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EDITORIALE

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Cari Lettori,
vi sarà sicuramente capitato che a una paziente alla quale avevate prescritto vitamina D è tornata comunicandovi di averla sostituita con una combinazione con vitamina K, come consigliatole da qualcuno ritenendola più efficace della sola vitamina D. Superata la sensazione di dispiacere o di disappunto vi sarete chiesti: qual è il razionale della combinazione e, soprattutto, è effettivamente sempre necessaria? In questo numero troverete una risposta. Noterete che gli Autori, ai quali abbiamo chiesto un contributo specifico, ricordano che effettivamente la vitamina K, originariamente identificata come fattore indispensabile per la coagulazione del sangue, svolge anche altre funzioni tra cui quella di contribuire alla regolazione del metabolismo dell'osso mediante la carbossilazione dell'osteocalcina. Tuttavia, sebbene gli studi osservazionali abbiano suggerito un'associazione tra bassi livelli plasmatici di entrambe le vitamine e un aumentato rischio di fratture e mortalità, i risultati degli studi di intervento risultano a tutt'oggi incoerenti. Gli Autori concludono che sono necessari ulteriori studi per documentare gli eventuali benefici della supplementazione combinata di vitamina D e K, e per identificare gli individui che potrebbero maggiormente beneficiarne. Va inoltre ricordato che le vitamine agiscono essenzialmente come nutrienti, quindi servono solo se mancano. La carenza e la documentazione di quest'ultima sono presupposti indispensabili per aspettarsi razionalmente dei benefici. Abbiamo già vissuto diverse esperienze con la supplementazione con vitamina D, dai risultati contradditori perché mancavano di questi presupposti essenziali. A differenza della vitamina D, la carenza di vitamina K è molto meno diffusa nella popolazione generale e si manifesta in condizioni particolari e specifiche: nelle patologie da malassorbimento intestinale (ad es. celiachia e fibrosi cistica) o in seguito all'uso cronico di antibiotici o di anticoagulanti antagonisti della vitamina K (come il warfarin) o in caso di dieta fortemente sbilanciata. Va inoltre considerato che la documentazione dello stato vitaminico K è più complessa rispetto a quella indicativa dello stato vitaminico D: non esiste, ad oggi, un indicatore specifico della carenza di vitamina K universalmente riconosciuto e facilmente dosabile. Come ulteriore dubbio sull'opportunità della sistematica e diffusa supplementazione combinata di vitamina D e K ricorderei che con l'eccessiva assunzione di vitamina D, specie in soggetti non carenti, sono stati osservati effetti indesiderati e non sarei sorpreso di riscontrarne anche con una supplementazione soprafisiologica di vitamina K, temibili considerato il suo ruolo in ambito cardiovascolare.
Nell'altro articolo di questo numero troverete un interessante aggiornamento sul possibile ruolo della vitamina D in alcune patologie respiratorie molto diffuse come la rinite allergica e l'asma. Nella rinite allergica pare che la vitamina D possa avere un ruolo preventivo o di attenuazione della manifestazione clinica grazie alle sue proprietà immunomodulanti, in particolare modu-

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lando l'equilibrio Th1/Th2. Tuttavia l'Autore riconosce che i risultati degli studi osservazionali attualmente disponibili sono talora contradditori e influenzati da variabili antropometriche quali etnia, età e sesso. A supporto di un possibile ruolo della vitamina D nei confronti del rischio di soffrire di rinite allergica vi sono i risultati di studi che ne prevedono la supplementazione nella gestante o in associazione a trattamenti sintomatici o mirati. Più convincenti mi sembrano le motivazioni ed evidenze disponibili sul possibile ruolo protettivo della vitamina D nei confronti dell'asma. Le possibili motivazioni sono almeno 3: la capacità della vitamina D di inibire la differenziazione delle cellule Th17 e la produzione di IL-17, aumentando al contempo i livelli della citochina antinfiammatoria IL-10; l'effetto protettivo sulla contrazione e il rimodellamento delle vie aeree, inibendo la crescita delle cellule muscolari lisce e dei fibroblasti delle vie aeree e l'espressione dei geni coinvolti nel rimodellamento della matrice extracellulare; infine, la carenza di vitamina D può compromettere l'integrità della barriera e alterare la composizione del microbioma intestinale, con una conseguente disbiosi che potenzialmente compromette le funzioni immunitarie sia locali che polmonari, aumentando così la suscettibilità all'asma. Le evidenze derivano da studi osservazionali di associazione, che documentano che bassi livelli di vitamina D correlano con un aumentato rischio di incorrere nell'asma, ma soprattutto da studi di intervento. Questi mostrano che un adeguato apporto di vitamina D prenatale durante la gravidanza fornisce un effetto protettivo contro lo sviluppo di asma/respiro sibilante ricorrente nei bambini o che la supplementazione con vitamina D può migliorare la qualità della vita dei pazienti e ridurre l'uso di corticosteroidi, il numero di attacchi e il rischio di ricovero ospedaliero per asma. Molto interessante appare, infine, il potenziale contributo della vitamina D per migliorare l'efficacia dell'immunoterapia allergica. Giustamente comunque l'Autore conclude che sono necessari ulteriori studi clinici multicentrici randomizzati controllati su larga scala e con follow-up a lungo termine per comprendere a fondo l'impatto della vitamina D nel trattamento delle malattie allergiche e determinare il dosaggio e la durata ottimali dell'integrazione con vitamina D.
Voi cosa ne pensate?
Buona lettura.

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Vitamina D e patologie respiratorie: focus su asma e rinite

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VITAMINA D E RINITE ALLERGICA

La rinite allergica (RA) è una comune malattia mediata dalle immunoglobuline E (IgE), che nel soggetto sensibilizzato reagiscono quando esposte ad allergeni inalatori. Clinicamente si manifestata con starnuti, congestione nasale, prurito nasale e rinorrea.

Secondo alcuni studi il livello di $1,25(OH)_2D$ è correlato all'equilibrio Th1/Th2 nei pazienti con RA, e la carenza di vitamina D sposta l'equilibrio Th1/Th2 a favore di Th2 [1]. Inoltre, il livello sierico di vitamina D nei pazienti con RA sembra sia inferiore a quello delle persone sane o del gruppo di controllo [2,3]. Un recente lavoro [4] effettuato sulla coorte di nascita del *Vitamin D Antenatal Asthma Reduction Trial* (VDAART) ha mostrato che, rispetto ai pazienti con carenza di vitamina D all'inizio e alla fine della gravidanza, l'insorgenza di RA e la sensibilizzazione agli aero-allergeni a 3 e 6 anni nella prole di madri con sufficiente vitamina D prenatale alla fine della gravidanza erano ridotte (OR = 0,47; 95% IC, 0,26-0,84). Bunyavanich et al. [5] hanno studiato 1.248 coppie madre-figlio nella coorte prenatale degli Stati Uniti e hanno scoperto che ogni 100 UI/die di assunzione alimentare di vitamina D nei primi tre mesi e negli ultimi tre mesi di gravidanza riduceva la probabilità che i bambini in età scolare soffrissero di RA rispettivamente del 21% e del 20%. Saad et al. [6] hanno scoperto in uno studio di coorte di 120 bambini egiziani con RA e 100 bambini sani che il livello medio di 25(OH)D dei pazienti con RA moderata/grave era significativamente inferiore a quello dei pazienti con RA lieve, e il livello medio di 25(OH)D del gruppo RA era negativamente correlato con il punteggio totale dei sintomi nasali e il livello totale di IgE. Tuttavia, è stato osservato che l'associazione tra vitamina D e RA è influenzata da variabili antropometriche, quali razza, età, sesso. Ad esempio, Mai et al. [7] hanno riportato che livelli più bassi di vitamina D nella popolazione adulta norvegese sono correlati a un aumento del rischio di RA negli uomini e a un rischio ridotto nelle donne. Gli autori hanno ipotizzato che ciò possa essere correlato al fatto che gli ormoni sessuali femminili potenziano le risposte Th1 e riducono le risposte Th2. Wegienka et al. [8] hanno scoperto che livelli più elevati di 25(OH)D nel sangue prenatale e del cordone ombelicale erano generalmente associati a minori esiti allergici, come eczema e sensibilizzazione ad allergeni presenti nell'aria. Questa associazione era più significativa nei bambini bianchi e meno evidente nei bambini neri. Inoltre, hanno osservato che i livelli di 25(OH)D erano negativamente associati alla sensibilizzazione ad allergeni presenti nell'aria solo nei bambini neri.

Alcune ricerche hanno confutato il legame tra vitamina D e RA. Uno studio trasversale condotto da Wu et al. [9], che includeva 32 pazienti con RA persistente e 25 controlli, non ha rilevato differenze significative nei livelli sierici di 25(OH)D tra i due gruppi. Un ampio studio trasversale [10] condotto in Corea su 15.212 adulti di età pari o superiore a 19 anni ha indicato, attraverso un'analisi di regressione lineare multivariata, che gli adulti con carenza di vitamina D non presentavano una maggiore probabilità di sviluppare asma, RA o sensibilizzazione alle IgE. Anche il più recente studio di randomizzazione mendeliana [11] non ha trovato prove di una relazione causale tra i livelli sierici di vitamina D e il rischio di RA negli individui di origine europea.

VITAMINA D E ASMA

L'asma è una comune malattia respiratoria cronica, caratterizzata da infiammazione cronica delle vie aeree e da elevata reattività delle stesse, che si manifesta con tosse, respiro sibilante, senso di costrizione toracica e difficoltà respiratorie. Il fenotipo più comune è l'asma allergico.

Hamzaoui et al. hanno raccolto campioni di sangue periferico da bambini piccoli con asma e hanno scoperto che la vitamina D

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inibiva significativamente la differenziazione delle cellule Th17 e la produzione di IL-17, aumentando al contempo i livelli della citochina antinfiammatoria IL-10 [12]. Uno studio trasversale condotto nella regione di Cipro [12] ha coinvolto 69 asmatici attivi e 671 adolescenti di età compresa tra 16 e 17 anni che non avevano mai avuto respiro sibilante o erano mai stati asmatici. È stato riscontrato che il livello medio di vitamina D nei bambini asmatici era inferiore e negativamente correlato alla gravità dell'asma. In precedenza, Bener et al. [14] hanno confrontato i livelli di vitamina D di 483 bambini asmatici con quelli di bambini sani in Qatar, proponendo inoltre che la carenza di vitamina D sia un importante fattore predittivo dell'asma infantile. Uno studio trasversale [15] condotto nel Regno Unito su 435.040 adulti ha rilevato che, rispetto alla carenza di vitamina D, il rischio di asma negli individui con concentrazioni di vitamina D basse e sufficienti si riduceva rispettivamente del 6,4 e del 9,8%, e che anche la loro funzionalità polmonare migliorava. Analogamente, molti studi hanno riportato che la carenza di 25(OH)D è correlata a un aumento del rischio di asma in neonati, adolescenti e adulti e a una riduzione della funzionalità polmonare, ed è influenzata da molti fattori come sesso, razza, etnia, fumo, uso o meno di corticosteroidi inalatori (ICS), modalità di sonno e suscettibilità genetica. Negli individui con un rischio genetico moderato, livelli più elevati di vitamina D erano associati a un rischio significativamente ridotto di asma. L'effetto protettivo della vitamina D era più evidente negli uomini, negli individui di età inferiore ai 60 anni, negli individui in sovrappeso e nei fumatori o ex fumatori. Un altro studio di coorte norvegese ha riportato che l'associazione tra livelli di vitamina D e funzionalità polmonare variava in base al sesso e allo stato allergico, con questa associazione particolarmente significativa tra i pazienti maschi affetti da asma [16]. La vitamina D sembra inoltre esercitare un effetto protettivo sulla contrazione e il rimodellamento delle cellule muscolari lisce delle vie aeree nell'asma. La vitamina D inibisce la crescita delle cellule muscolari lisce delle vie aeree riducendo l'espressione della ciclina D1 e inducendo la fosforilazione della proteina del retinoblastoma e della checkpoint chinasi 1 [17]. Inibisce inoltre l'espressione e la proliferazione del dominio 33 della metallopeptidasi ADAM indotta dal fattore di crescita endoteliale vascolare (VEGF), riducendo il rimodellamento delle vie aeree [18]. Inoltre, Plesa et al. hanno dimostrato che la vitamina D può inibire la proliferazione e la migrazione dei fibroblasti bronchiali sopprimendo le vie di segnalazione di ERK1/2 e Akt e sovraregolando i geni coinvolti nell'arresto del ciclo cellulare, come p21 e p27. Riduce inoltre l'espressione dei geni coinvolti nel rimodellamento della matrice extracellulare, come il collagene di tipo I e la metallopeptidasi della matrice 2 (MMP2) [19]. Questi meccanismi indicano che la vitamina D può svolgere un ruolo fondamentale nella regolazione del rimodellamento delle vie aeree nell'asma, rafforzando così la sua associazione con la condizione e il suo potenziale come terapia aggiuntiva per la gestione dell'asma.

Inoltre, studi recenti sottolineano una stretta interrelazione tra vitamina D, microbiota intestinale e asma. La carenza di vitamina D può compromettere l'integrità della barriera e alterare la composizione del microbioma, con una disbiosi intestinale che potenzialmente compromette le funzioni immunitarie sia locali che polmonari, aumentando così la suscettibilità all'asma. Le infezioni respiratorie possono alterare il microbioma intestinale, riducendo i batteri che producono acidi grassi a catena corta (SCFA), il che a sua volta influisce sulla funzione e sul destino delle cellule immunitarie, esacerbando ulteriormente i sintomi dell'asma [20,21].

EVIDENZE SULLA SUPPLEMENTAZIONE DI VITAMINA D IN RINITE E ASMA

Data la consolidata associazione tra carenza di vitamina D e malattie allergiche, numerosi studi sono stati dedicati a indagare i benefici clinici dell'integrazione di vitamina D in diverse popolazioni e i risultati sono stati relativamente promettenti. Uno studio clinico randomizzato controllato (RCT) significativo e su larga scala è lo studio VDAART [22]. Lo studio VDAART è stato condotto in tre centri negli Stati Uniti. Ha incluso 881 donne in gravidanza non fumatrici di età compresa tra 18 e 39 anni, che si trovavano tra la 10ª e la 18ª settimana di gestazione e presentavano un rischio elevato di sviluppare asma nella prole. Queste donne sono state divise in modo casuale per ricevere il gruppo di intervento (4400 UI di vitamina D al giorno) o il placebo (un multivitaminico contenente 400 UI di vitamina D al giorno) fino al parto. Lo studio ha esaminato i livelli materni di 25(OH)D nelle fasi avanzate della gravidanza e le condizioni di asma e respiro sibilante ricorrente nella prole. Mentre l'analisi *intention-to-treat* e l'analisi stratificata basata sui livelli di 25(OH)D delle madri durante la gravidanza indicavano che l'integrazione materna di vitamina D non aveva alcun impatto sulla comparsa di asma e respiro sibilante ricorrente nella prole all'età di 3 e 6 anni. Un'ulteriore analisi dello stato prenatale precoce e tardivo della vitamina D, dei livelli basali di vitamina D delle madri all'inizio dello studio e del momento di inizio dell'integrazione, ha portato i ricercatori a concludere che un adeguato apporto di vitamina D prenatale durante la gravidanza fornisce un effetto protettivo contro lo sviluppo di asma/respiro sibilante ricorrente nei bambini prima dei 3 anni. Lo studio ha anche rilevato che un intervento precoce durante la gravidanza può ridurre significativamente il rischio di asma o respiro sibilante ricorrente nella prole, con ogni settimana di intervento precoce che riduce del 15% le probabilità che la prole sviluppi asma e respiro sibilante ricorrente. Rispetto all'integrazione giornaliera di 400 UI di vitamina D, l'assunzione giornaliera di 4.400 UI di vitamina D tra la 9ª e la 12ª settimana può ridurre il rischio di asma o respiro sibilante ricorrente fino al 55%. Contemporaneamente, un'analisi secondaria della VDAART ha evidenziato che l'integrazione prenatale di vitamina D ha un effetto protettivo sull'incidenza di RA e sensibilizzazione agli allergeni presenti nell'aria a 3 e 6 anni.

Uno studio randomizzato, in triplo cieco, parallelo, controllato con placebo [23], condotto in Spagna, ha incluso 112 pazienti con un'età media di 55 anni affetti da asma e con livelli sierici di 25(OH)D inferiori a 30 ng/mL. La durata dello studio è stata di 6 mesi. Il gruppo di intervento ha ricevuto 16.000 UI di integratori orali di colecalciferolo settimanalmente, mentre il gruppo di controllo ha aggiunto un placebo al trattamento di routine per l'asma. I risultati hanno mostrato che, rispetto al placebo, l'integrazione orale settimanale di 25(OH)D può migliorare significativamente i punteggi dell'*Asthma Control Test* (ACT) entro 6 mesi. Può anche migliorare la qualità della vita dei pazienti, ridurre l'uso di corticosteroidi orali e il numero di attacchi d'asma, e ridurre il rischio di ricovero ospedaliero per asma.

Nel contesto dell'RA, uno studio RCT condotto da Guo et al. [24] ha scoperto che l'integrazione di vitamina D può potenziare l'effetto terapeutico dello spray nasale di

FIGURA 1.
Sintesi degli effetti della vitamina D rispetto alle patologie respiratorie allergiche.

mometasone nella RA da moderata a grave. Ciò ha comportato una riduzione più significativa del punteggio totale del TNSS dei pazienti, delle sottopopolazioni dei linfociti T (CD3+, CD4+), del rapporto CD4+/CD8+, del TNF-α e del punteggio totale del questionario sulla qualità della vita della rinocongiuntivite (RQLQ). I livelli di CD8+, IFN-γ, IL-10 e vitamina D sierica sono risultati aumentati in modo più significativo rispetto al gruppo di controllo e al test iniziale. Liu et al. [25] hanno inoltre osservato che i pazienti trattati con vitamina D come terapia aggiuntiva presentavano livelli sierici di 25(OH)D più elevati, punteggi più bassi per quanto riguarda i sintomi della RA, livelli di IL-4 e di eosinofili nel sangue periferico, e un tasso di efficacia del trattamento della RA più elevato, rispetto a quelli trattati con la sola desloratadina citrato diidrato (DCD). Pertanto, l'integrazione di vitamina D nel trattamento di routine può fungere da efficace trattamento adiuvante per i pazienti con RA, sopprimendo l'infiammazione.

Gli studi sopra menzionati presentano numerose limitazioni. In primo luogo, la popolazione dello studio potrebbe essere monocentrica, a breve termine e su piccola scala. In secondo luogo, la selezione della gravità della malattia nei soggetti dello studio potrebbe essere eccessivamente ampia. In terzo luogo, la maggior parte degli studi potrebbe non considerare l'assunzione di vitamina D nella dieta e i dati relativi al tempo di esposizione solare del paziente. In quarto luogo, molti questionari autocompilati potrebbero presentare un bias di richiamo. Pertanto, studi successivi dovrebbero considerare l'impatto delle differenze di età, sesso, gravità, razza, ecc. sull'efficacia clinica dell'integrazione di vitamina D, e sono necessari ulteriori studi clinici multicentrici su larga scala e con follow-up a lungo termine, nonché studi clinici randomizzati controllati. Inoltre, è fondamentale determinare il dosaggio e la durata ottimali dell'integrazione di vitamina D e comprendere a fondo l'impatto della vitamina D sull'efficacia del trattamento delle malattie allergiche.

VITAMINA D E IMMUNOTERAPIA ALLERGENE-SPECIFICA

L'immunoterapia allergica (AIT) è un approccio terapeutico per le malattie allergiche che modula il sistema immunitario del paziente aumentando progressivamente la dose di allergeni, riducendo così la risposta allergica a specifici allergeni. Questo metodo è comunemente utilizzato per il trattamento di condizioni come l'allergia ai pollini, l'allergia agli acari della polvere domestica (HDM), alcuni acidi grassi e l'allergia al veleno d'api. L'AIT può essere somministrata tramite iniezioni sottocutanee, gocce sublinguali o compresse sublinguali. Può ridurre i Th2 allergene-specifici, stimolare le cellule T regolatorie e le cellule B e produrre anticorpi bloccanti IgG e IgA, inducendo così tolleranza agli allergeni nei pazienti, riducendo i sintomi e migliorando la qualità della vita. Dato il lungo ciclo di trattamento e l'elevata richiesta di compliance da parte del paziente, si stanno attualmente esplorando nuove strategie, come nuovi adiuvanti, allergeni ricombinanti e immunomodulatori, per fornire piani di trattamento più sicuri, efficaci e convenienti e una tolleranza a lungo termine più duratura. In questo contesto, la vitamina D è stata identificata come un possibile potenziatore, migliorando l'efficacia dell'immunoterapia indotta da polline di graminacee.

Li et al. [26] hanno condotto un'analisi di regressione su 153 pazienti con RA sottoposti a AIT, rivelando che una carenza di vitamina D sierica potrebbe influire sull'efficacia della AIT nei bambini con RA. Majak et al. [27] hanno condotto un'analisi secondaria retrospettiva dei dati combinati di uno studio prospettico, randomizzato e controllato con placebo che ha coinvolto 36 bambini con asma sottoposti a AIT. Hanno scoperto che i pazienti con livelli sierici più elevati di 25(OH)D hanno sperimentato riduzioni più significative nei punteggi dei sintomi dell'asma e negli effetti di riduzione dei corticosteroidi indotti da AIT durante il periodo di AIT di 12 mesi. Questi pazienti hanno anche mostrato una maggiore produzione di TGF-β nel sangue periferico e una maggiore espressione di cellule Foxp3 positive, suggerendo che la vitamina D potrebbe fungere da efficace adiuvante per AIT. In uno studio su bambini con asma allergici agli HDM, il gruppo AIT più vitamina D ha ottenuto un punteggio totale dei sintomi dell'asma inferiore al 6° mese e la più alta intensità media di fluorescenza di Foxp3 al 12° mese, rispetto all'utilizzo della sola AIT [28]. Uno studio condotto a Bangkok, in Thailandia [29], ha dimostrato che, rispetto al placebo, i pazienti adulti allergici agli HDM sottoposti a AIT e integrati con vitamina D hanno mostrato una riduzione significativa dei punteggi relativi ai sintomi e al farmaco

e un aumento dei tassi di risposta al trattamento. Si ritiene che questo miglioramento dei sintomi allergici sia dovuto alla riduzione significativa della quantità di cellule T regolatorie disfunzionali (CRTH2 + Treg) da parte della vitamina D. Ciò supporta ulteriormente il potenziale valore della vitamina D nell'AIT. Questi risultati offrono anche nuove strategie terapeutiche per l'AIT e aprono la strada a nuove possibilità nel trattamento delle malattie allergiche.

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VITAMIN D
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Vitamina D e associazione con vitamina K: è necessaria?

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INTRODUZIONE

L'osteoporosi, conseguente alla riduzione della qualità e/o della densità ossea, è una patologia metabolica osservabile in donne dopo la menopausa, così come in altre condizioni legate all'invecchiamento, a malattie infiammatorie o autoimmuni, all'uso prolungato di farmaci (ad es. glucocorticoidi, chemioterapici ecc.) o a deficit nutrizionali. Tale condizione comporta la diminuzione della resistenza scheletrica con aumento del rischio di fratture da fragilità, in costante aumento a livello globale tale da essere un importante problema per il sistema socio-sanitario.
Sulla base di queste problematiche si sta cercando di ottimizzare interventi terapeutici farmacologici e di stile di vita atti a prevenire le conseguenze di tale patologia. La vitamina D, nota per la sua capacità di favorire l'assorbimento intestinale del calcio e di regolare il metabolismo scheletrico, è stata estensivamente studiata anche per i suoi effetti sul sistema immunitario, cardiovascolare e muscolare. Tuttavia, nonostante la possibilità di sintesi endogena a livello cutaneo per l'esposizione alla luce solare, l'ipovitaminosi D è largamente diffusa in molte fasce della popolazione, in particolare tra gli anziani, nei quali si osserva una combinazione di ridotta sintesi cutanea, scarsa esposizione solare e insufficiente apporto alimentare. Tale carenza si associa a un aumentato rischio di osteoporosi, fratture, debolezza muscolare e iperparatiroidismo secondario [1].
Oltre alla vitamina D, anche per la vitamina K è stato evidenziato un ruolo importante nel mantenimento della salute dell'osso. In particolare, la forma K2 partecipa all'attivazione di proteine vitamina K-dipendenti, fondamentali sia per la regolazione della mineralizzazione ossea che per la prevenzione di calcificazioni vascolari [2].
In particolare, molteplici evidenze mostrano come vitamina D e vitamina K agiscano in modo sinergico contribuendo, con meccanismi complementari, all'equilibrio tra deposizione minerale ossea e inibizione della calcificazione ectopica. In questo contesto, uno stato subottimale di una delle due vitamine può compromettere l'efficacia dell'altra, evidenziando la possibilità di considerarne la contemporanea integrazione nella prevenzione e nel trattamento di patologie legate alla fragilità ossea e al rischio cardiovascolare.
Sulla base di queste premesse, il presente lavoro si propone di analizzare il ruolo della vitamina D e della vitamina K sulla salute dell'osso, approfondendone le fonti, il metabolismo e lo stato nutrizionale, con un focus particolare sulla loro interazione e sulle implicazioni cliniche di una loro eventuale integrazione combinata.

VITAMINA D

La vitamina D promuove l'assorbimento intestinale del calcio facilitandone il trasporto attivo attraverso la mucosa intestinale. È una vitamina liposolubile che può essere assunta con la dieta attraverso alimenti come pesce grasso, olio di fegato di merluzzo, uova e, in misura minore, prodotti lattiero-caseari, ma viene principalmente sintetizzata a livello cutaneo in seguito all'esposizione solare. Una volta assorbita o sintetizzata, viene idrossilata nel fegato a 25(OH)D, il principale metabolita circolante utilizzato per valutare e classificare lo stato vitaminico. La 25(OH)D viene poi convertita a livello renale nella sua forma biologicamente attiva, la 1,25-diidrossivitamina D [1,25$(OH)_2$D], anche nota come calcitriolo, che esercita un'azione sia sul metabolismo osseo che sulla funzione immunitaria [1,3].
Storicamente, l'interesse clinico per la vitamina D si è concentrato sulla prevenzione del rachitismo nei bambini; tuttavia, negli ultimi decenni è emersa con crescente evidenza la sua rilevanza anche per la salute dell'adulto e, in particolare, dell'anziano. Una carenza prolungata di vitamina D porta a una riduzione dell'assorbimento intestinale di calcio, innescando un aumento compensatorio del paratormone (PTH). Questo ormone stimola il riassorbimento osseo attraverso l'attivazione degli osteoclasti, con conseguente acce-

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lerazione del rimodellamento scheletrico e progressiva riduzione della densità minerale ossea (BMD), aumentando così il rischio di fratture. Anche il sistema cardiovascolare risente della carenza di vitamina D, sebbene le evidenze siano ancora preliminari. Studi osservazionali hanno associato bassi livelli di vitamina D a disfunzione endoteliale, ipertensione, infiammazione cronica e aumento del rischio cardiovascolare [4]. In particolare, la vitamina modulare l'espressione genica di vari componenti del sistema renina-angiotensina e svolgere un ruolo protettivo contro i danni vascolari attraverso effetti antinfiammatori e antiproliferativi a livello endoteliale [4].

La carenza di vitamina D rappresenta oggi un problema di salute pubblica diffuso a livello globale e interessa ampie fasce di popolazione. L'anziano è particolarmente vulnerabile alla carenza di vitamina D, a causa della ridotta esposizione solare, della diminuita capacità di sintetizzarla e della riduzione degli apporti di alimenti, compresi quelli che ne sono ricchi.

La valutazione dello stato della vitamina D è facilmente documentabile attraverso il dosaggio sierico di 25(OH)D, considerato il miglior indicatore dello stato di questa vitamina nell'organismo, e in Italia le Linee Guida per il trattamento dell'ipovitaminosi D della Società Italiana dell'Osteoporosi, del Metabolismo Minerale e delle Malattie dello Scheletro (SIOMMMS) indicano una condizione di "insufficienza" quando i valori di 25(OH)D sono compresi tra 20 e 30 ng/ml e di "carenza" con una concentrazione inferiore a 20 ng/ml [5].

I livelli di assunzione di riferimento per gli adulti variano tra 5 e 20 µg/die nei diversi documenti internazionali. I Livelli di Assunzione di Riferimento di Nutrienti ed energia per la popolazione italiana (LARN) indicano un'assunzione raccomandata per la popolazione (PRI) pari a 15 µg per gli adulti fino a 74 anni e 20 µg per la fascia di età ≥ 75 anni [6]. Tuttavia, l'apporto alimentare spesso non è sufficiente per raggiungere tali livelli, rendendone necessaria la supplementazione. Numerose evidenze scientifiche supportano la supplementazione di vitamina D per la prevenzione di fratture [1]. Tuttavia, sono ancora limitate le evidenze sugli effetti a lungo termine, e alcuni studi suggeriscono la possibilità di effetti avversi, come la precipitazione del calcio a livello vascolare [1].

VITAMINA K

La vitamina K, anch'essa vitamina liposolubile, è disponibile in due principali forme: la vitamina K1 (fillochinone), presente principalmente nelle verdure a foglia verde (cavoli, broccoli, spinaci), e la vitamina K2 (menachinone), contenuta nei latticini fermentati e prodotta dai batteri lattici intestinali. Originariamente identificata come fattore indispensabile per la coagulazione del sangue, attualmente si ritiene svolga anche altre funzioni quali la regolazione del metabolismo dell'osso, dell'infiammazione, l'inibizione dei processi di calcificazione vascolare e la riduzione del rischio cardiovascolare [7].

La biodisponibilità di vitamina K è relativamente bassa e influenzata da fattori legati alla matrice alimentare e alle caratteristiche individuali. La vitamina K1 introdotta con la dieta viene assorbita nel duodeno e nel digiuno e trasportata prevalentemente al fegato, dove regola la sintesi dei fattori della coagulazione, mentre la vitamina K2 è diretta ai tessuti extraepatici, come l'osso e la parete vascolare, dove regola l'attività delle principali proteine vitamina K-dipendenti, la proteina Gla della matrice (MGP) e l'osteocalcina (OC). Quest'ultima, prodotta dagli osteoblasti, subisce un'attivazione post-traduzionale attraverso un processo di carbossilazione enzimatica. Una delle principali funzioni dell'osteocalcina carbossilata (cOC) sembra essere quella di facilitare il trasporto del calcio dal sangue e altri tessuti all'osso favorendone l'incorporazione nell'idrossiapatite [8] (Fig. 1).

A differenza della vitamina D, la carenza di vitamina K è meno diffusa nella popolazione generale e tende a manifestarsi in situazioni specifiche, come nelle patologie da malassorbimento (ad esempio celiachia e fibrosi cistica), in seguito all'uso cronico di antibiotici o anticoagulanti antagonisti della vitamina K (come il warfarin), o in caso di dieta fortemente sbilanciata [9].

La documentazione dello stato di vitamina K è più complessa rispetto alla vitamina D, poiché non esiste, ad oggi, un marcatore specifico universalmente riconosciuto. Attualmente la valutazione si basa sull'analisi integrata di marcatori specifici, distinti per tessuto bersaglio. A livello del tessuto osseo, i principali indicatori di carenza funzionale di vitamina K sono l'osteocalcina non carbossilata (ucOC) e il rapporto ucOC/cOC, entrambi associati a ridotta attività degli osteoblasti, aumentato riassorbimento osseo e aumentato rischio di fratture di femore [2].

Invece, le concentrazioni plasmatiche di proteina Gla della matrice non carbossilata (ucMGP) e di proteina Gla della matrice non carbossilata e non fosforilata (dp-ucMGP) rappresentano biomarcatori sensibili dello stato di vitamina K a livello vascolare. Una ridotta attività della vitamina K, evidenziata da elevati livelli di dp-ucMGP, si ritiene possa contribuire alla progressione di calcificazioni arteriose e al deterioramento della funzione vascolare, soprattutto in pazienti con malattia renale cronica o diabete, in cui il metabolismo della vitamina K risulta spesso alterato [7].

Gli attuali livelli di assunzione raccomandati per gli adulti variano tra 60 e 170 µg/die nei diversi documenti internazionali. In Italia nella popolazione adulta e anziana i LARN indicano un'assunzione adeguata (AI) di 135 µg/die per gli uomini e 125 µg/die per le donne [6].

Numerosi studi hanno mostrato come bassi apporti dietetici di vitamina K, ridotte concentrazioni plasmatiche di K1 e livelli elevati di ucOC siano fortemente correlati a un aumento del rischio di fratture da fragilità, ma la correlazione con la BMD risulta meno evidente [10]. Una meta-analisi di studi osservazionali condotta su 80.982 individui ha evidenziato una correlazione inversa tra l'assunzione dietetica di vitamina K e il rischio di fratture [10]. All'opposto, gli studi randomizzati controllati (RCT) mostrano risultati contrastanti. Infatti, una recente meta-analisi di studi condotti in donne in postmenopausa affette da osteoporosi ha confermato tali difformità [11], suggerendo che l'integrazione di vitamina K non sia al momento raccomandata [11]. Negli anziani, supplementazioni giornaliere di K1 per periodi di 12-48 mesi sono risultate efficaci nel ridurre le concentrazioni di ucOC, pur non riuscendo a prevenire in modo significativo la perdita di massa ossea [11]. Altri risultati suggeriscono che la supplementazione di K1 per 2-4 anni possa esercitare un effetto protettivo nella prevenzione delle fratture in donne in postmenopausa affette da osteoporosi [11].

Evidenze inerenti la supplementazione di vitamina K2 riportano un aumento del contenuto minerale osseo del femore e un miglioramento della resistenza ossea in donne in postmenopausa [11]. Un altro studio ha confermato come l'integrazione giornaliera di MK-4 riduca i livelli sierici di ucOC, e rallenti la perdita minerale ossea a livello dell'avambraccio [11]. Infine, una meta-ana-

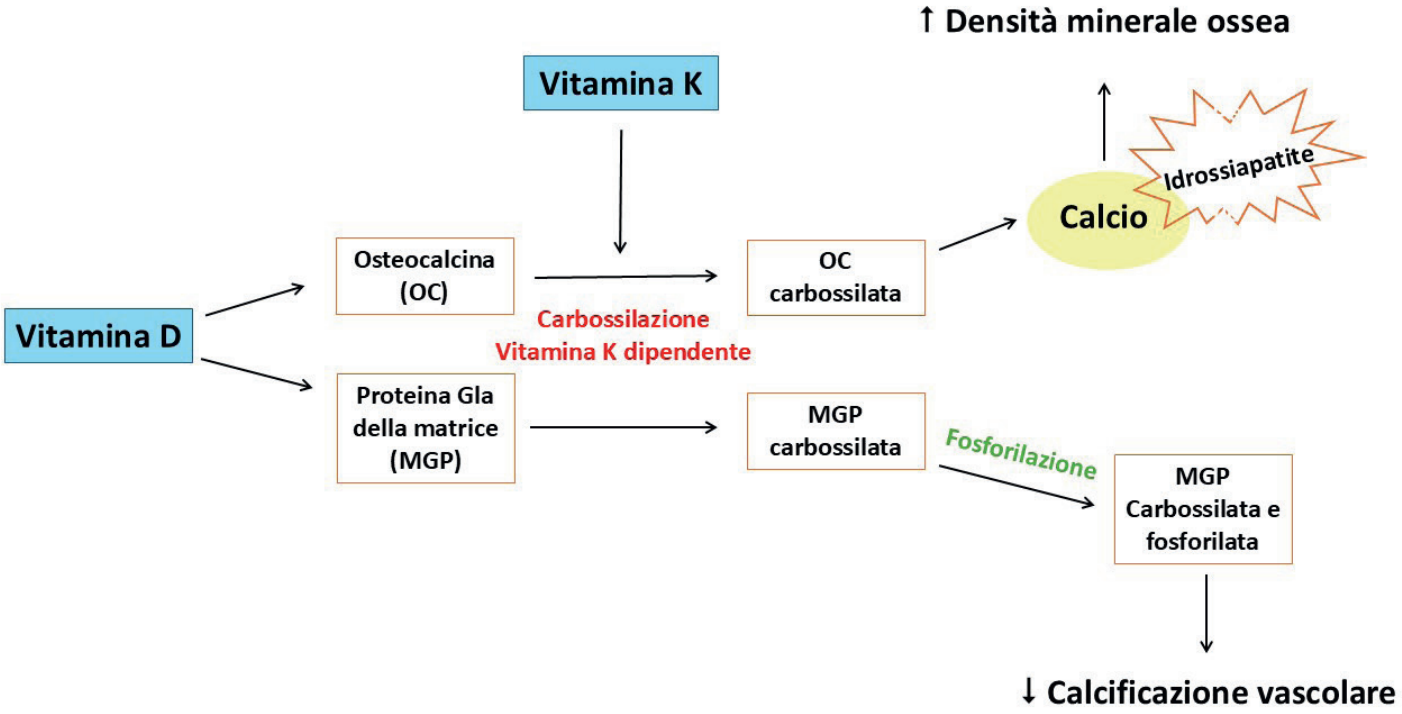

FIGURA 1.
Ruolo sinergico della vitamina D e K sulla salute dell'osso e cardiovascolare.

lisi su 19 RCT ha mostrato come la vitamina K2 possa contribuire al mantenimento e al miglioramento della BMD, nonché alla prevenzione delle fratture nelle donne in postmenopausa con osteoporosi, mentre tali effetti non sono stati osservati in assenza di osteoporosi [11].

Diversi studi osservazionali hanno documentato un'associazione inversa tra l'assunzione di K2 e calcificazioni vascolari, sia a livello coronarico che aortico [12]. In uno studio condotto su donne in menopausa, livelli di assunzione più elevati di K2 sono risultati correlati a una minor prevalenza di calcificazioni a livello delle coronarie [12]. Gli studi d'intervento volti a esplorare gli effetti della supplementazione di vitamina K nella prevenzione di alcune malattie cardiovascolari e nella modulazione di alcuni marcatori cardiometabolici sono però limitati e presentano risultati contrastanti, come anche dimostrato da recenti meta-analisi [12,13]. In particolare, mentre alcuni studi hanno evidenziato come l'integrazione per 36 mesi di MK-7 migliorasse la rigidità delle arterie in donne in postmenopausa [13], al contrario altre evidenze non hanno riportato benefici in pazienti anziani affetti da patologie cardiovascolari [13].

COMBINAZIONE DI VITAMINA D E VITAMINA K: È NECESSARIA?

Un numero crescente di evidenze suggerisce come l'interazione sinergica tra vitamina D e vitamina K possa apportare benefici per la salute scheletrica e cardiovascolare. Infatti, un recente studio ha evidenziato che bassi livelli plasmatici di entrambe le vitamine sono associati a un aumento del rischio di mortalità per tutte le cause rispetto a soggetti con livelli adeguati [14].

In questo contesto, la supplementazione combinata di vitamina D e K è proposta come strategia protettiva nella prevenzione dell'osteoporosi. A supporto, recenti meta-analisi [15,16] indicano come tale combinazione risulti più efficace della sola vitamina D nella protezione scheletrica. Tuttavia, diversi altri studi non hanno riscontrato un'associazione significativamente positiva tra i livelli entrambe le vitamine e la BMD o la qualità dell'osso trabecolare in donne in postmenopausa [17]. La maggior parte delle evidenze disponibili deriva da studi condotti nella popolazione generale, comprendenti sia analisi osservazionali sullo stato delle vitamine D e K in relazione a diversi "outcomes" clinici, sia studi clinici d'intervento che prevedono la somministrazione di entrambe le vitamine. Nonostante le raccomandazioni suggeriscano di valutare lo stato vitaminico prima di iniziare la supplementazione, diverse evidenze supportano l'integrazione combinata di vitamina D_3 e K anche in assenza di una valutazione preliminare, soprattutto in soggetti anziani.

È stato osservato come l'integrazione combinata di vitamina D_3 con vitamina K2, incrementi la BMD nelle donne in postmenopausa [2]. In uno studio caso-controllo condotto su pazienti anziani con frattura dell'anca e controlli, ridotti livelli sierici di 25-idrossivitamina D e vitamina K1 nei pazienti rispetto ai controlli, sono risultati associati a un aumentato rischio di frattura dell'anca [2].

Una recente meta-analisi su 8 RCT (971 partecipanti), ha confermato che la supplementazione combinata di vitamina D3 e vitamina K incrementi significativamente la BMD [2]. Analogamente, in un altro RCT con placebo in donne in postmenopausa con osteopenia è stata somministrata MK-7 insieme a vitamina D3 e calcio per tre anni. I risultati hanno mostrato che un aumento significativo della carbossilazione dell'osteocalcina rispetto al placebo (che riceveva solo vitamina D3 e calcio), sebbene i cambiamenti nei biomarcatori del turnover osseo siano risultati simili nei 2 gruppi [2].

In un altro RCT è stato valutato l›effetto della

somministrazione di K1 o MK-4 in aggiunta a bifosfonati, calcio e vitamina D (quest›ultima combinazione considerata come placebo) in donne con osteoporosi in postmenopausa con stato subottimale di vitamina K [2], non evidenziando miglioramenti nella BMD o nei marcatori del turnover osseo.
Infine, in un altro RCT, 122 donne in postmenopausa sono state assegnate in modo randomizzato a quattro gruppi d'intervento [2]. Tre gruppi hanno consumato salmone di allevamento arricchito rispettivamente con: 1) alti livelli di vitamina D e K1, 2) alti livelli di vitamina D e bassi di K1, o 3) bassi livelli di vitamina D e alti di K1. Tutti e tre i gruppi ricevevano anche supplementazione di calcio. Il quarto gruppo ha ricevuto invece solo vitamina D e calcio. È stato è osservato un effetto positivo sui marcatori dell'osso in tutti i gruppi, senza tuttavia differenze significative nei diversi gruppi.

CONCLUSIONE

Le evidenze disponibili suggeriscono un potenziale effetto sinergico tra la vitamina D e la vitamina K nella protezione della salute scheletrica, mentre i dati sulla loro interazione nella prevenzione delle malattie cardiovascolari restano ancora limitati e contrastanti. Sebbene gli studi osservazionali abbiano suggerito un'associazione tra bassi livelli plasmatici di entrambe le vitamine a un aumentato rischio di fratture e mortalità, i risultati degli studi di intervento risultano meno consistenti. La supplementazione combinata di vitamina D_3 e vitamina K2 sembra favorire il miglioramento della densità minerale ossea, soprattutto nelle donne in postmenopausa, anche se l'effetto sui biomarcatori del metabolismo osseo non è sempre evidente. Inoltre, l'eterogeneità dei protocolli di studio, dei dosaggi utilizzati e delle popolazioni analizzate richiede ulteriori studi per chiarire gli effettivi benefici della supplementazione combinata e per identificare gli individui che potrebbero maggiormente beneficiarne.

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