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REVIEW

Clinical significance of type 2 iodothyronine deiodinase polymorphism

Fabio Maino, Silvia Cantara, Raffaella Forleo, Tania Pilli and Maria Grazia Castagna

Department of Medical, Surgical and Neurological Sciences, University of Siena, Siena, Italy

ABSTRACT

Introduction: Biological activity of thyroid hormones (TH) is regulated by enzymes known as deiodinases. The most important is represented by the type 2 deiodinase (D2), which is the main T4-activating enzyme, ubiquitous in human tissues and therefore essential in many metabolic processes. A single nucleotide polymorphism (SPN) of D2, known as Thr92Ala (rs225014), has been reported in the general population while other polymorphisms are less frequently described.

Areas covered: Several authors investigated the potential metabolic effect of these polymorphisms in the general population and in specific groups of patients. Thr92Ala polymorphism was mainly studied in patients with autoimmune or surgical hypothyroidism and in patients with physical/psychological disorders that could be related to an overt hypothyroidism. Susceptibility to develop more severe type 2 diabetes or insulin resistance has also been evaluated. Commentary: There is an increasing evidence that the presence of D2 polymorphisms may play a pivotal role in a better definition and customized therapeutic approach of patients with hypothyroidism and/or type 2 diabetes, suggesting that these patients should be screened for D2 polymorphisms. Nevertheless, further research should be performed in order to clarify the association between D2 polymorphisms, metabolic alterations and clinical conditions of the carrier patients.

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1. Physiological role of deiodinases

Thyroid hormones (TH) play a crucial role in the physiological development and in the majority of metabolic processes [1]. Thyroxine (T4), which is secreted from the thyroid gland, should be converted to 3,5,3′-triiodothyronine (T3) in order to exert its biological activity. This activation is regulated by enzymes known as deiodinases [Deiodinase 1 (D1) and Deiodinase 2 (D2)], which includes also an inactivating enzyme, namely the Deiodinase 3 (D3), that inactivates both T4 and T3 [2]. TH require transporter proteins to enter the intracellular compartment and play their role [3]. There are different types of TH transporter proteins: the most important is the monocarboxylate family, which includes the monocarboxylate 8 (MCT8) and the monocarboxylate 10 (MCT10) transporters. Additional transmembrane transporters, involved in TH uptake and efflux in several cell types, are the organic anion transporting polypeptides (e.g. OATP1C1, OATP1A2, OPTP1A4) and the large neutral amino acid transporters (LAT1 and LAT2) [4]. Once inside the cell, the intracellular T3 binds to two different nuclear TH receptors, TRα and TRβ, which mediate the biological effects of TH via transcriptional control of multiple sets of T3 responsive genes [1]. Deiodinases play a pivotal role in many aspects of human physiology, such as the regulation of plasma T3 concentration [2], the feedback on thyroid axis which regulates TSH and TRH secretion [5–7] and the clearance of sulfated iodothyronines [8]. D1 is located in the plasma membrane and has a slow turnover rate of about 8 h [9]. The D1 gene (DIO1) is highly sensitive to T3, with about 175-fold induction during the transition from hypothyroid to hyperthyroid state, functioning as an indicator of systemic thyroid status [10]. D1 plays a scavenger role mainly by deiodinating sulfated forms of iodothyronines during their excretion in the bile and urine [8]. D2 could be considered as the main T4-activating enzyme due to its high affinity for T4. T4 is converted to T3 by D2 at the intracellular level. D2 is a classical type-1 membrane protein residing on the endoplasmic reticulum (ER) membrane, with a relatively short half-life (~ 45 min) [9] due to ubiquitination and proteasome uptake [11]. D3 is highly expressed in the placenta where it plays a crucial role by protecting the developing embryo from excessive TH levels and contributes to a decreased T4 to T3 conversion, in a illness condition [12,13].

2. Type 2 deiodinase polymorphisms in the general population

In healthy subjects, about 30% of serum T3 is derived from thyroid secretion and 70% from the extrathyroidal conversion of T4 to T3 catalyzed by D1 and D2 [2]. Human D2 is encoded by the DIO2 gene and accounts for about 70% of circulating serum T3 [2]. A single nucleotide polymorphism (SPN) known as Thr92Ala (rs225014) has been reported in the general population and the prevalence of the DIO2 Ala/Ala homozygous variant in European population ranges between 12.9% and 14.9% [14] . This polymorphism, involved in TH conversion and metabolism, may have impact on TH levels and therefore

CONTACT Maria Grazia Castagna m.g.castagna@ao-siena.toscana.it Department of Medical, Surgical and Neurological Sciences, University of Siena, Policlinico Santa Maria alle Scotte, Viale Bracci 16 53100 Siena, Italy

important effects on several clinical aspects, such as quality of life, cognition, atherosclerosis, bone mineral density, cholesterol metabolism, and heart rate [15–20]. Peeters et al. [21], in a study population of 155 Caucasian healthy subjects, did not find by sequencing any variation of the region around the selenocysteine insertion sequence (SECIS) element of D2 gene. However, the screening of the human expressed sequence tag database (dbEST) showed a very frequent A/G polymorphism at nucleotide 674 of D2 sequence, predicting a change in amino acid 92 of the protein (D2 G/A Thr92Ala). No significant effect of the D2-Thr92Ala polymorphism was observed on plasma TSH levels, iodothyronine levels or their ratios in this healthy population [21]. However, they were not able to exclude that intracellular TH levels may be affected by this polymorphism. Wouters et al. [22], in a large study population of healthy subjects, found that the Ala/Ala genotype of the D2-Thr92Ala polymorphism was present in 10.7% of the general population. Thr92Ala polymorphism was not associated with alterations in TSH, fT4, fT3, fT3/fT4 ratio, presence of metabolic syndrome or other comorbidities, use of medication, HRQoL, and cognitive functioning. In another study, Peeters et al. [23] identified a different polymorphism in the 5′-UTR of the D2 gene (D2-ORFa-Gly3Asp) and investigated the association of D2-ORFa-Gly3Asp (SNP rs12885300) with serum iodothyronine levels in healthy blood donors and elderly men. These authors found that this new polymorphism was associated with iodothyronine levels in blood donors but not in elderly men and hypothesized that this result might be explained by the reduction of the skeletal muscle during aging resulting in a corresponding decrease in the contribution to the D2-mediated T3 production [23].

3. Type 2 deiodinase polymorphisms and thyroid hormone levels

Several clinical studies reported that D2 is critical in controlling TH signaling [24]. In fact, most of the circulating T3 (about 70%) derives from peripheral deiodination of T4 by D2 [2]. Considering that a 30% of T3 is physiologically produced by the thyroid, this contribution is obviously missing in the athyreotic patients and during LT4 replacement therapy, both the serum and intracellular T3 levels rely exclusively on the peripheral conversion of T4 to T3 mediated by the D2 [2].

Conflicting results derived from several studies suggest that not all patients treated with LT4 have the same ability to convert T4 to T3 in the peripheral tissues [25–27]. Recent studies on D2 polymorphisms have tried to address the heterogeneous capability to convert T4 to T3 in subjects treated with LT4 [28–30]. Torlontano et al. [28] showed that in 191 patients with differentiated thyroid cancer (DTC) submitted to total thyroidectomy and radioiodine therapy (131-I), a higher doses of LT4 was needed to reach target values of TSH in the presence of Thr92Ala polymorphism of D2. Specifically, the homozygous Ala/Ala subjects needed LT4 levels of about 20% higher than non-carriers of this polymorphism. However, these results were not confirmed by Heemstra et al. [29] in a cross-sectional study, in which 154 patients with DTC and 141 patients with autoimmune thyroiditis were studied. No association was observed between plasma levels of TH and LT4 therapy in the presence of the D2-Thr92Ala polymorphism [29]. These data were also supported by Al-azzam et al. [30] who did not observe any correlation between the four DIO2 polymorphisms studied (rs225011, rs7140952, rs225012, rs 2,839,858) and the LT4 doses or TSH, FT3 and FT4 levels in patients affected by primary hypothyroidism.

A recent study correlated the D2-Thr92Ala polymorphism with D2 activity and serum FT3 levels [31]. In details, Castagna et al. [31] measured serum FT3 and FT4 prior to surgery and after thyroidectomy in patients treated with LT4. Inclusion criterion was the presence of similar TSH levels before and after surgery in each patient. The mean post-surgical FT3 values were significantly lower in patients carrying the mutated allele whereas no difference between pre and post-surgical levels was observed in wild-type patients. Moreover, these authors reported that the D2-Ala mutant was less efficient than D2 wild type in converting T4 to T3 in muscle and pituitary cells *in vitro* [31].

Hoftijzer et al. [32] demonstrated that LT4 replacement therapy was associated to an altered set point of the hypothalamus-pituitary-thyroid axis in thyroidectomized DTC patients homozygous for D2-ORFa-Gly3Asp polymorphism. Their data suggest that the negative feedback of T4 on TSH secretion is weaker in patients homozygous for the D2-ORFa-Gly3Asp than in wild-type and heterozygous subjects. This hypothesis was suppported by higher TSH levels in combination with similar FT4 values in homozygous patients compared to controls [32].

4. Type 2 deiodinase polymorphisms and psychiatric/psychological status in hypothyroid patients

The D2-Thr92Ala is also involved in some psychiatric/psychological conditions, such as bipolar disorder and mental retardation [33,34]. On the contrary, it has been shown that a normal expression is indirectly related to the risk of depression [35]. These data indicate that the regulation of T4 to T3 conversion plays an important role in many psychological processes. Several studies tried to investigate this aspect correlating the well-being in patients on monotherapy with LT4 versus combined therapy with T3+ T4. Panicker et al. [36] evaluated 552 subjects in monotherapy with LT4 or in combined therapy (T3-T4) assessing the level of psychological well-being by a questionnaire (General Health Questionnaire – GHQ). They showed that the D2-Thr92Ala polymorphism, present in 16% of the study population, was associated with a worse GHQ score when subjects were treated with LT4 alone. Furthermore, improvement of the GHQ score was observed when the same subjects were treated with combined therapy. In a recent study, Carlè et al. [37] investigated three polymorphisms of the D2 gene: rs225014 (Thr92Ala), rs22501, and rs12885300 (ORFa-Gly3Asp), which may affect the intracerebral T4 conversion to T3. They also studied the role of the MCT10 rs17606253 polymorphism, which may affect the transport of TH into the brain. They found that the combination of polymorphisms in MCT10 (rs17606253) and DIO2 (rs225014) positively affect the

preference for LT3+ LT4 replacement therapy in hypothyroid patient.

On the other hand, several studies did not find any association between D2 polymorphism and psychological processes in hypothyroid patients [22,38,39].

Wouters et al. [22] evaluated the health-related quality of life (HRQoL) using the RAND-36 questionnaire, a generic questionnaire on well being. Women using LT4 experienced a significant reduction in HRQoL in several RAND-36 domains. However, no differences in any of the RAND-36 domain scores were observed between the Thr/Thr and the Ala/Ala carriers in all three groups evaluated (the general population, the LT4 users, and their matched controls). These results confirm an earlier report by Appelhof et al. [38], which demonstrated that patients homozygous for the Thr92Ala polymorphism obtained the worst scores on the majority of the well-being questionnaires, but the difference between genotypes was significant only for one of the 21 subscales tested (Profile of Mood States anger subscale). About neurocognition, patients homozygous for Thr92Ala showed the worst scores (significant only for one of the 21 subtests) without differences among the ORFa-Gly3Asp genotypes groups. Proportion of patients with preference for combined T3+ T4 treatment was not significantly associated with Thr92Ala or ORFa-Gly3Asp genotypes [38]. Finally, Medici M et al. [39] in a recent large retrospective population-based cohort study did not find an association between Thr92Ala and outcomes of T4 therapy, such as quality-of-life and cognitive functions.

5. Type 2 deiodinase polymorphisms and type 2 diabetes mellitus (T2DM)

D2-Thr92Ala has also been associated with other metabolic alterations, such as insulin resistance (IR), elevated body mass index and T2DM [40–45]. Dora et al. in their case-control study found that the frequency of the Ala allele in homozygosis was significantly higher in T2DM than in control subjects (16.4 vs. 12.0%) with a OR of 1.41 (95% CI 1.03–1.94) for Ala/Ala genotype in T2DM2 patients after adjusting for sex and age [42]. However, the relationship between the Thr92Ala polymorphism and the T2DM patients is not clear yet. Mentuccia et al. [41] using the hyperinsulinemic-euglycemic clamp in not diabetic patients reported that the D2-Thr92Ala variant is strongly associated with IR. Canani et al. [40] found that the Thr92Ala polymorphism is associated with greater IR in T2DM patients and with lower D2 activity in tissue samples. Moreover, a recent meta-analysis reported that subjects who are homozygous for Thr92Ala had 4.8% higher HbA1C levels, suggesting that Thr92Ala homozygosity is associated with worse glycemic control in T2DM patients [46]. These findings suggest that the D2-generated T3 in skeletal muscle plays a role in IR. Specifically, an inactivating mutation in DIO2 could lead to decreased intracellular availability of T3 and consequently to decreased transcription of GLUT4 in insulin-sensitive tissues, such as skeletal muscle and adipose tissue, contributing to IR.

Estivalet et al. [47] investigated the effect of the D2-Thr 92Ala (rs225014) and the peroxisome proliferator-activated receptor (PPAR) γ2 Pro12Ala (rs1801282) polymorphisms on IR in patients with T2DM. They found that patients carrying D2 Ala/Ala genotype had a higher fasting plasma insulin and HOMA-IR index as compared to patients carrying Thr/Ala or Thr/Thr genotypes. A significant synergistic effect was observed between D2-Thr92Ala and PPARγ2 Pro12Ala polymorphisms on HOMA-IR index. Carriers of both D2 Ala/Ala genotype and PPARγ2 Ala12 allele showed the highest HOMA-IR values. Leiria et al. [48] found a different polymorphism of D2 related to IR. Homozygosis for the allele T of the rs225017 (A/T) polymorphism was associated with IR in patients with T2DM, whereas patients carrying a combination of the T/T genotype of the rs225017 polymorphism and the Ala/Ala genotype of the Thr92Ala polymorphism showed an increased HOMA-IR index when compared with patients carrying other genotype combinations.

On the contrary, other studies did not find any association between D2 polymorphism IR and/or T2DM [14,44,45]. Mentuccia et al. [44] found no association among the D2-Thr 92Ala variant and T2DM, impaired glucose tolerance or BMI, and, not consistent with previous findings, the D2-Thr92Ala variant tended to be associated with increased rather than decreased insulin sensitivity in the Amish population. Similarly, in the Framingham Study [45] no association of the DIO2 polymorphism and T2DM risk was reported.

6. Type 2 deiodinase polymorphisms and other clinical implications

A wider spectrum of diseases and conditions have also been associated with the D2-Thr92Ala polymorphism, such as psychiatric alterations [49,50], hypertension [51], osteoarthritis [52,53], myocardial remodeling [54], accelerated bone turnover [55], and response to lung injury [56,57], indicating that the regulation of T4 to T3 conversion plays an important role in many physiological processes.

7. Expert commentary

Despite evidences that the D2 polymorphisms may play a pivotal role in a better definition and customized therapeutic approach of patients with hypothyroidism, there are no sufficient data to support the use of combined therapy (T3 plus T4) yet. Limited data suggest that psychological well being and preference for L-T4 + L-T3 combination therapy may be influenced by polymorphisms in TH pathway genes, specifically in TH transporters and deiodinases. As matter of fact, the European Thyroid Association guidelines suggest that LT4 + LT3 combination therapy should be considered only as an experimental treatment modality in compliant LT4-treated hypothyroid patients who have persistent complaints despite serum TSH values within the reference range.

8. Five-year view

In view of the inconclusive results, futures studies should be addressed to correlate the presence of D2 polymorphisms with TH levels and the physical/psychological aspects of the hypothyroid patients, in order to define which therapy (T4 alone or

combined T3+ T4) is the best option in the treatment of hypothyroidism in patients carrying the D2-Thr92Ala polymorphism.

Key issues

- D2-Thr92Ala polymorphism has been found in the general population and the prevalence of the DIO2 Ala/Ala homozygous variant ranges between 12.9% and 14.9%.
- D2-Thr92Ala polymorphism in hypothyroid patients can be related to lower levels of intracellular T3 and consequently to a peripheral hypothyroidism.
- D2-Thr92Ala polymorphism may be related to a lower quality of life and well-being status.
- D2-Thr92Ala polymorphism has been related to more severe type 2 diabetes.

Future research should be addressed to detect new strong correlation between polymorphism, metabolic alteration and clinical condition of hypothyroid patients.

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