlation between zinc levels and thyroid function [135]. Zn deficiency can down regulate the activity of the TRH degrading enzyme in the hypothalamus and pituitary [136]. This results in increased levels of TSH and PRL. In cases of hypothyroidism and severe alopecia zinc levels can be found to be reduced [137]. In patients with Down syndrome, supplementing with Zn sulfate can improve thyroid function [138]. Under experimental conditions a combined state of deficiency of iodine, selenium and Zn can alter significantly the morphology of the thyroid gland [139].

Low levels of Zn have been described as being related to uncoupling of mitochondrial function acting at the level of cytochrome *b* and c [140] interfering also with ubiquinone [141]. Further interactions of Zn in the body come from its role in signal transduction arising from mobile reactive Zn. Zinc regulation is related to Zn-finger proteins, metallothioneins, Zn importers and Zn transporters [142,143]. Zinc can influence cardiac function, and other organs such as secretory glands, i.e. pancreas, prostate, and mammary glands [144].

8.3. Magnesium

Magnesium plays a central role in energy balance as well as in a process described as cellular timekeeping [145]. The daily energetic processes of the organism are related to the circadian control of NAD (+) bioavailability [146]. In addition to NAD, intracellular magnesium regulation appears to underlie a similar mechanism [147].

In our original publication of the WOMED model of thyroid disease we have already discussed the relation of magnesium to changes in perfusion of the thyroid [16]. We also reviewed the significance of magnesium in all processes that require energy which is delivered by magnesium-ATP. Magnesium-ATP is produced in Complex V of the oxidative phosphorylation (OXPHOS) chain of molecules [148,149]. A central role of magnesium in thyroid economy can be found in relation to iodine uptake [150]. This essential event, however, is generally ignored in publications that describe the metabolism of iodine [151]. Experimental data have shown that high doses of magnesium increase the activity of the thyroid [152]. Magnesium deficiency can influence bioavailability and tissue distribution of selenium which then appears diminished [153]. This description is similar to our clinical observations [16].

Magnesium deficiency during pregnancy affects the size and function of the placenta [154]. Stanton and Lowenstein described the relation between pregnancy, menopause and magnesium levels [155]. Magnesium levels are lower in pregnant women as well as in women taking oral contraceptives as compared to controls; in the menopause magnesium levels were found to be higher. Magnesium loss due to stress [156] could contribute to magnesium deficiency during pregnancy. We have described this mechanism as part of the complex known as pre-natal maternal stress [157].

There is a series of negative effects on fertility and pregnancy that can be assigned to magnesium deficiency or to alteration of the regulating channel. Similar to thyroid economy, steroid hormone synthesis is also an active process that requires energy [158]. Usually such biochemical steps are generally taken for granted, and the relation to energy dependency is forgotten. Magnesium and its cell transport mechanisms, i.e. the transient receptor potential cation channel subfamily M member 7 (TRPM7) [159,160], have known important relations to reproduction processes. Initiation of embryo development is influenced by TRPM7 channels [161–164]. On the other hand magnesium deficiency has deleterious effects on fetal outcome [165]. TRPM is functionally expressed in human endometrial cells during the luteal phase [166]. Looking at magnesium supplementation per se one finds a positive effect of magnesium on pregnancy outcome [167].

A graphical demonstration of the magnesium deficiency syndrome is given in Fig. 8. Magnesium deficiency contributes significantly to the clinical picture found in patients with thyroid disease. This association was not considered by Mildred Seelig when she first described the
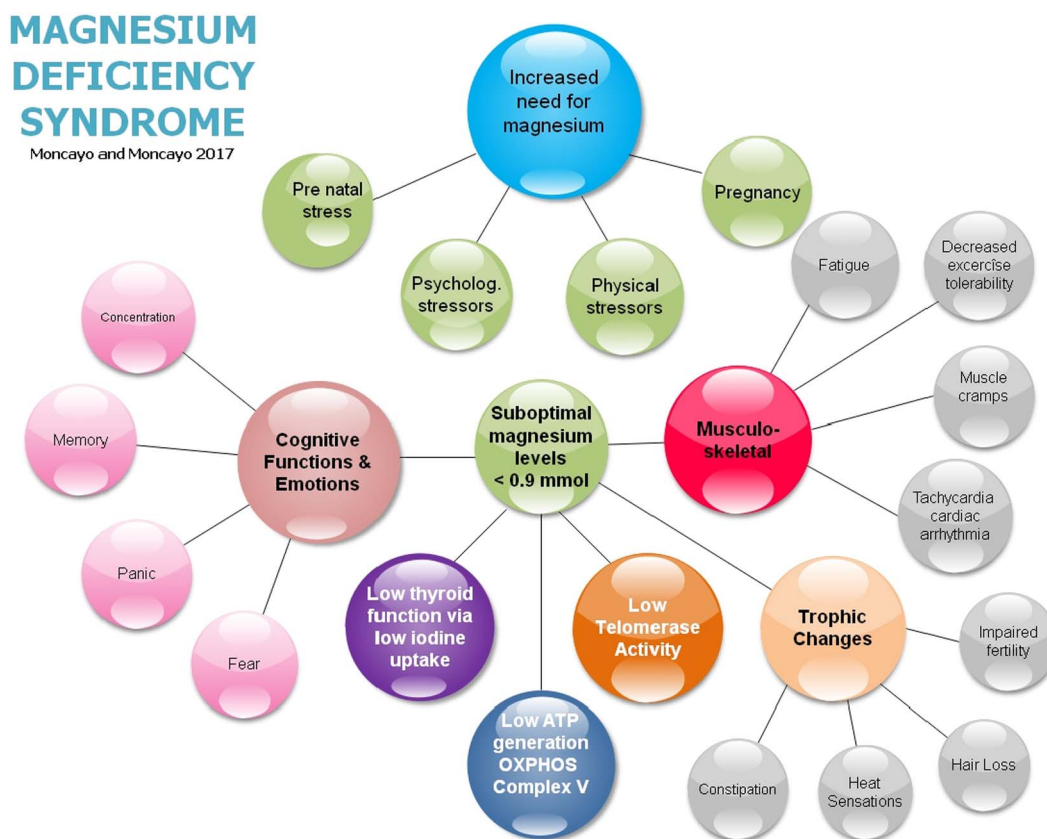
Fig. 8. The magnesium deficiency syndrome 2017 by Moncayo and Moncayo.

syndrome in 1964 [168].

8.4. Riboflavin and flavoproteins

An element that receives little attention in the context of thyroid hormone effects is vitamin B12, i.e. riboflavin. It plays a role in the process of thyroid hormone deiodination in the form of flavoproteins [56,57,169]. Flavoproteins in the form of the nicotinamide adenine dinucleotide phosphate (NADPH) are involved in the function of the membrane–bound thyroid oxidase located at the apical pole of thyroid cells which are required for the generation of H_2O_2 [170–172]. H_2O_2 is indispensable for thyroid hormone synthesis.

In steroid hormone synthesis, placenta mitochondria need the presence of NADH in order to have a functioning cholesterol side-chain cleavage enzyme system [173].

8.5. Selenium and coenzyme Q10 (CoQ10)

We consider that the main place for selenium in body functions is in its protective property in the form of selenoproteins [174]. The main groups involved are glutathione peroxidase and the deiodinases [175]. Thioredoxin reductase plays an important role in the response to iodine excess [176]. As mentioned before thyroid damage can occur in situations of iodine excess and selenium deficiency [177]. Under experimental conditions a combined iodine and selenium deficiency can alter the tissue distribution pattern of trace elements [178]. Sustained physical and psychological stress in men has been shown to induce lower levels of zinc, iron, and selenium [179]. Both the structure, i.e. loss of cristae, and the electron transport function of mitochondria can be altered in selenium deficiency [180]. These actions on mitochondrial biogenesis are complemented by thyroid hormones [181]. Besides the known action of deiodinases as seleno-proteins [182], a new interesting observation has been contributed by

Leoni et al. [183] who showed a positive influence of selenium on the expression of TSH-induced sodium-iodide symporter (NIS) activity. Finally it has to be stressed that selenoprotein synthesis is also an active process which requires ATP (e.g. Fig. 1 in [184]). In our model of the endocrine we associate energy supply via ATP with magnesium.

Recently data has appeared as to the negative disruptor effect on mitochondrial function which can occur through high fructose diet. Rats subjected to this diet presented high levels of ROS, reduced glutathione content, and reduced aconitase activity. The administration of glycyrrhizin can attenuate these alterations [185].

In our own studies we have seen the association of diminished concentrations of CoQ10 with hyperperfusion of the thyroid [16]. Another important association is that of low levels of CoQ10 following amiodarone administration [186]. Extensive information on the CoQ10 can be found in the publication by Wang and Hekimi [187]. Thyroid disease is not yet included.

CoQ10 is a component of the mitochondria and is considered as one of the small connecting molecules together with cytochrome *c* [188]. There is an interaction between CoQ10 and the 3Fe-4S cluster for effective electron transfer in complex II [189]. Mitofusins appear to be related to CoQ10 synthesis since knock-outs Mfn2 models results in low concentrations [190]. Mfn2 is important for the mitochondrial-endo-plasmic reticulum tethering [191,192].

CoQ10 restores oocyte mitochondrial function and fertility during reproductive aging [193]. The obesity related mitochondrial experimental changes in mouse oocytes can be prevented and rescued with CoQ10. Some of the underlying changes were lower levels of ATP and citrate [194].

In pregnant Holstein heifers, selenium supplementation can increase progesterone levels [195]. A similar effect can be seen during the menstrual cycle [196]. Selenium supplementation during pregnancy can have positive effects on glucose metabolism [197].

Vadhanavikit and Ganther [82,198] have described an interrelation
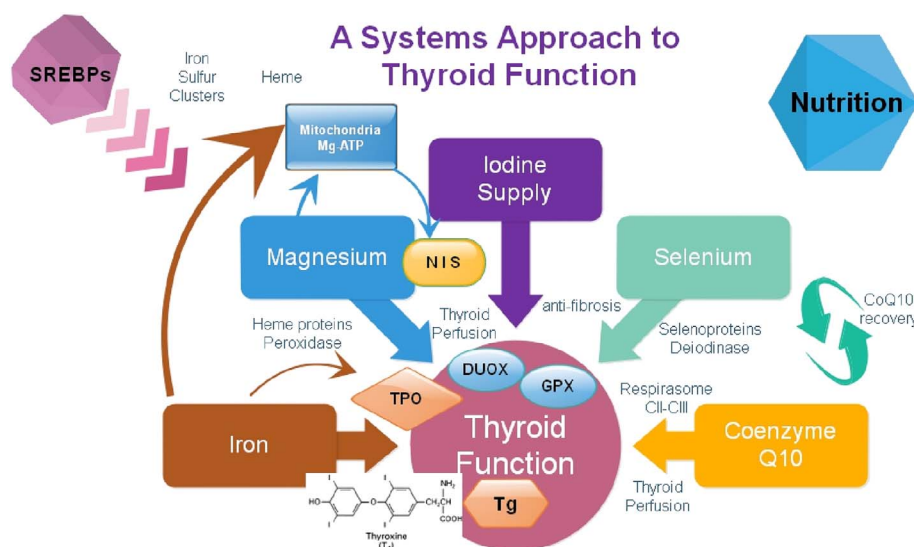
Fig. 9. Basic thyroid diagnostics.

Fig. 10. Integrated systems approach to thyroid function.Abbreviations used: SREBPs: sterol regulatory element binding proteins; Mg-ATP: magnesium ATP, NIS: natrium iodide symporter, TPO: thyroid peroxidase, DUOX: dual oxidases, GPX: glutathione peroxidases, Tg: thyroglobulin. CII–CIII: complex II and III of the mitochondrial respiratory chain.

between selenium and CoQ10 in the sense that CoQ10 levels can decrease in situations of selenium deficiency. In humans, Alehagen et al. [199] have shown that combined supplementation with selenium and CoQ10 effectively reduces cardiovascular mortality in situations of selenium deficiency.

9. A new player: sterol regulatory element binding proteins - SREBPs

In 1993 a nuclear protein that binds to the sterol regulatory element of LDL receptor promoter was described [200,201]. These proteins now called SERBPs have been found to be involved in more functions than just lipid and cholesterol metabolism [202–205] as they can regulate the ATP citrate-lyase gene [206]. More interesting is the fact that they can regulate some of the elements involved in thyroid function such as the NIS gene in the thyroid [207] as well as mammary epithelial cells [208], the thyroid peroxidase [209], and the thyroglobulin gene [210]. Besides these relations to thyroid function there are also interaction between the SERBPs and steroidogenesis. Following the activation of cAMP and protein kinase A via LH stimulation, there is the addition interaction of the cholesterol-sensing SCAP-SREBP2 path which will

coordinate steroidogenesis [211]. The connection between thyroid economy and lipids is given by the regulatory action of thyroid hormone on the SREBP-2 gene [212]. Under experimental conditions high dose selenium can up-regulate the activity of SERBP1 [213]. These data bring new light into the tuning of the endocrine.

10. Conclusions

We describe a systems approach model of thyroid disease which is based on clinical observations and satisfactory clinical experience resulting in benefit for the patients. We must caution that some of the concepts brought here are an extrapolation of basic research, i.e. there is yet no clinical confirmation. Still these ideas should motivate other researchers to conceive further research activities and to improve prevailing simplistic models of thyroid function (Fig. 1 in [214]).

Advancements in biochemistry now show a complex interaction of players related to thyroid function as well as to steroid hormone synthesis. These actors can be found in mitochondrial structures. A central element is the synthesis of heme proteins which will participate both in thyroid as well as in steroid hormone synthesis. While a solitary determination of TSH in blood can indeed present a summary of the

physiological condition of the thyroid axis, the single elements described above have to be present in the body in sufficient concentration. Adjusting TSH levels via thyroxine medication does not cover these complex intrinsic needs. For this reason it is necessary to carry out determinations of magnesium and iron in blood and not just thyroid parameters. In some patients selenium and CoQ10 have also to be determined. Riboflavin status should be checked when alterations of deiodination are suspected. When any deficient state is found we recommend supplementing each element since they all interact together in order to maintain the endocrine (Table 1). The relationships described in this paper are summarized graphically in Fig. 9. Citations are included in the text and in the reference list.

The details of the systems approach to thyroid function are shown graphically in Fig. 10.

Transparency Document

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