



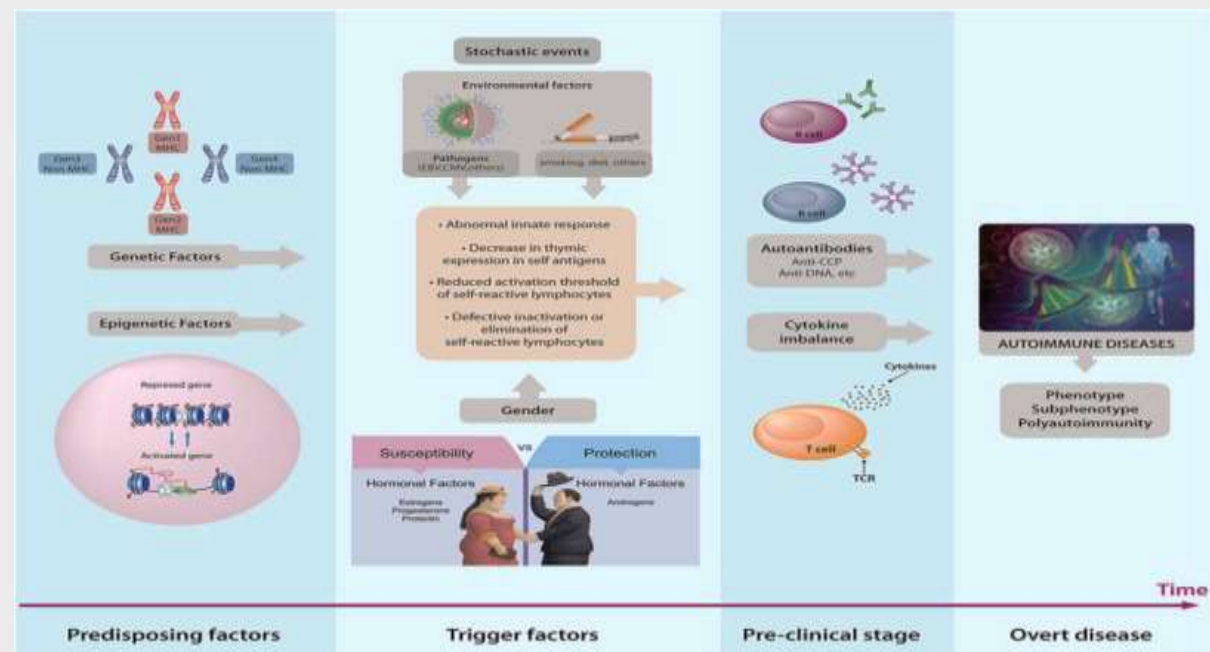
Le patologie tiroidee autoimmuni (AITD)

► La prevalenza delle AITD, tra cui la tiroidite di Hashimoto, la malattia di Graves-Basedow e la tiroidite post-partum, è stimata essere più alta del 5-10 % nella popolazione generale (l'alterazione della funzione tiroidea varia tra il 7-9% nelle femmine e l'1-2% nei maschi in diverse popolazioni).

► La Tiroidite linfocitaria cronica o di Hashimoto (HT), è una tipica malattia autoimmune a cellule T mediata caratterizzata dalla presenza di anticorpi anti-tireoperossidasi (anti-TPO) e/o anticorpi anti-tiroglobulina (anti-Tg) o da forme sieronegative con possibile alterazione funzionale tiroidea fino ad ipotiroidismo subclinico o franco, da infiltrazione ghiandolare di linfociti B e T con predominanza del sottotipo CD4+ Th1helper che porta ad un quadro di gozzo diffuso o nodulare o ad atrofia ghiandolare.

► Nel morbo di Basedow (con o senza oftalmopatia di Graves), l'infiltrazione linfocitica è lieve e coinvolge principalmente le cellule CD4+T2 helper, che inducono la produzione di anticorpi leganti e alcun feedback negativo ipotalamo-ipofisario portando ad un quadro di ipertiroidismo conclamato o subclinico.

► La patogenesi delle AITD, come altre malattie autoimmuni, è multifattoriale, combinando influenze genetiche, immunitarie, ambientali e ormonali



Considerazioni speciali



In letteratura vi è abbondanza di studi che correlano malattie reumatiche sistemiche e patologie tiroidee autoimmuni ma vi è scarsa omogeneità:

- ▶ *Le patologie reumatiche sistemiche sono eterogenee e riconoscono meccanismi patogenetici differenti*
- ▶ *Tireopatie autoimmuni sono estremamente frequenti*
- ▶ *Studi osservazionali con livelli di evidenza bassi al massimo moderati*
- ▶ *Mancanza di gruppo di controllo*



FALSE



The background is a dark blue gradient. In the center, there is a light blue, textured graphic resembling a notepad or a piece of paper. On this graphic, there is a large, dark blue question mark. To the left of the question mark, the word 'VERO' is written in a light blue, outlined font. To the right, the word 'FALSO' is written in the same style. Overlaid on the question mark and the words is the main text of the slide. The text is in a white, sans-serif font with a slight drop shadow. The word 'autoimmune' is highlighted in a yellow-green color. The overall composition suggests a quiz or a question about the existence of rheumatic manifestations in autoimmune thyroid diseases.

Esistono manifestazioni
reumatiche nelle
patologie **autoimmune**
della tiroide

Thyroid *AND* rheumatic manifestations

Fibromyalgia

Rheumatoid

chronic pain

Arthritis

Osteoarthritis

Thyroid disease

Autoimmune connective tissue disease

Autoimmune thyroid disease

Thyroid gland

course

REVIEW ARTICLE



Rheumatic associations of autoimmune thyroid disease: a systematic review

Tagoe CE et al



I pazienti con patologie tiroidee autoimmuni hanno un'aumentata prevalenza anche di manifestazioni reumatiche sistemiche che non riconoscono una chiara origine autoimmune

- ❑ 15% dei pazienti con AITD presenta come manifestazione clinica le osteoartriti (spinali e della mano).
- ❑ Il 30 -40% circa di pazienti con AITD presenta sindromi dolorose come la fibromialgia e la sindrome da dolore cronico diffuso .
- ❑ Tra il 26 e il 34% circa dei pazienti con AITD lamenta forme di artriti infiammatorie con pattern simile all'artrite reumatoide, alle artriti psoriasiche, alle connettiviti o spondiloartropatia .

Gli stessi autori hanno ipotizzato una percentuale ancora maggiore nella real life in quanto tutti i pazienti erano eutiroidei

.....The quality of evidence was deemed to be low for most of the studies

These findings suggest that AITD may be a risk factor for CWP and FMS, peripheral osteoarthritis, and axial OA.High rates of association between RA and AITD are reported in other studies, some of which report an influence on disease prognosis .

However, these reports did not suggest AITD as a cause of inflammatory arthritis and the possible influence of AITD on RA disease severity was not a focus of this review.

Although the literature supports the association between AITD and rheumatic manifestations, the precise role of AITD in terms of direct causation versus modulation of the rheumatic presentation of co-existing autoimmune disease cannot be determined.

Conclusion

The presence of AITD not only increases the risk of clinically significant thyroid disease such as hypothyroidism in the particular case of CLT and HT, but possibly increases the frequency of axial OA, and probably increases the presence of peripheral OA characterized by Heberden's and Bouchard's nodes, knee, and hip OA. It probably increases the prevalence of FMS in some populations, including AITD with no ACTD overlap and in RA patients..... the data suggest a specific pattern of association

We believe the preponderance of the evidence available now justifies the assessment of thyroid autoantibodies as part of routine rheumatology practice to better assess the disease burden of AITD in rheumatic diseases, not only generally through its endocrine and cardiovascular effects, but specifically due to its rheumatic manifestations



Dal punto di vista dell'endocrinologo ...

- ▶ Non è stata riscontrata alcuna associazione tra le manifestazioni reumatiche precedentemente dette e le patologie disfunzionali (in particolare l'ipotiroidismo) in assenza di anticorpi anti tiroide
- ▶ L'ipotesi è che la presenza di anticorpi anti tiroide siano parte di un processo infiammatorio generalizzato che può avere manifestazioni reumatiche ascrivibili ad una sindrome precisa.

Esistono
manifestazioni
reumatiche nelle
patologie
autoimmune della
tiroide

VERO



FALSO





I pazienti con malattie reumatiche sistemiche possono presentare maggiore prevalenza di patologie tiroidee rispetto alla popolazione generale



Artriti non infettive, connettiviti e vasculiti

- ▶ E' nota una maggior incidenza di disfunzioni tiroidee tra pazienti affetti da artriti non infettive, vasculiti e connettiviti come il lupus eritematoso sistemico, la sindrome di Sjogren, l'artrite reumatoide, la sclerosi sistemica e l'arterite temporale.
- ▶ In particolare tali patologie risultano maggiormente associate all'ipotiroidismo da tiroidite di Hashimoto rispetto all'ipertiroidismo da morbo di Basedow verosimilmente per una minor immunogenicità di quest'ultimo. Una maggiore associazione si riscontra nei soggetti di età <40 aa.
- ▶ E' stato riscontrata un'associazione tra un alto grado di attività dell'artrite reumatoide e l'ipotiroidismo e si è osservato un peggiore outcome nei pazienti con sclerosi sistemica ed ipertiroidismo

Rheumatoid arthritis and thyroid dysfunction: A cross-sectional study and a review of the literature

Literature review investigating the prevalence of thyroid dysfunction among RA patients.

Study	Location	Number of patients	Results
Caron 1992 [27]	France	68 RA patients	33.8% of RA patients had thyroid dysfunction disorder
Shiroky, 1993 [28]	Canada	91 RA patients, 93 controls	30% of RA patients had thyroid dysfunction compared to 11% in controls
Rateman 2008 [42]	The Netherlands	358 RA patients	RA patients had a threefold odds ratio for having clinical hypothyroidism compared to the general population in the Netherlands (6.8% vs. 2.7%, P value < 0.001)
Przygodzka 2009 [30]	Poland	100 RA patients and 55 controls	Autoimmune thyroid disease was nonsignificantly increased among RA patients compared to controls (16% vs. 9%). No difference in prevalence of antithyroglobulin antibodies (TgAb) and antithyroidperoxidase antibodies (TPOAb).
Ilias, 1999 [43]	Greece	69 RA patients, 65 osteoarthritis patients	RA patients exhibited statistically significant lower mean TSH values than OA patients. However, RA patients with low TSH values did not have elevated FT4I. The levels of autoantibodies did not differ between the two groups.
Pongratz, 2000 [44]	Austria	383 RA patients, 409 osteoarthritis patients	Patients with RA had a significantly higher prevalence of antithyroid antibodies (9.1% vs. 3.7%)
Somers, 2001 [40]	UK	22,888 RA patients	High prevalence of autoimmune thyroid disease among RA patients compared to the general population
Innocendo, 2004 [45]	Brazil	25 RA patients, 113 controls	TgAb and/or TPOAb antibodies were present in 32% of the RA patients and in 4% of controls.
Atzeni, 2008 [46]	Italy	70 RA patients	Twenty-six patients (37%) with RA were positive for TPOAb and 16 (23%) for TgAb.
Magnus 1995 [47]	Norway	100 RA patients	Increased prevalence of TgAb among RA patients as compared to the normal population from the same geographical area (11.0% vs. 2.8%, p < 0.001)
Joshi 2017 [48]	India	52 RA patients	Hypothyroidism was observed in 38.4% of RA patients. A significant association was observed between TSH levels and disease activity parameters (ESR and DAS-28)
Lazurova, 2009 [49]	Slovakia	80 RA and SLE patients, 34 controls	The prevalence of chronic autoimmune thyroiditis in the group of patients with SLE and RA was significantly higher than that in the control subjects (24% vs. 8%, P < 0.05)
Roldan, 2012 [39]	Colombia	800 RA patients	9.8% of RA patients had autoimmune thyroid disease; 37.8% had TPOAb; 20.8% had TgAb.
Silman 1989 [36]	UK	504 family members of 58 multicase RA families	6% had concurrent thyroid disease. Thyroglobulin antibodies were present 5% of males and 11% of females. Thyroid microsomal antibody was present in 5% of males and 15% of females. Such values were significantly higher than the published rate for the general population.
McCoy, 2012 [29]	USA	650 RA patients, 650 controls	There was no significant difference in the prevalence of clinical hypothyroidism, sub-clinical hypothyroidism, Graves' disease, or the use of levothyroxine between groups at diagnosis of RA or at follow-up. The prevalence of hypothyroidism in both groups was 14–16%, and the prevalence of Graves' disease was 0.6%.

Practice points

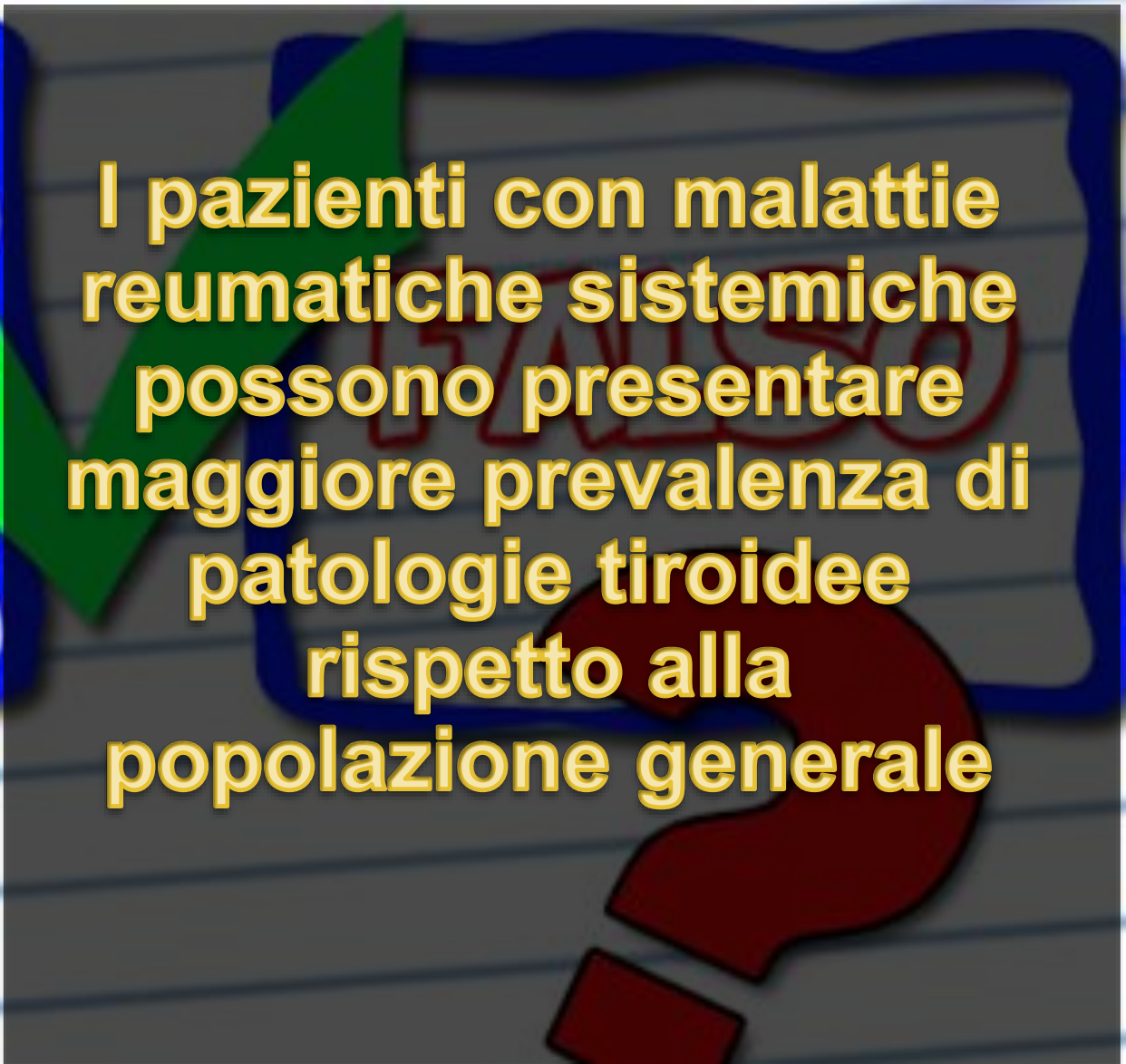
- Rheumatoid arthritis patients are associated with increased risk of both hyperthyroidism and hypothyroidism.
- Older age, female sex, higher BMI, and higher SES were all shown to be independent predictors for hypothyroidism and hyperthyroidism.
- Smoking status was found an independent risk factor for hypothyroidism but not for hyperthyroidism.

Research agenda

- Prospective studies are needed to assess more precisely the link between rheumatoid arthritis and thyroid disorders considering the impact of autoantibodies and immunosuppressant therapy on such a relationship.



VERO



**I pazienti con malattie
reumatiche sistemiche
possono presentare
maggiore prevalenza di
patologie tiroidee
rispetto alla
popolazione generale**



VERO

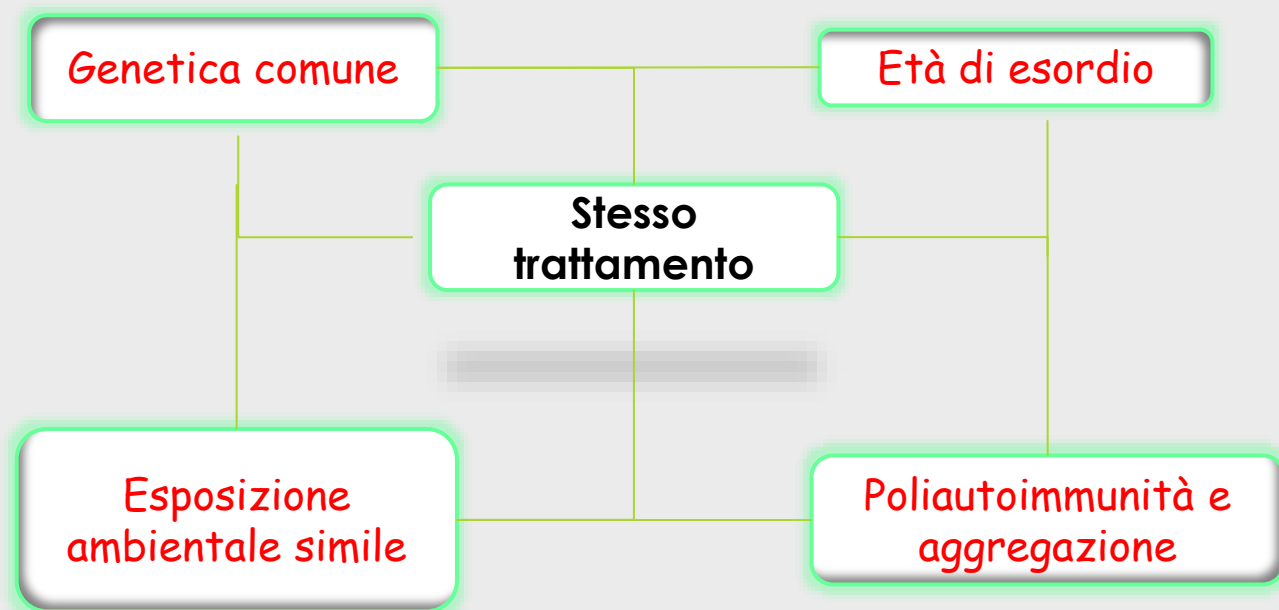
FALSO

**Chi è affetto da tiroiditi
autoimmune è più a rischio
di sviluppare altre
patologie autoimmuni**



Meccanismi comuni delle patologie autoimmuni (autoimmune tautology)

- Le patologie autoimmuni spesso condividono gli stessi meccanismi immunogenici, in particolare dagli studi di associazione genomici si sono identificati specifici loci comuni per patologie autoimmuni tiroidee e reumatologiche che riconoscono un meccanismo patogenetico basato sull'autoimmunità





Uno studio prospettico con **3069 soggetti affetti da tiroidite di Hashimoto** e **1023 controlli** ha considerato una vasta gamma di disordini autoimmuni riscontrando in alcuni casi una prevalenza nettamente aumentata nei soggetti con tiroidite autoimmune:

- ▶ Artrite reumatoide 2.4 % vs 0.007 %
- ▶ Polimialgia reumatica 1.4% vs 0.003%
- ▶ Lupus eritematoso sistemico: 0.8% vs 0.001%
- ▶ Sindrome di Sjogren 0.9 % vs 0.002%
- ▶ Sclerosi sistemica 0.5 % vs 0%



Prevalence and Relative Risk of Other Autoimmune Diseases in Subjects with Autoimmune Thyroid Disease

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ABSTRACT

BACKGROUND: Common autoimmune disorders tend to coexist in the same subjects and to cluster in families.

METHODS: We performed a cross-sectional multicenter study of 3286 Caucasian subjects (2791 with Graves' disease; 495 with Hashimoto's thyroiditis) attending UK hospital thyroid clinics to quantify the prevalence of coexisting autoimmune disorders. All subjects completed a structured questionnaire seeking a personal and parental history of common autoimmune disorders, as well as a history of hyperthyroidism or hypothyroidism among parents.

RESULTS: The frequency of another autoimmune disorder was 9.67% in Graves' disease and 14.3% in Hashimoto's thyroiditis index cases ($P = .005$). Rheumatoid arthritis was the most common coexisting autoimmune disorder (found in 3.15% of Graves' disease and 4.24% of Hashimoto's thyroiditis cases). Relative risks of almost all other autoimmune diseases in Graves' disease or Hashimoto's thyroiditis were significantly increased (>10 for pernicious anemia, systemic lupus erythematosus, Addison's disease, celiac disease, and vitiligo). There was relative "clustering" of Graves' disease in the index case with parental hyperthyroidism and of Hashimoto's thyroiditis in the index case with parental hypothyroidism. Relative risks for most other coexisting autoimmune disorders were markedly increased among parents of index cases.

CONCLUSION: This is one of the largest studies to date to quantify the risk of diagnosis of coexisting autoimmune diseases in more than 3000 index cases with well-characterized Graves' disease or Hashimoto's thyroiditis. These risks highlight the importance of screening for other autoimmune diagnoses if subjects with autoimmune thyroid disease present with new or nonspecific symptoms.

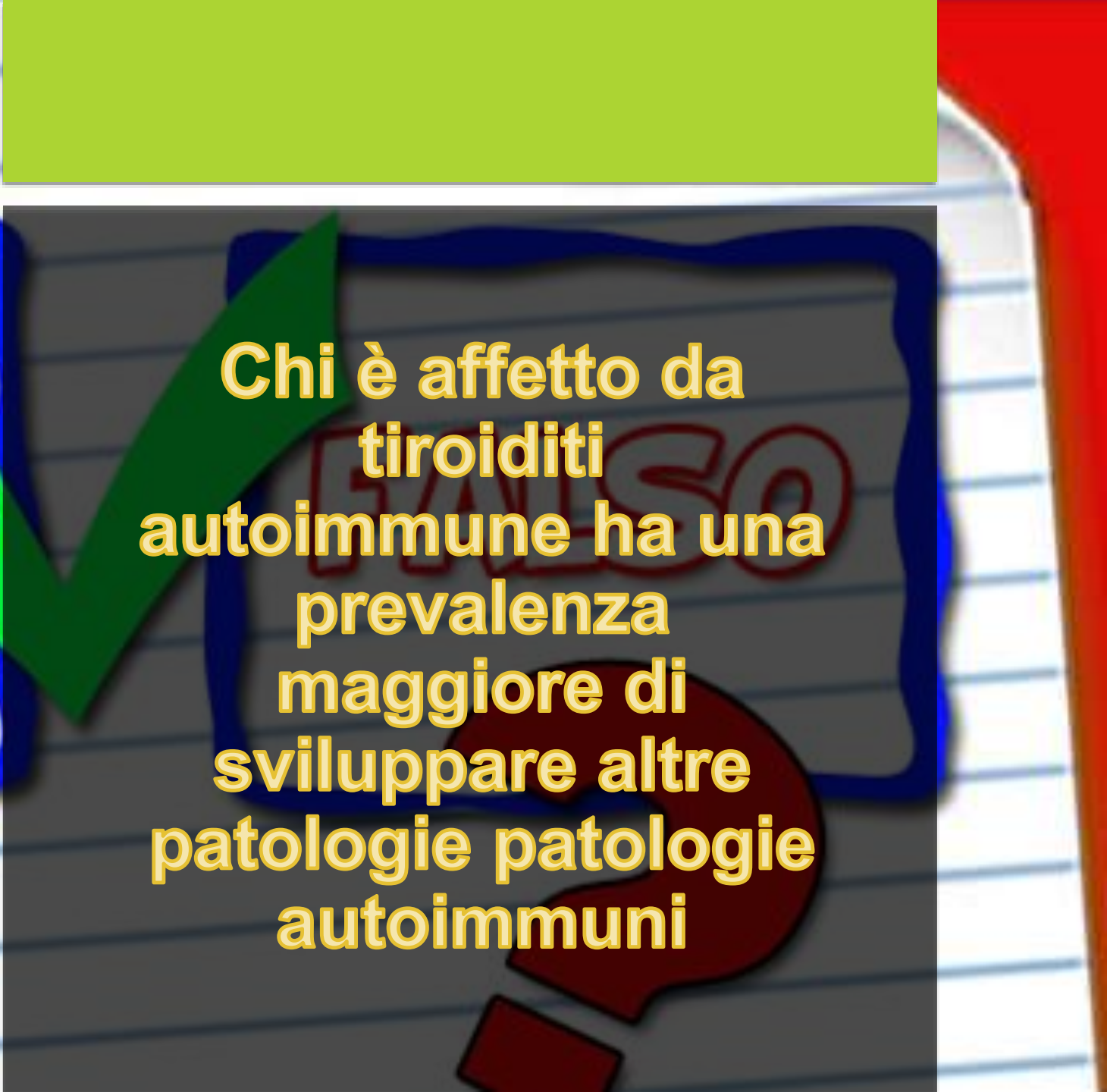
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CLINICAL SIGNIFICANCE

- Patients with a primary diagnosis of autoimmune thyroid disease are at significantly increased risk of additional autoimmune diseases, and these risks can be quantified.
- There is clear evidence for parental and index case clustering of Graves' disease and Hashimoto's thyroiditis.
- Screening for other autoimmune diagnoses might be indicated if subjects with autoimmune thyroid disease present with new or nonspecific symptoms.



VERO



**Chi è affetto da
tiroiditi
autoimmune ha una
prevalenza
maggiore di
sviluppare altre
patologie patologie
autoimmuni**

FOCUS



- ▶ Artrite reumatoide e disordini tiroidei autoimmuni

Artrite reumatoide e patologie tiroidee autoimmuni

- ▶ L'associazione tra artrite reumatoide(RA) e tiroidite autoimmune (AT) è tra le più studiate in letteratura, riconoscendo una prevalenza di RA nei pazienti con AT aumentata di 1-3 volte e viceversa una prevalenza di AT nei pazienti con RA aumentata di 1-6 volte
- ▶ Un recente studio italiano ha riscontrato una prevalenza di AR nei soggetti affetti da morbo di Graves dell'1.9% (numerosità campionaria 3209), uno studio del 2010 inglese invece osservava una prevalenza del 3.5% (numerosità campionaria 2791)
- ▶ E' stato dimostrato che altri fattori possono contribuire all'associazione tra queste patologie ad esempio la suscettibilità genetica HLA mediata e fattori ambientali come il fumo di sigaretta





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Autoimmune thyroid disorders and rheumatoid arthritis: A bidirectional interplay

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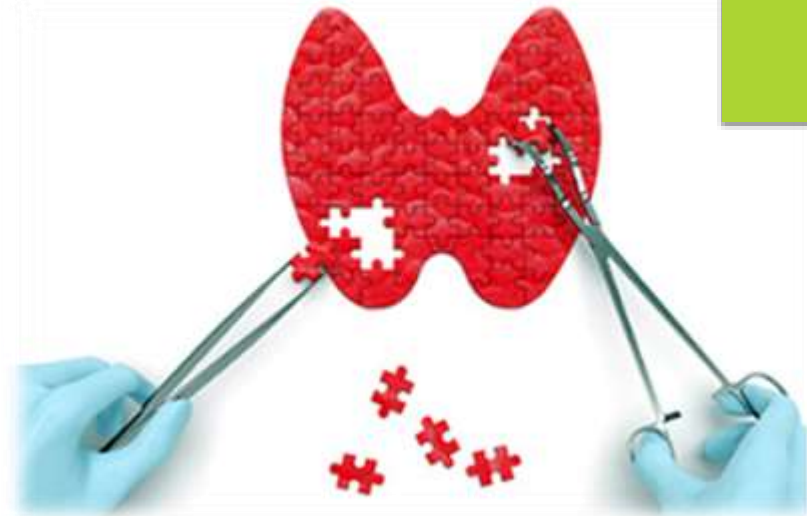
The association between RA and thyroid disorders is well-known since more than a century, but many aspects remain to be clarified. Questions about genetic and epigenetic basis of this association and prognostic role of one disease on the other are still unresolved. The evaluation of thyroid autoimmunity and functional status is might be screening in RA patients. The correction of a condition of hypothyroidism improves RA activity, being able to enhance the quality of life of RA patients.

Influenza dei disturbi tiroidei
sull'attività e sull'outcome
clinico dell'AR

Impatto delle Terapie
dell'AR sulla tiroide e
viceversa

conclusioni e take home messages

- ▶ Spesso i sintomi muscolo-scheletrici manifestati dal paziente con patologia tiroidea autoimmune sono aspecifici e non indirizzano verso una diagnosi ben definita di patologia reumatica
- ▶ L'associazione delle patologie tiroidee autoimmuni e le patologie reumatiche sistemiche può essere dovuta all'autoimmunità, allo stato infiammatorio, allo stato endocrino-metabolico, alla suscettibilità genetica ed a fattori ambientali (tautologia autoimmune)
- ▶ La disfunzione tiroidea può esacerbare patologie reumatiche sistemiche (periartrite, rigidità articolare, mialgie...) per tale motivo uno screening della funzione tiroidea è auspicabile (TSH-R?)
- ▶ Data l'evidenza di un'aumentata prevalenza di patologie tiroidee autoimmuni, in particolare di tiroidite di Hashimoto, nei pazienti con patologie reumatiche, e viceversa, è consigliabile uno screening «bi-direzionale» al momento della diagnosi iniziale o in presenza di nuovi sintomi



Reumatologo

Endocrinologo



FIDES SPES CARITAS PRVDENTIA IVSTITIA FORTITVDO TEMPERANTIA