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 Il ruolo della vitamina D
nella riabilitazione post
ictus: tra luci e ombre

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Maurizio Rossini

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Cari Lettori,

in questo numero torniamo a parlare di possibili effetti extra scheletrici della vitamina D, in ambiti tra l'altro completamente diversi: quello dermatologico e quello neurologico.

In due malattie infiammatorie cutanee, in particolare psoriasi e dermatite atopica, l'alterazione della barriera cutanea sembra giocare un ruolo importante nella loro patogenesi. L'Autore, partendo dall'osservazione che la psoriasi migliora con l'esposizione ai raggi solari e che la cute, irradiata dal sole, sintetizza vitamina D aveva precedentemente condotto delle indagini sulla psoriasi evidenziando che la vitamina D, oltre le sue note funzioni, gioca un ruolo sull'espressione di alcune delle proteine costituenti le *Tight junctions* (TJ), strutture fondamentali dell'"organo barriera". Anche la dermatite atopica migliora con l'esposizione ai raggi solari e l'esposizione a fonti artificiali di raggi UV è considerata tra le possibili terapie di questa dermatosi. Per spiegare questo fenomeno sono state avanzate varie ipotesi: azione immunomodulatoria dei raggi UV che inducono apoptosi delle cellule infiammatorie, inibiscono le cellule di Langerhans e modificano la produzione di citochine oppure azione diretta dei raggi UV che riducono la colonizzazione dello *Staphylococcus aureus*, ma si poteva considerare anche l'effetto dell'esposizione ai raggi solari sulla sintesi di vitamina D. In questo numero l'Autore ci sintetizza i risultati di un suo recente lavoro¹ che fornisce nuove evidenze sulla relazione tra polimorfismi del recettore della vitamina D, l'espressione delle proteine costituenti le TJ e alcune manifestazioni cliniche in pazienti adulti affetti da dermatite atopica.

È noto che la vitamina D è importante per il mantenimento della forza muscolare attraverso la sua azione sugli specifici recettori nel tessuto muscolare. I pazienti sottoposti a riabilitazione, specie in ambito neurologico e sia in regime di ricovero che ambulatoriale, sono una popolazione ad alto rischio incline a sviluppare un deficit di vitamina D e a manifestare le conseguenze di tale condizione. Nel secondo articolo di questo numero vengono presi in considerazione gli studi riguardanti l'efficacia della supplementazione con vitamina D in corso di riabilitazione dopo ictus cerebrale. L'Autore conclude che attualmente i risultati sono contraddittori ma che le ricerche disponibili presentano molte limitazioni, tra cui soprattutto, come spesso avvenuto anche in altri ambiti di studio, la ridotta dimensione del campione, l'insufficiente durata del periodo di osservazione o la mancata valutazione preliminare dello stato vitaminico per la quale non si può escludere che siano stati inclusi pazienti non carenti. L'articolo, riassumendo i metodi indagati e i risultati sino a ora disponibili, fornisce informazioni utili per la pianificazione della supplementazione nel percorso riabilitativo di pazienti con ictus ischemico, anche se sono necessarie ulteriori ricerche per l'implementazione di queste conoscenze nella pratica clinica.

Nel recente rapporto OsMed relativo all'anno 2023 dell'Agenzia Italiana del Farmaco (AIFA)², nonostante la contrazione del consumo (DDD/1000 abitanti/die, Fig. 1)) e della spesa di circa il 15% rispetto all'anno precedente, la spesa a carico del Servizio Sani-

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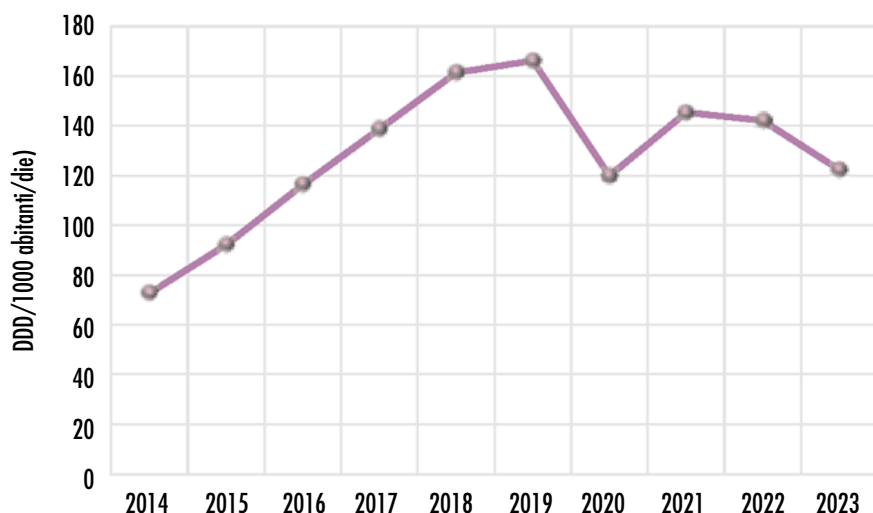


FIGURA 1.

Andamento temporale 2014-2023 del consumo (DDD/1000 abitanti/die) di vitamina D e analoghi (da AIFA, 2023, mod.)².

tario Nazionale per la vitamina D risulta di circa 200 milioni di euro/anno. Vi si afferma che i dati "confermano l'utilizzo di colecalciferolo e metaboliti per indicazioni extra-scheletriche per le quali gli RCT non hanno fornito prove di efficacia". Vi si afferma inoltre che "la ricca letteratura

riguardante l'utilizzo della vitamina D nel COVID-19 non ha dimostrato alcun beneficio". Per entrambe queste affermazioni, come si può notare dalla selezione bibliografica della nostra rivista, mi pare che la letteratura in merito sia in realtà perlomeno contraddittoria. Nello stesso rapporto vi in-

vito a osservare la curva nel consumo di vitamina D post nota 96 nel 2020, primo anno del COVID-19, il recupero negli anni successivi 2021 e 2022 e il successivo calo nell'anno post-COVID 2023 (Fig. 1). Nel citato rapporto OsMed è riportato inoltre che la vitamina D risulta al terzo posto tra le categorie terapeutiche di classe A acquistate privatamente dal cittadino con una spesa ulteriore pari a 76 milioni di euro (26% sul totale della spesa), in aumento rispetto all'anno precedente.

Cosa ne pensate?

Buona lettura... e Buon Anno

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Con il termine "organo barriera" intendiamo l'insieme degli epitelii dell'organismo, dalla cui integrità dipende la nostra sopravvivenza. Numerosi componenti contribuiscono alla costituzione della barriera. Infatti, si riconosce una barriera chimica, immunologica, microbica e una fisica. Quest'ultima a livello della cute è decisamente più complessa rispetto a quella degli altri epitelii ed è regolata da un ben definito insieme di molecole coinvolte nel metabolismo della filaggrina, nella formazione dell'involucro corneo, nella sintesi delle lamelle lipidiche intercellulari, nell'organizzazione dei corneodesmosomi, nella desquamazione e nella formazione delle *tight junctions* (TJ), che riducono gli spazi intercellulari tra le cellule epiteliali fino alla loro scomparsa. In particolare, proprio lo strato corneo e le TJ, presenti in esso soprattutto nello strato compatto¹, sono responsabili della permeabilità^{2,5}, che negli altri epitelii è garantita dal sistema delle TJ. Inoltre, recenti indagini hanno dimostrato che l'inibizione parziale o totale delle proteine costituenti le TJ modifica la permeabilità epiteliale intervenendo nel metabolismo della filaggrina e dei lipidi con anomala formazione dello strato corneo^{1,2}.

In due malattie infiammatorie cutanee, in particolare psoriasi e dermatite atopica, l'alterazione della barriera sembra giocare un ruolo importante nella loro patogenesi.

Infatti, una serie di indagini da noi condotte sulla psoriasi ha evidenziato che la vitamina D, oltre le sue note funzioni, gioca un ruolo sull'espressione di alcune delle proteine costituenti le TJ. Partendo dall'osservazione che la psoriasi migliora con l'esposizione ai raggi solari e che la cute, irradiata dal sole, sintetizza vitamina D, abbiamo indagato il ruolo di questa vitamina. In particolare, abbiamo dimostrato che nei pazienti affetti da psoriasi la vitamina D è ridotta e correla inversamente con il PASI (*Psoriasis Area Severity Index*)⁶ e con il livello ematico dei linfociti T reg⁷; i VDR (*Vitamin D Receptor*) nelle lesioni psoriasiche sono ridotti del 50% rispetto alla cute sana; i VDR presentano polimorfismi che correlano con la clinica⁸; infine, la riduzione dei VDR si associa alla ridotta espressione di alcune

proteine costituenti le TJ, in particolare claudina-1, occludina e zonulina-1⁹. In conclusione, nella psoriasi risulta una correlazione tra il deficit di vitamina D e l'alterazione delle TJ e, quindi, un'alterata permeabilità della cute. In base a questi risultati abbiamo rivolto la nostra attenzione alla dermatite atopica (DA). La dermatite atopica è la manifestazione cutanea dell'atopia, tratto ereditario poligenico ad alta prevalenza che può interessare altri epitelii (rinite allergica, asma, ecc.) in cui, come già detto, l'integrità della barriera è garantita anche dalle TJ. È più frequente in età pediatrica con una prevalenza che oscilla tra il 10 e il 30% e decisamente meno frequente nell'adulto (5-7%). È una patologia infiammatoria caratterizzata da alterazione della permeabilità della barriera per il deficit di filaggrina, il cui gene risulta mutato nel 30-50% dei pazienti. Nella DA è predominante una risposta immunologica di tipo Th2 con aumento di alcune citochine, come IL-4, IL-5 e IL-13, che svolgono un ruolo essenziale nel reclutamento degli eosinofili e nella sintesi di IgE. A tal riguardo si deve ricordare che si riconoscono due forme di DA: quella estrinseca, decisamente più frequente e caratterizzata da aumento delle IgE circolanti, e la forma intrinseca, circa il 20% dei casi, con valori di IgE nella norma. Infine, si deve ricordare che la DA è gravata da alcune comorbidià, come la psoriasi¹⁰.

Inoltre, anche la DA migliora con l'esposizione ai raggi solari¹¹. Infatti, l'esposizione a fonti artificiali di raggi UV è considerata tra le possibili terapie di questa dermatite¹². Il lavoro di Napolitano et al.¹³, in particolare, evidenzia che negli adulti affetti da DA ó su 10 migliorano dopo esposizione ai raggi UV. Per spiegare questo fenomeno sono state avanzate varie ipotesi: azione immunomodulatoria dei raggi UV che inducono apoptosi delle cellule infiammatorie, inibiscono le cellule di Langerhans e modificano la produzione di citochine¹⁴; azione diretta dei raggi UV che riducono la colonizzazione dello *Staphylococcus aureus*, ma si deve considerare anche l'effetto dell'esposizione ai raggi solari sulla sintesi di vitamina D. Inoltre, alcuni studi hanno dimostrato una correlazione tra

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Conflitto di interessi

L'Autore dichiara nessun conflitto di interessi.

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severità della DA e la concentrazione ematica di vitamina D senza riuscire a evidenziare un legame tra queste variabili. Inoltre, differenti trial clinici sulla supplementazione di vitamina D in bambini hanno dato risultati contraddittori.

Pertanto, al fine di chiarire un eventuale ruolo della vitamina D abbiamo arruolato 43 adulti affetti da DA moderata o severa non in terapia sistemica da almeno tre mesi, ai quali sono stati effettuati, dopo la raccolta di dati anamnestici, prelievi ematici, biopsie della cute in zona lesionale (LS) e non (NLS). Inoltre, per ognuno di essi è stato valutato l'indice di severità EASI (*Eczema Area Severity Index*) e tutti hanno eseguito *prick tests* (STP) (Tab. I). Sono state eseguite valutazioni con PCR (*Polymerase Chain Reaction*) per lo studio di alcuni polimorfismi del VDR (Tab. II) su sangue, ed esami istochimici per studiare l'espressione dei VDR, dell'occludina, della claudina e della ZO-1 sia su NLS che su LS e la relativa espressione genica. La regressione logistica multivariata è stata utilizzata per esplorare l'associazione tra vari polimorfismi del VDR (variabili dipendenti) o proteine TJ (variabili dipendenti) e caratteristiche cliniche e patologiche dei pazienti con DA (variabili indipendenti). In questo articolo riporteremo la parte dei risultati relativi ai polimorfismi del VDR¹⁵ perché non tutti sono stati ancora oggetto di pubblicazione. I risultati di questo studio trasversale identificano un legame tra i polimorfismi del VDR, l'espressione delle proteine VDR e TJ e le caratteristiche cliniche in una coorte di pazienti con DA. In particolare, abbiamo osservato un OR più basso per l'insorgenza di DA in individui con il polimorfismo del VDR eterozigote A1012G, mentre i polimorfismi del VDR omozigoti cumulativi ≥ 2 (Tab. III) erano collegati a una maggiore probabilità di sviluppare reazioni allergiche.

Tra le proteine costituenti le TJ, la claudina e ZO-1 erano quelle maggiormente espresse. L'espressione della proteina VDR è stata associata alla presenza di lesioni generalizzate di DA, mentre la claudina ha dimostrato un'associazione significativa con un SPT positivo. Mentre studi precedenti hanno indagato le differenze nella frequenza del polimorfismo del VDR e nei livelli di espressione di VDR e TJ tra pazienti con DA e controlli sani, lo scopo del nostro studio è stato quello di caratterizzare le interrelazioni tra SNP (*single-nucleotide polymorphism*), VDR e l'espressione delle proteine TJ nelle biopsie cutanee di questa coorte di pazienti affetti

TABELLA I.
Caratteristiche cliniche e di laboratorio.

Sesso, n (%)	
• Maschi	17 (39,5)
• Femmine	26 (60,5)
Età	
• < 60 anni	36 (83,7)
• ≥ 60 anni	7 (16,3)
Età di insorgenza della malattia n (%)	
• Infanzia/adolescenza	28 (65,1)
• Adulti	15 (34,9)
Body Mass Index (BMI)	
• < 30 kg/m ²	35 (81,4)
• ≥ 30 kg/m ²	8 (18,6)
Localizzazione n (%)	
• Flessure	9 (20,9)
• Generalizzato	18 (41,9)
• Testa/collo	14 (32,6)
• Mani	2 (4,7)
EASI score	
• Mild (EASI < 16)	5 (11,6)
• Moderate-to-severe (EASI ≥ 16 o < 16 con coinvolgimento del viso e delle mani)	38 (88,4)
Asma, n (%)	
• Presente	8 (18,6)
• Assente	35 (81,4)
Rinocongiuntivite, n (%)	
• Presente	14 (32,6)
• Assente	29 (67,4)
Skin prick test, n (%)	
• Positivo	20 (46,5)
• Negativo	23 (53,5)
IgE totali (IU/ml), n (%)	
• < 100 IU/ml	18 (41,9)
• ≥ 100 IU/ml	25 (58,1)
25(OH)D	
• ≥ 30 ng/ml	15 (34,9)
• < 30 ng/ml	28 (65,1)

da DA e associarle alle loro caratteristiche cliniche. Ad oggi, infatti, nessun lavoro ha correlato i polimorfismi del VDR con le caratteristiche cliniche della dermatosi. I nostri risultati suggeriscono che i polimorfismi del VDR possono effettivamente essere associati alle caratteristiche cliniche della DA. Abbiamo scoperto che gli individui con stato eterozigote A1012G avevano probabilità significativamente più basse di sviluppare la DA precocemente (OR: 0,046, IC 95%: 0,004-0,510, $p = 0,012$), suggerendo un potenziale effetto protettivo di questo polimorfismo sull'insorgenza della malattia. Del resto, Richetta et al. hanno riportato un minor rischio di sviluppare psoriasi quando questo polimorfismo, sia in eterozigosi che in omozigosi, era presente rispetto al genotipo *wild-type*¹⁶.

Abbiamo anche osservato che la presenza di Apal in omozigosi mostrava una tendenza a probabilità più elevate (OR di 5,99) di sviluppare la malattia precocemente, indicando un potenziale rischio associato a questo polimorfismo. È interessante notare che Apal (rs7975232) è associato a livelli più bassi di espressione e ridotta stabilità del mRNA VDR¹⁷, e bassi livelli di vitamina D sono associati alla DA. Inoltre, Heine et al.¹⁸ hanno dimostrato un'associazione tra il polimorfismo Apal e le forme gravi di DA.

I nostri risultati hanno mostrato un'associazione statisticamente significativa tra la presenza di polimorfismi cumulativi omozigoti > 2 del VDR e un SPT positivo (10/20, 50%) rispetto a SPT negativo (1/23, 4,3%; $p = 0,0003$). A sostegno di questa osservazione, è stato riportato che un basso livello di vitamina D è associato a livelli più elevati di IgE negli atopici^{19,20}.

I polimorfismi del VDR sono stati anche correlati con l'espressione del recettore nelle biopsie cutanee lesionali (LS) della nostra coorte di pazienti con DA. Abbiamo osservato un'associazione positiva per il polimorfismo Apal quando si trova nello stato eterozigote con l'espressione di VDR. Questo risultato è in contrasto con altri che riportano che i polimorfismi in Apal sono associati a una ridotta stabilità del RNA messaggero e a livelli più bassi di espressione^{21,22}. Tuttavia, un altro studio su bambini turchi ha descritto un legame significativo tra Apal in eterozigosi e rischio di asma²³. Da notare che mancano studi funzionali sull'associazione tra i polimorfismi Apal e l'espressione della proteina VDR.

TABELLA II.
Polimorfismi target.

Gene	Polimorfismo	SNP ID	Posizione sul cromosoma 12 (assemblaggio hg38)	Localizzazione genetica (NM 000376)	Posizione ATG in VDR (NM_000376)
VDR	A-1012G	rs4516045	47906043	Promotore VDR	c.-1172A>G
VDR	FokI	rs2228570 rs107365810	47879112	Esone 3 (codifica)	c.2T>C
VDR	BsmI	rs1544410	47846052	Introne 9	c.1024+283G>T
VDR	Apal	rs7975232	47845054	Introne 9	c.1025-49G>T
VDR	TaqI	rs731236	47844974	Esone 10 (codifica)	c.1056T>C

TABELLA III.
Frequenza di genotipi specifici per diversi polimorfismi a singolo nucleotide del VDR nei pazienti con AD.

Polimorfismo	Numero di casi (%)
rs4516035 A1012G	
Genotipo	N (%)
AA (tipo selvatico)	15 (34,9)
AG (eterozigote)	23 (53,5)
GG (omozigote)	5 (11,6)
rs2228570 FokI	
Genotipo	N (%)
TT (tipo selvaggio)	5 (11,6)
TC (eterozigote)	17 (39,5)
CC (omozigote)	21 (48,8)
rs1544410 BsmI	
Genotipo	N (%)
GG (tipo selvatico)	18 (41,9)
GT (eterozigote)	20 (46,5)
TT (omozigote)	5 (11,6)
rs7975232 Apal	
Genotipo	N (%)
GG (tipo selvatico)	10 (23,3)
GT (eterozigote)	19 (44,2)
TT (omozigote)	14 (32,6)
rs731236 TaqI	
Genotipo	N (%)
TT (tipo selvaggio)	19 (44,2)
TC (eterozigote)	19 (44,2)
CC (omozigote)	5 (11,6)

Per quanto riguarda le indagini sulle proteine costituenti le TJ, abbiamo osservato che la claudina e la ZO-1 erano le più espresse nelle biopsie cutanee delle lesioni di pazienti con DA, mentre il VDR e l'occludina erano le più basse. Nessuno studio ha riportato i livelli di espressione relativi a queste proteine. In letteratura sono presenti solo studi caso-controllo. Inoltre, il nostro lavoro ha rivelato una correlazione negativa tra la vitamina D e l'espressione di ZO-1 ($\rho = -0,43$; $p = 0,0058$). In uno studio di Yuki et al.²⁴, i livelli di proteina TJ sono stati quantificati nei tessuti epidermici di tre pazienti con DA e tre soggetti normali. Le biopsie cutanee sono state prelevate da siti non lesionali di DA (NLS) e siti cutanei lesionati (LS). Nel NLS di DA, la claudina-1, l'occludina e le proteine ZO-1, hanno rilevato condizioni simili a quelle della pelle normale. Tuttavia, nei LS, le intensità del segnale di claudina-1 e ZO-1 erano marcatamente ridotte. Questi dati sembrano essere in contrasto con i nostri risultati, anche se sono stati esaminati solo tre campioni di pazienti e la nostra analisi è stata limitata ai LS.

Meckel et al.²⁵ hanno osservato una correlazione inversa tra le concentrazioni sieriche di 25(OH)D e l'infiammazione della mucosa in 230 soggetti con colite ulcerosa, insieme a un'alterazione dell'espressione proteica di VDR, occludina e diminuzione dell'espressione proteica di ZO-1. Questi risultati sono in linea con i nostri risultati. Abbiamo anche trovato un'associazione positiva tra l'espressione di ZO-1 e il BMI (*body mass index*) ≥ 30 . La zonulina è considerata l'unico mediatore fisiologico noto per regolare la permeabilità intestinale in modo reversibile modulando le TJ intercellulari e l'obesità ed è stata associata a un aumento della permeabilità e dell'assorbimento intestinale²⁶.

Abbiamo anche osservato un livello più elevato di espressione di claudina nei pazienti

che presentavano SPT positivo. De Benedetto et al.²⁷ hanno riportato una ridotta espressione di claudina-1 nei NLS di DA, mentre Gruber et al.²⁸ e Yuki et al.²⁴ hanno dimostrato che la claudina-1 era sovraregolata nel NLS di soggetti con DA. Nel complesso, questi risultati suggeriscono un ruolo complesso e dipendente dal contesto della claudina-1 nella DA, influenzato da fattori genetici e considerazioni ambientali.

In conclusione, nel nostro studio su pazienti italiani con DA abbiamo identificato associazioni significative tra polimorfismi del VDR, espressione di VDR, proteine TJ e caratteristiche cliniche della DA. Questi risultati forniscono importanti informazioni sulla complessa interazione tra fattori genetici, carenza di vitamina D e proteine TJ nella patologia della DA, sottolineando la natura complessa della fisiopatologia di questa dermatosi e l'identificazione di potenziali marcatori per la diagnosi precoce della DA.

Infine, malgrado alcune analogie con la psoriasi da noi evidenziate, come il ruolo protettivo di A1012G eterozigote, la ridotta espressione del VDR, ecc., emergono differenze che, se correttamente interpretate, potrebbero ulteriormente chiarire il ruolo della vitamina D nei complessi meccanismi che regolano la permeabilità degli epitelii.

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Il ruolo della vitamina D nella riabilitazione post ictus: tra luci e ombre

VITAMIN D

UpDates

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Nonostante i progressi della medicina del XX secolo, la carenza di vitamina D è ancora una pandemia ¹: circa 1 miliardo di persone in tutto il mondo soffrono di carenza di vitamina D. Classicamente, la carenza di vitamina D è associata al rachitismo nei bambini mentre, negli adulti, la carenza di vitamina D si manifesta come osteomalacia, una condizione dolorosa di mineralizzazione scheletrica difettosa, o come osteoporosi che causa fragilità scheletrica e fratture ^{1,2}. La vitamina D svolge anche un ruolo importante nella regolazione della proliferazione e della differenziazione in una varietà di cellule e tessuti non associati al metabolismo del calcio ¹⁻⁴. I recettori per la vitamina D (VDR) sono stati trovati in una varietà di tessuti e cellule corporee, tra cui cervello, cuore, seno, prostata, gonadi, colon, pancreas, monociti e linfociti T e B attivati ³⁻⁶. La vitamina D è importante per il mantenimento della forza muscolare attraverso la sua azione sui VDR nel tessuto muscolare ⁷.

I pazienti sottoposti a riabilitazione, sia in regime di ricovero che ambulatoriale, sono una popolazione ad alto rischio incline a sviluppare un deficit di vitamina D e a manifestare le conseguenze di tale condizione ^{8,9}. I risultati funzionali di questi pazienti dipenderanno dalla diagnosi corretta e dal trattamento appropriato del deficit vitaminico.

Al fine di valutare l'efficacia dell'integrazione di vitamina D nei pazienti sottoposti a programmi riabilitativi, abbiamo preso in considerazione gli studi riguardanti la riabilitazione dopo ictus cerebrale. È stata studiata l'efficacia della riabilitazione dopo l'integrazione di vitamina D nei pazienti con ictus, sono stati verificati i risultati delle ricerche, l'efficacia dell'integrazione, il tipo, la forma e la quantità di vitamina D somministrata. Sono stati confrontati i criteri per l'inclusione negli studi, la durata e le scale utilizzate (Fig. 1).

L'EFFETTO DELL'INTEGRAZIONE DI VITAMINA D SULLA RIABILITAZIONE POST-ICTUS

La carenza di vitamina D può essere associata a un rischio aumentato di insorgenza, gravità e prognosi futura dell'ictus. Influisce anche sul declino cognitivo e sulle prestazioni fisiche, che si osservano nei pazienti con ictus che hanno esiti peggiori nella riabilitazione neurologica ¹⁰.

A causa delle numerose limitazioni dei test della vitamina D nel siero e del metodo e della quantità della sua somministrazione, vi è poca certezza sulla possibilità di migliorare gli esiti della riabilitazione nei sopravvissuti all'ictus in ogni caso ¹¹. Molti studi hanno presentato risultati ottimisti e hanno dimostrato che l'integrazione di vitamina D dopo l'ictus ha migliorato i livelli di qualità della vita e ha facilitato il ritorno alla vita normale dei pazienti.

Studi su piccoli campioni hanno mostrato risultati migliori per i pazienti che hanno assunto un'integrazione con vitamina D dopo l'ictus ^{12,13}.

Due piccoli studi in aperto condotti da Gupta et al. in India hanno dimostrato che l'iniezione intramuscolare di colecalciferolo ad alto dosaggio (600.000 UI) migliorava i punteggi su varie scale di ictus e aumentava la sopravvivenza dei pazienti post-ictus. Uno studio randomizzato, controllato, in aperto ha incluso 73 pazienti con ictus ischemico acuto. Ogni paziente è stato sottoposto a test per i livelli sierici di 25(OH)D prima di entrare nello studio. Un totale di 53 pazienti con 25(OH)D basale < 75 nmol/L sono stati assegnati in modo casuale ai due studi. Il primo gruppo ha ricevuto un'iniezione intramuscolare di 600.000 UI di colecalciferolo una sola volta e colecalciferolo orale a una dose di 60.000 UI una volta al mese con

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L'Autore dichiara nessun conflitto di interessi.

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Benefici di livelli adeguati di vitamina D



Sempre più studi suggeriscono che mantenere un livello normale di vitamina D migliora la funzione cardio- e cerebrovascolare. Inoltre, la vitamina D influenza la progressione, lo sviluppo e la prognosi dell'ictus.

ICTUS EMORRAGICO

- Non ci sono prove scientifiche che bassi livelli di vitamina D influenzino il rischio di ictus emorragico.
- I pazienti con ictus emorragico spesso soffrono di carenza di vitamina D e l'integrazione di vitamina D riduce gli effetti dannosi della malattia.

ICTUS ISCHEMICO

- Studi scientifici suggeriscono che bassi livelli di vitamina D possono essere associati con un aumentato rischio di ictus ischemico. $1,25(\text{OH})_2\text{D}_3$ può indurre l'espressione dell'IGF-, che contribuisce al controllo e alla protezione delle cellule nervose.
- L'IGF-1 ha dimostrato di avere proprietà anticoagulanti mediante l'attivazione del plasminogeno.

FIGURA 1.

Ruolo della vitamina D nell'ictus ischemico ed emorragico.

un grammo di calcio elementare al giorno insieme alla consueta cura post-ictus. Il secondo gruppo di controllo ha ricevuto solo le normali cure ospedaliere. I livelli sierici di vitamina D e iPTH sono stati testati a 3 e 6 mesi dallo studio, e il follow-up stesso è durato 6 mesi. Nello studio è stata utilizzata la scala di Rankin modificata (mRS) e sono stati ottenuti punteggi elevati dopo 6 mesi. Questo risultato conferma l'effetto benefico dell'integrazione di vitamina D nei pazienti post-ictus¹⁰.

Uno studio randomizzato, controllato e non in cieco di Narasimhan e Balasubramanian ha confrontato i risultati nei pazienti con ictus ischemico che assumevano integrazione di vitamina D con quelli senza integrazione. Lo studio ha utilizzato la *Scandinavian Stroke Scale* (SSS), una scala affidabile e ampiamente utilizzata nei pazienti con malattia cerebrovascolare ischemica. Il primo gruppo di pazienti ha ricevuto una dose di 60.000 UI di colecalciferolo somministrata tramite iniezione intramuscolare; il secondo gruppo non ha ricevuto vitamina D. I pazienti di entrambi i gruppi sono stati esaminati all'inizio dello studio e dopo tre mesi. I risultati indicavano un significativo miglioramento nei risultati tra i pazienti post-ictus che hanno assunto integratori di vitamina D¹³. L'integrazione di vitamina D nei pazienti post-

ictus ha avuto un effetto positivo sui risultati della riabilitazione.

Un piccolo studio giapponese di Momosaki et al. su 100 pazienti non ha mostrato alcun miglioramento nei pazienti con ictus trattati con vitamina D. Dopo la randomizzazione, ciascuno dei 100 soggetti ha assunto una forma orale di vitamina D₃ a una dose di 2000 UI/giorno o un placebo. Ogni paziente ha ricevuto 450 capsule, ciascuna contenente 400 UI di vitamina D₃, il che significa che i pazienti hanno assunto le capsule cinque volte al giorno. La vitamina D₃ è stata sempre assunta alla stessa ora, dopo pranzo. Lo studio con riabilitazione e integrazione di vitamina D è durato 8 settimane. Durante il ricovero del paziente e 8 settimane dopo la dimissione, il personale riabilitativo ha valutato l'indice di Barthel di ogni paziente, lo stadio di Brunnstrom (braccio, mano e gamba sul lato interessato), la forza di prensione della mano (bilateralmente) e la circonferenza del polpaccio (bilateralmente). Un totale di 97 pazienti ha completato lo studio giapponese. Si è riscontrato un miglioramento nei punteggi dell'indice di Barthel all'ottava settimana di riabilitazione come endpoint primario; sono stati osservati outcome secondari nella prestazione dell'indice di Barthel, nella forza di compressione della mano e nella circon-

ferenza del polpaccio. Non sono state riscontrate differenze negli altri endpoint secondari tra i gruppi. Nessuna di queste differenze era statisticamente significativa, il che indica che l'integrazione giornaliera con 2000 UI di vitamina D₃ nei pazienti dopo un ictus acuto era inefficace e non forniva i benefici previsti. Un potenziale errore era dovuto al fatto che i livelli sierici di 25-idrossivitamina D non erano considerati come criterio di inclusione dei pazienti per lo studio; i ricercatori hanno giustificato la scelta con l'ipotesi che quasi tutti i pazienti anziani sottoposti a riabilitazione hanno una carenza di vitamina D e, quindi, lo studio sulla carenza in sé non è stato incluso nei pazienti che hanno partecipato allo studio^{14,15}. Altri limiti evidenziati dagli autori includono la piccola numerosità del gruppo di studio, la breve durata dell'integrazione e dell'intero studio, rendendo impossibile determinare con precisione il ruolo a lungo termine e sporadico dell'integrazione di vitamina D nei pazienti con ictus. Un'altra limitazione estremamente importante è stata il confronto di un solo campione di vitamina D con un campione di placebo¹¹.

Lo studio del 2021 di Torrisi et al. ha evidenziato miglioramenti nei pazienti con ictus sottoposti a neuroriabilitazione intensiva e integrazione di vitamina D, nonché

dopo la neuroriabilitazione stessa. È stato condotto uno studio randomizzato, in doppio cieco, parallelo, monocentrico, della durata di 12 settimane, su 40 pazienti dopo ictus ischemico ed emorragico. I partecipanti sono stati assegnati in modo casuale, in una proporzione 1:1, tra due gruppi paralleli: il gruppo sperimentale in cui sono state somministrate per via orale 2000 UI/giorno di colecalciferolo e il gruppo di controllo in cui i pazienti non hanno ricevuto alcuna integrazione di vitamina D. Tutti i pazienti arruolati nello studio hanno eseguito una neuroriabilitazione intensiva consistente in training cognitivo e motorio. Tutti i pazienti hanno completato il ciclo riabilitativo. Tutti i partecipanti allo studio sono stati sottoposti a screening in due fasi, all'inizio e alla fine della riabilitazione. I pazienti sono stati valutati utilizzando la scala GSE, la scala di valutazione della depressione *Montgomery Aasberg* (MADRS) e la *Functional Independence Measure* (FIM). Sono stati monitorati i livelli sierici di vitamina D e calcio. Sono stati osservati miglioramenti significativi nei pazienti del gruppo sperimentale e del gruppo di controllo sia nelle prestazioni psicologiche che funzionali. I pazienti che assumevano integratori di vitamina D hanno mostrato una maggiore variabilità rispetto ai pazienti che non li assumevano. I risultati hanno indicato che la neuroriabilitazione intensiva aveva un effetto benefico sul recupero funzionale dopo un ictus; inoltre, è stato dimostrato un netto miglioramento nel gruppo sperimentale, suggerendo che anche l'integrazione di vitamina D può svolgere un ruolo positivo¹⁶. Tuttavia, l'integrazione di vitamina D nei pazienti con ictus non ha migliorato i risultati in maniera statisticamente significativa.

Secondo Utkan Karasu e Kaymak Karataş, l'integrazione di vitamina D può aumentare l'efficacia della riabilitazione nei pazienti post-ictus. Ciò è particolarmente importante nei pazienti che si trovano nei primi tre mesi dopo un ictus e che saranno sottoposti a riabilitazione neurologica per la prima volta. Lo studio retrospettivo ha incluso 76 pazienti con ictus. I pazienti nello studio hanno avuto un ictus (ischemico/emorragico) per la prima volta nella loro vita. Sono stati utilizzati il *Brunnstrom Recovery Stage* (BRS) per l'arto inferiore e la scala *Functional Assessment of Movement* (FAC) per misurare i risultati in termini di funzione motoria. I livelli sierici di 25(OH)D misu-

rati in ng/mg sono stati esaminati durante la prima settimana dello studio. I pazienti sono stati divisi in due gruppi: quelli sottoposti a integrazione di vitamina D durante la riabilitazione e quelli che non hanno ricevuto tale integrazione. Per 4-12 settimane, i pazienti hanno assunto vitamina D orale (50.000 UI) durante la riabilitazione e la dose totale di vitamina D variava da 200.000 a 600.000 UI. I livelli di vitamina D prima della riabilitazione e i punteggi BRS e FAC, nonché i cambiamenti nei punteggi prima e dopo il processo di riabilitazione, nei pazienti con ictus sono stati registrati e confrontati sia nel gruppo di controllo che in quello di studio. Dopo il periodo di riabilitazione è stato riscontrato un cambiamento positivo e statisticamente significativo nei punteggi FAC e BRS nel gruppo che ha ricevuto vitamina D. Inoltre, è stato confrontato l'effetto dell'integrazione di vitamina D sui punteggi FAC e BRS nei pazienti che hanno iniziato il trattamento riabilitativo entro i primi 3 mesi dopo l'ictus. È stato riscontrato che il cambiamento nei punteggi FAC e BRS era statisticamente significativo nei pazienti trattati con vitamina D. Questi risultati hanno dimostrato l'effetto benefico dell'assunzione di vitamina D nei pazienti durante il percorso di riabilitazione dopo l'ictus. L'integrazione di vitamina D durante la riabilitazione post-ictus può avere un effetto positivo sulla mobilità degli arti inferiori e sulla funzione motoria secondo Utkan Karasu e Kaymak Karataş¹⁷. In questo studio, l'integrazione di vitamina D nei pazienti con ictus ha avuto un effetto positivo e i pazienti hanno avuto risultati migliori nella riabilitazione.

Sari et al.¹² hanno studiato gli effetti dell'integrazione di vitamina D sui risultati della riabilitazione e sull'equilibrio nei pazienti con emiplegia dovuta a ictus ischemico. Sono stati inclusi nello studio settantadue pazienti con ictus ischemico con bassi livelli ematici di vitamina D ricoverati in ospedale per la riabilitazione dell'emiplegia. È stata fatta una suddivisione in due gruppi: il gruppo A ha ricevuto vitamina D tramite iniezione intramuscolare (300.000 UI di vitamina D); il gruppo B ha ricevuto soluzione salina tramite iniezione intramuscolare. I pazienti sono stati esaminati all'inizio del processo di studio e al terzo mese. Per esaminare gli effetti sono stati utilizzati la scala di Brunnstrom, l'indice di Barthel modificato, la scala di equilibrio di Berg e la scala

di deambulazione funzionale (FAS). Entro la fine del terzo mese, è stata riscontrata una differenza significativa tra i due gruppi nell'indice di Barthel modificato e nella scala di equilibrio di Berg. Non è stata osservata alcuna modifica statisticamente significativa nei punteggi della scala di Brunnstrom o della scala di deambulazione funzionale (FAS). Nei pazienti dopo ictus ischemico, l'integrazione di vitamina D (300.000 UI) non ha influenzato in modo significativo il recupero motorio e la mobilità. Lo studio ha dimostrato che l'integrazione di vitamina D ha accelerato il recupero e aumentato i livelli di attività nei pazienti. Il risultato conferma la validità dell'ipotesi che sarebbe appropriato estendere gli studi di follow-up con più pazienti dopo ictus¹². L'integrazione di vitamina D nei pazienti post-ictus non ha chiaramente migliorato i risultati.

Un recente studio è stato condotto in Polonia su 94 pazienti sottoposti a trattamento riabilitativo dopo un ictus ischemico. I soggetti inclusi nello studio (n = 80) sono stati sottoposti a un periodo di riabilitazione di 6 settimane utilizzando la facilitazione neuromuscolare propriocettiva (PNF, 60 minuti al giorno), la terapia dello specchio (MT, 30 minuti al giorno) e la terapia occupazionale (OT, 45 minuti al giorno). L'indice di Barthel (BI) e la scala di Rankin modificata (mRS) sono stati utilizzati per le valutazioni funzionali. Sono stati condotti esami di laboratorio per i livelli sierici di vitamina D e dell'*Insulin-like Growth Factor-1* (IGF-1). C'è stato un aumento significativo nei punteggi BI (differenza mediana = 2,0 punti [pz]; P < 0,001) e nei livelli di IGF (differenza mediana = 124,6 ng/ml; P < 0,001) dopo la riabilitazione. C'è stata una diminuzione significativa nei punteggi mRS (differenza mediana = 7,0 pz; P < 0,001), ma non c'è stata alcuna differenza significativa nei livelli di vitamina D (P = 0,40). È stato dimostrato l'effetto dell'età (B = -0,01, P = 0,04) e del livello di vitamina D nel siero (B = -0,02, P = 0,01) sul punteggio BI. È stato osservato l'effetto dei risultati dell'indice di massa corporea (BMI) (B = -0,07, P = 0,02) sul punteggio mRS. Livelli di vitamina D nel siero più bassi ed età più avanzata possono essere associati a peggiori risultati funzionali nei pazienti con primo ictus ischemico¹⁸.

CONCLUSIONI

C'è una mancanza di coerenza nei risultati ottenuti tra gli studi che hanno indagato la correlazione tra integrazione con vitamina D nei pazienti con ictus e miglioramento dei risultati della riabilitazione. Le ricerche presentano molte limitazioni. A volte, i livelli sierici di 25-idrossivitamina D non sono stati misurati nei pazienti inclusi nello studio, il che significa che gli autori hanno selezionato pazienti con livelli di vitamina D alti o normali piuttosto che con carenza. Un'altra grande limitazione è la dimensione del campione, che è spesso troppo piccola. Un numero maggiore di partecipanti potrebbe aver determinato risultati differenti, inoltre, gli autori hanno preso in considerazione modelli differenti, diversi regimi di somministrazione, quantità di vitamina D o persino tempi di trattamento più lunghi per i pazienti. Spesso il breve periodo di studio non ha permesso di esaminare gli effetti a lungo termine dell'integrazione.

Poiché l'ictus è la principale causa di disabilità e gli anziani hanno spesso gravi carenze di vitamina D, gli studi che valutano l'efficacia dell'integrazione di vitamina D dovrebbero essere estesi. I risultati presentati sopra includono molte informazioni rilevanti per la pianificazione della riabilitazione nei pazienti con ictus ischemico nel periodo di recupero e compensazione, ma sono necessarie ulteriori ricerche per l'implementazione di queste conoscenze nella pratica clinica.

Ci sono sempre più prove che la vitamina D ha un impatto positivo sulla prevenzione delle malattie cardiovascolari e contribuisce a migliori risultati riabilitativi nei pazienti con ictus. Numerosi studi che testano l'efficacia dell'integrazione di vitamina D nei pazienti post-ictus si scontrano con le molte limitazioni nella metodologia che inficiano i risultati. A causa del basso numero di studi e di altre limitazioni, non è univoco che l'integrazione di vitamina D nei pazienti con ictus abbia sempre un effetto positivo sul miglioramento della riabilitazione. Considerando che l'ictus è la prima causa di disabilità e che gli anziani hanno elevate carenze di vitamina D, è necessario espandere gli studi che testano l'efficacia dell'integrazione di vitamina D. È auspicabile che gli studi futuri

sull'integrazione di vitamina D in soggetti sottoposti a trattamento riabilitativo siano controllati e randomizzati, condotti con un ampio campione di oltre 1000 pazienti e con almeno 5 anni di follow-up.

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