VITAMIN D

UpDates Vol. 7 - N. 3 - 2024

Sito Web www.vitamind-journal.it

Editoriale

Carenza di vitamina D, fratture da stress e recupero post-traumatico

Livelli circolanti di vitamina D e rischio di insorgenza di diabete mellito tipo 2: c'è un legame

Selezione bibliografica

www.pacinimedicina.it

Edizione
Pacini Editore Srl
Via Gherardesca 1 • 56121 Pisa
Tel. 050 313011 • Fax 050 3130300
Info@pacinieditore.it - www.pacinieditore.it

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Stampa
Industrie Grafiche Pacini • Pisa

ISSN: 2611-2876 (online)

Registrazione presso il Tribunale di Pisa n. 2/18 del 23-2-2018
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EDITORIALE

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VITAMIN D
UpDates
2024;7(3):76-77

Cari Lettori
in questo numero trovate un aggiornamento su alcuni effetti scheletrici ed extra-scheletrici della vitamina D.
Come sapete le cosiddette fratture da stress sono causate da carichi ripetuti e stress meccanici che superano la capacità di riparazione del tessuto osseo e sono comuni in particolare tra atleti, militari e individui che praticano attività fisica intensa. Ebbene i pazienti che vi incorrono presentano frequentemente carenza di vitamina D ed è d'altra parte noto che livelli adeguati di vitamina D accelerano la formazione del callo osseo e migliorano la qualità della rigenerazione ossea. Ciò sembra da attribuirsi a un duplice ruolo della vitamina D: quello immunomodulante nella prima fase marcatamente infiammatoria della "fracture healing" e quello sulla mineralizzazione.
Nel secondo articolo trovate invece un importante aggiornamento sul possibile ruolo della vitamina D nel ridurre il rischio di insorgenza di diabete tipo 2. Il razionale c'è da tempo: la vitamina D ha recettori intranucleari anche nelle beta cellule pancreatiche e potrebbe svolgere pertanto un ruolo nell'omeostasi glucidica. Studi osservazionali hanno effettivamente documentato un'associazione tra ipovitaminosi D e la presenza di diabete tipo 2, ma gli studi di intervento con la supplementazione di vitamina D hanno sino a ora riportato risultati contrastanti sul controllo glicemico e sulla resistenza insulinica in soggetti con prediabete. Inoltre pochi erano sino a ora gli studi nella popolazione generale e sul possibile ruolo di varianti genetiche del recettore della vitamina D. Da qui l'importanza di un recente grande studio prospettico di coorte che ha osservato una significativa associazione tra livelli circolanti di 25(OH)D superiori a 75 nmol/L e rischio ridotto di sviluppare diabete tipo 2 rispetto ai soggetti con livelli di 25(OH)D minori di 25 nmol/L, indipendentemente dalla condizione di prediabete e specie in presenza di alcuni polimorfismi genetici. Ciò è stato considerato nelle nuove linee guida sulla vitamina D dell'*Endocrine Society* [1] che alla raccomandazione n. 10 suggerisce la supplementazione con vitamina D, in aggiunta alla correzione dello stile di vita, nei soggetti a elevato rischio di prediabete per ridurre il rischio di progressione a diabete tipo 2.
Le stesse nuove linee guida [1] raccomandano per la prima volta la supplementazione dei bambini e degli adolescenti fino a 18 anni non solo per prevenire il rachitismo ma anche per ridurre il rischio di infezioni del tratto respiratorio, riconoscendo un beneficio specifico extra-scheletrico alla vitamina D.
Un altro importante e originale riconoscimento di un beneficio extra-scheletrico da parte delle stesse linee guida [1] è rappresentato dalla sesta raccomandazione che consiglia la supplementazione con vitamina D di tutti i soggetti con oltre 75 anni di età vista la possibilità di ridurre il rischio di mortalità. Ciò mi fa ricordare la segnalazione che avevo fatto all'Agenzia Italiana del Farmaco (AIFA) in veste allora di Presidente della Società Italiana dell'Osteoporosi, del

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How to cite this article: Rossini M. Editoriale. Vitamin D - UpDates 2024;7(3):76-77.

Metabolismo Minerale e delle Malattie dello Scheletro (SIOMMMS) in relazione alla nota 96 [2]: facevo notare che la nota trascura gli anziani non prevedendo per loro, indipendentemente dalla determinazione della 25(OH)D, la supplementazione a carico del Servizio Sanitario Nazionale, nonostante siano comprensibilmente e notoriamente a rischio di cronica carenza. Tra gli effetti della nota 96 sulla prescrizione di vitamina D, come riportato successivamente dalla stessa AIFA [3], vi è stata in effetti una riduzione nell'uso di vitamina D anche negli anziani [3], fatto questo che ritengo preoccupante e non espressione di migliorata appropriatezza d'uso. La nuova raccomandazione contenuta nelle recenti linee guida [1] sulla supplementazione con vitamina D di tutti gli anziani mi fa anche ricordare il Progetto avviato in Regione Veneto 20 anni fa [4], che prevedeva la supplementazione con vitamina D in tutta la popolazione anziana, in particolare nei mesi invernali.

Cosa ne pensate?
Buona Lettura

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VITAMIN D
UpDates
2024;7(3):40-43
https://doi. org/10.30455/2611-2876-2024-5

Carenza di vitamina D, fratture da stress e recupero post-traumatico

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Riassunto

La vitamina D è essenziale per l'assorbimento intestinale di calcio e fosfato, oltre che per il mantenimento di una buona performance muscolare e di un'ottimale funzione immunitaria. Infatti, valori costantemente bassi di vitamina D compromettono la mineralizzazione dello scheletro e aumentano il rischio di fratture ossee. Tra queste, le fratture da stress, causate da sollecitazioni meccaniche ripetute, sono state associate a carenza di vitamina D e rappresentano un problema comune tra atleti e militari. La correzione e il mantenimento di adeguati livelli di vitamina D, insieme all'ottimizzazione dei livelli di calcio, rappresentano una delle strategie più efficaci per rafforzare lo scheletro e, di conseguenza, prevenire il rischio di fratture. Pertanto, questa revisione offre una panoramica sui meccanismi attraverso cui la vitamina D influisce sulla salute ossea e sul recupero post-traumatico, fornendo una base solida per future ricerche e interventi clinici.

INTRODUZIONE

La vitamina D è un nutriente essenziale che svolge un ruolo cruciale nel mantenimento della salute ossea. La sua importanza è ben documentata non solo per la prevenzione di malattie ossee, ma anche per il suo ruolo nella modulazione del sistema immunitario, nella contrazione muscolare e nella prevenzione di malattie croniche. Tuttavia, la carenza di vitamina D è un problema diffuso a livello globale, influenzato da vari fattori, tra cui la stagionalità, la latitudine, l'obesità, la malnutrizione, nonché l'infiammazione acuta e l'infezione che possono ridurre i livelli sierici di vitamina D [1].

La carenza di vitamina D è stata associata a una maggiore incidenza di fratture ossee, tra cui le fratture da stress, causate da carichi ripetuti e stress meccanici, che sono comuni tra atleti, militari e individui che praticano attività fisica intensa. La capacità dell'osso di riparare questi microdanni dipende in gran parte dalla disponibilità di nutrienti essenziali, tra cui la vitamina D. Numerose evidenze suggeriscono che una carenza di vitamina D possa compromettere la mineralizzazione ossea, aumentando la suscettibilità alle fratture da stress. Inoltre, il recupero post-traumatico da fratture da stress è un processo complesso che richiede un adeguato supporto nutrizionale per garantire una guarigione efficace. La vitamina D gioca un ruolo fondamentale nella rigenerazione ossea e nella guarigione delle fratture, accelerando il processo di recupero, migliorando la qualità del callo osseo e riducendo i tempi di immobilizzazione [2].

In un contesto in cui la prevalenza della carenza di vitamina D è in aumento, è fondamentale comprenderne appieno le implicazioni sulla salute ossea e identificare le migliori pratiche per la sua gestione. Pertanto, la nostra revisione si propone di esplorare il ruolo della vitamina D nella prevenzione delle fratture da stress e nel recupero post-traumatico, analizzando l'associazione tra carenza di vitamina D e aumentata incidenza di fratture, nonché i benefici della sua supplementazione nel processo di guarigione.

RUOLO DELLA VITAMINA D NELLA SALUTE DELLE OSSA

La vitamina D è una vitamina liposolubile cruciale per la regolazione del metabolismo del calcio e del fosforo. La vitamina D può essere

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Conflitto di interessi
Gli Autori dichiarano nessun conflitto di interessi.

How to cite this article: Tarantino U, Cariati I. Carenza di vitamina D, fratture da stress e recupero post-traumatico. Vitamin D – Updates 2024;7(3):40-43. https://doi.org/10.30455/2611-2876-2024-5

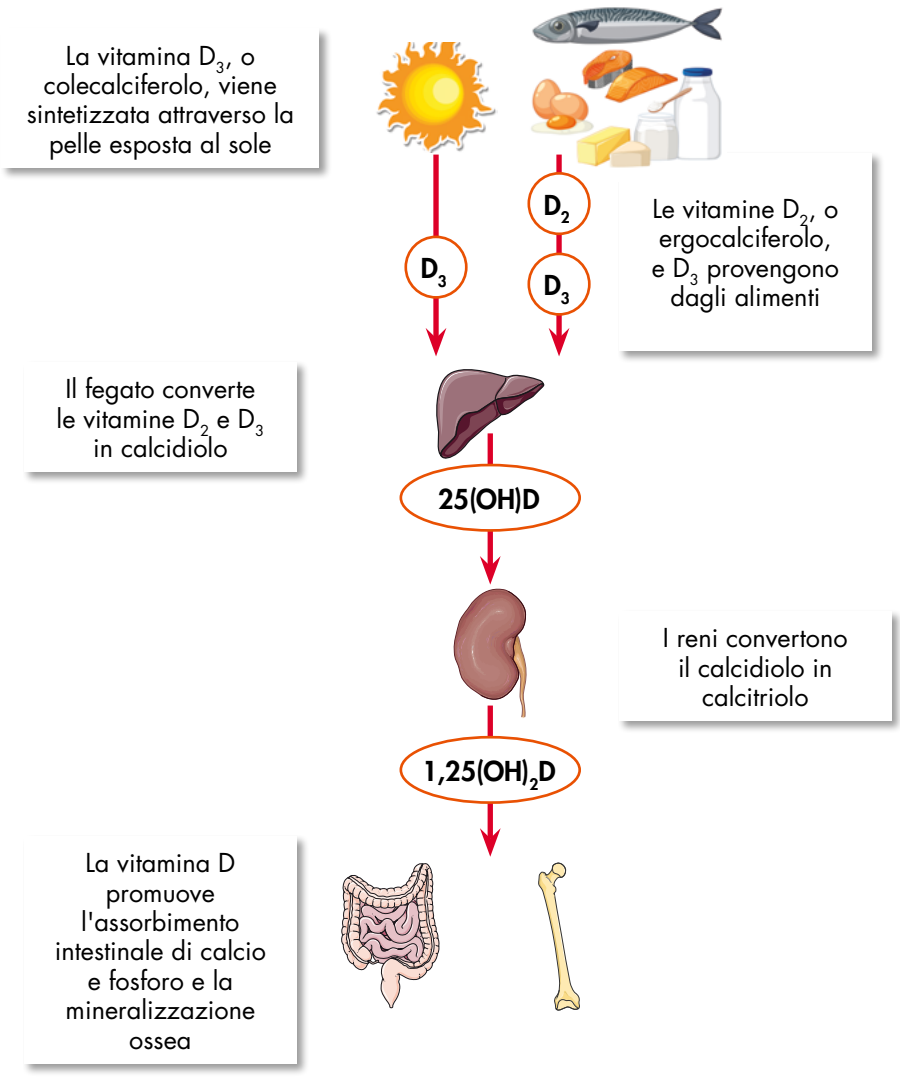

FIGURA 1.
Sintesi e metabolismo della vitamina D.

ottenuta attraverso l'esposizione al sole, che induce la sintesi cutanea della vitamina D_3 o colecalciferolo, e tramite l'assunzione di cibi e integratori contenenti vitamina D_2 o ergocalciferolo, e vitamina D_3. Nell'organismo, la vitamina D viene convertita nel fegato in 25-idrossivitamina D [25(OH)D] o calcidiolo, la principale forma circolante. Nei reni la 25(OH)D viene convertita nella sua forma attiva, la 1,25-diidrossivitamina D [$1,25(OH)_2D$], nota come calcitriolo, la quale agisce su specifici recettori presenti in vari tessuti, contribuendo al mantenimento dell'omeostasi [3] (Fig. 1).
Numerosi studi hanno dimostrato che livelli adeguati di vitamina D sono associati a una maggiore densità minerale ossea, indicatore chiave della forza e della resistenza delle ossa. Questa, infatti, promuove l'assorbimento intestinale del calcio e del fosforo, necessari per la mineralizzazione della matrice ossea. Tuttavia, in condizioni di carenza di vitamina D, l'assorbimento del calcio è inefficiente, causando ipocalcemia. Tale condizione stimola la secrezione di paratormone (PTH), che mobilizza il calcio dalle ossa per mantenere i livelli sierici di calcio, causando demineralizzazione ossea e aumentando il rischio di fratture [4].
La vitamina D aumenta l'espressione delle proteine leganti il calcio nell'intestino, facilitando il trasporto trans-cellulare del calcio nel flusso sanguigno. Inoltre, agisce direttamente sulle cellule ossee, stimolando l'attività degli osteoblasti e riducendo l'attività degli osteoclasti. Tali azioni sono associate alla presenza del recettore della vitamina D (VDR), un recettore nucleare che, legandosi al calcitriolo, regola l'espressione dei geni coinvolti nel metabolismo del calcio, nella crescita cellulare e nella funzione immunitaria. Infatti, la disfunzione del VDR può alterare l'omeostasi tissutale, contribuendo all'insorgenza di disordini muscolo-scheletrici, tra cui osteoporosi e sarcopenia [5]. Inoltre, una grave carenza di vitamina D può causare, nei bambini, rachitismo, una condizione caratterizzata da difetti nella mineralizzazione ossea che porta a deformità scheletriche, mentre negli adulti può provocare osteomalacia, condizione in cui la mineralizzazione dell'osso neoformato è inadeguata, causando debolezza muscolare e dolore osseo diffuso [6].
Numerosi studi epidemiologici e clinici supportano il ruolo della vitamina D nella prevenzione delle fratture. In particolare, una meta-analisi di studi clinici randomizzati ha dimostrato che la supplementazione di vitamina D, soprattutto se combinata con il calcio, riduce significativamente il rischio di fratture negli anziani con carenze di vitamina D [7]. Un altro studio ha evidenziato che pazienti con fratture da stress presentavano frequentemente livelli insufficienti di vitamina D, suggerendo che una corretta integrazione potrebbe prevenire tali lesioni [8].
Nel complesso, tali evidenze confermano il ruolo della vitamina D nel mantenimento di un'ottimale massa ossea e suggeriscono la necessità di monitorare e mantenere livelli adeguati di vitamina D, soprattutto nei soggetti a rischio, attraverso un'adeguata esposizione al sole, una dieta equilibrata e, se necessario, l'utilizzo di vitamina D.

FRATTURE DA STRESS E RECUPERO POST-TRAUMATICO: IL RUOLO DELLA VITAMINA D

Le fratture da stress sono lesioni causate da microtraumi ripetuti che superano la capacità di riparazione del tessuto osseo. La carenza di vitamina D è un fattore di rischio significativo per lo sviluppo di queste fratture, poiché tale vitamina è cruciale per la salute e l'adattamento delle ossa agli stress meccanici. Questo tipo di frattura è comune negli arti inferiori, dove le ossa sopportano il peso del corpo e gli impatti ripetuti durante attività come corsa e salti [9].
Diversi studi hanno evidenziato che individui con bassi livelli di vitamina D presentano un rischio maggiore di fratture da stress, specialmente tra atleti, in quanto esposti a

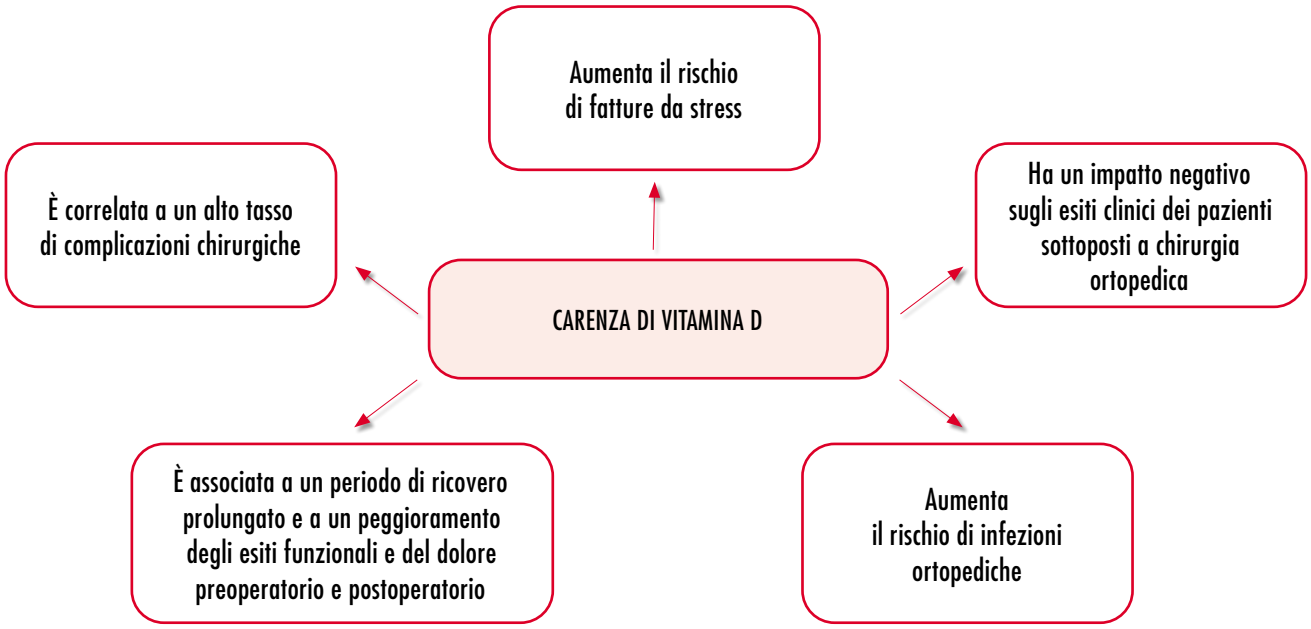

FIGURA 2.
Carenza di vitamina D: conseguenze in ambito ortopedico.

carichi ripetuti, e militari, sottoposti ad attività fisiche intense. In particolare, è stato dimostrato che cambiamenti nel protocollo di allenamento, nell'attrezzatura utilizzata o nell'inizio di un nuovo sport, soprattutto negli atleti non professionisti, sono cause frequenti di lesioni da stress, suggerendo l'importanza della supplementazione di vitamina D durante periodi di intenso allenamento o servizio [10].

Anche il recupero post-traumatico da fratture ossee è un processo complesso che richiede un adeguato supporto nutrizionale per garantire una guarigione efficace. In questo contesto, la vitamina D svolge un ruolo cruciale grazie alla sua capacità di modulare l'attività degli osteoblasti e degli osteoclasti, assicurando un equilibrio dinamico essenziale per la riparazione ossea. Diverse evidenze hanno dimostrato che livelli adeguati di vitamina D accelerano la formazione del callo osseo e migliorano la qualità della rigenerazione ossea [11]. Pertanto, una carenza di vitamina D può compromettere significativamente il processo di guarigione delle fratture, causando una scarsa formazione del callo osseo, prolungando i tempi di guarigione e aumentando il rischio di complicanze, come la *non union* (Fig. 2). A tal riguardo, pazienti fratturati con carenza di vitamina D mostrano una guarigione più rapida e una migliore qualità del callo osseo se ricevono una supplementazione di vitamina D rispetto ai soggetti carenti [12]. Un altro studio ha evidenziato che pazienti con fratture del femore trattati con vitamina D e calcio avevano tempi di guarigione significativamente ridotti rispetto al gruppo di controllo non sottoposto a supplementazione [13]. Pertanto, l'azione fisiologica della vitamina D è un elemento chiave nel processo di guarigione post-traumatico, essenziale sia nella fase infiammatoria, grazie alle sue proprietà immunomodulanti, sia per la formazione, mineralizzazione e rimodellamento del callo osseo.

PREVENZIONE E GESTIONE DELLA CARENZA DI VITAMINA D

La prevenzione e la gestione della carenza di vitamina D sono fondamentali per mantenere la salute ossea e prevenire conseguenze come le fratture da stress. In questo contesto, la sintesi cutanea della vitamina D tramite l'esposizione alla luce solare è la fonte principale di vitamina D per molte persone. È consigliabile esporsi al sole per circa 15-30 minuti al giorno, sebbene fattori come la latitudine, la stagione e la pigmentazione della pelle possano influenzare la quantità di vitamina D prodotta. Inoltre, una dieta ricca di alimenti contenenti vitamina D è essenziale. Alcune buone fonti di vitamina D includono pesce, come salmone, sgombro e tonno, olio di fegato di merluzzo, tuorli d'uovo, fegato di manzo e alimenti fortificati come latte, succo d'arancia e cereali. Integrare questi alimenti nella dieta quotidiana può aiutare a mantenere livelli adeguati di vitamina D [14]. Ciononostante, in molti casi, l'integrazione di vitamina D è necessaria, soprattutto per le persone a rischio di carenza, come gli anziani, gli individui con esposizione limitata al sole e quelli con problemi di assorbimento. In questi soggetti, il monitoraggio regolare dei livelli di calcidiolo nel sangue è importante per controllare e gestire i livelli di vitamina D. Gli esami del sangue possono aiutare a determinare se le dosi di integrazione sono adeguate o se sono necessari aggiustamenti. Nel complesso, la prevenzione della carenza di vitamina D e la sua adeguata integrazione richiedono un approccio multifattoriale che deve includere esposizione al sole, dieta equilibrata e, quando necessario, la supplementazione [15].

CONCLUSIONI

La vitamina D è essenziale per la salute ossea, prevenendo fratture da stress e migliorando il recupero post-traumatico. Questo è particolarmente vero per i soggetti a rischio di fratture da stress, come gli atleti e i militari, la cui attività fisica intensa sottopone il tessuto osseo a sollecitazioni continue e

sovraccarichi che potrebbero favorire lo sviluppo di microdanni e, di conseguenza, le fratture da stress. Una carenza di tale vitamina compromette la mineralizzazione ossea e prolunga i tempi di guarigione. Al fine di prevenire e gestire questa carenza, si raccomanda un'adeguata esposizione al sole, una dieta ricca di vitamina D e, se necessario, integrazioni. Per gli individui a rischio di carenza, il monitoraggio regolare dei livelli di vitamina D è fondamentale per mantenere la salute delle ossa e ridurre il rischio di fratture da stress.

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VITAMIN D
UpDates
2024;7(3):44-46
https://doi. org/10.30455/2611-2876-2024-6

Livelli circolanti di vitamina D e rischio di insorgenza di diabete mellito tipo 2: c'è un legame?

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Il diabete mellito colpisce oltre 500 milioni di persone nel mondo e la sua prevalenza, specialmente del diabete tipo 2, è in costante aumento negli ultimi decenni (con un incremento globale stimato di circa il 50% nel 2045). A livello globale, i decessi dovuti al diabete e alle sue complicanze croniche nel 2019 sono stati stimati attorno a 6 milioni.[1]

L'alterata glicemia a digiuno e la ridotta tolleranza glucidica descrivono delle condizioni di prediabete. Queste due condizioni, singolarmente e in combinazione fra loro, sono anch'esse assai frequenti a livello mondiale (colpendo circa il 7-10% della popolazione globale) e rappresentano non solo fattori di rischio per lo sviluppo del diabete mellito tipo 2, ma anche dei fattori di rischio associati allo sviluppo di complicanze vascolari e renali a lungo termine [1]. In assenza di strategie terapeutiche efficaci (che sono principalmente basate sulle modifiche dello stile di vita), circa il 5-10% della popolazione con prediabete ogni anno progredisce a diabete tipo 2 conclamato.

La carenza/insufficienza di vitamina D è stata associata alla coesistenza di molteplici patologie croniche extra-scheletriche [tra cui obesità, malattia cardiovascolare, alcune forme di neoplasia, diabete ed epatopatia steatosica non alcolica (NAFLD)], suggerendo la possibilità che la vitamina D possa svolgere molteplici e benefici effetti pleiotropici a livello extra-scheletrico, grazie alla distribuzione ubiquitaria del suo specifico recettore [2-4]. La vitamina D, infatti, ha recettori intranucleari che sono espressi su molte cellule e tessuti, incluse le beta cellule pancreatiche, e sembra svolgere, pertanto, un ruolo nell'omeostasi glucidica [2,5,6]. Studi osservazionali hanno dimostrato l'esistenza di una associazione tra bassi livelli sierici di vitamina D e la presenza di diabete tipo 2. Sebbene alcuni studi di intervento abbiano suggerito che la supplementazione con vitamina D possa esercitare un potenziale effetto benefico sul controllo glicemico e sul grado di resistenza insulinica, lavori su ampia scala e alcune metanalisi di trial clinici randomizzati hanno riportato dei dati contrastanti [7]. Per esempio, nel trial clinico randomizzato D2d, che arruolava circa 2.400 soggetti adulti con prediabete senza tener conto del loro stato vitaminico basale, la supplementazione orale con vitamina D_3 per 24 mesi non riduceva il rischio di sviluppare diabete rispetto al placebo [8]. Al contrario, una recente meta-analisi di 4.190 partecipanti, che includeva dati individuali di tre ampi trial clinici randomizzati (incluso anche il trial D2d), ha dimostrato come la supplementazione con vitamina D in soggetti con prediabete (in particolare, nei soggetti che mantenevano valori circolanti di 25(OH)D ≥ 125 nmol/L [≥ 50 ng/mL] durante il trial rispetto a quelli con valori di 25(OH)D compresi tra 50 e 74 nmol/L) è risultata efficace nel ridurre il rischio di circa il 15% di sviluppare diabete tipo 2 nel corso di ~3 anni di trattamento [9]. Tuttavia, tale osservazione non è necessariamente traslabile anche alla popolazione generale adulta con normale glicemia a digiuno. In particolare, esistono attualmente in letteratura pochi studi epidemiologici condotti nella popolazione generale adulta, che abbiano valutato il rischio di insorgenza di diabete mellito tipo 2 all'interno dell'intero spettro di tolleranza glucidica (cioè in presenza di normoglicemia e forme di prediabete, che includono alterata glicemia a digiuno e ridotta tolleranza ai carboidrati). Inoltre, non è ancora del tutto chiaro se varianti genetiche del recettore della vitamina D (VDR), che è espresso in molteplici tessuti, siano in grado di modulare l'associazione tra stato vitaminico D e rischio a lungo termine di sviluppare diabete.

Un recente studio prospettico di coorte, che è stato pubblicato ad aprile 2024 sul *Journal of Clinical Endocrinology & Metabolism* da Fu et al. [10], ha cercato di rispondere a

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Conflitto di interessi
L'Autore dichiara nessun conflitto di interessi.

How to cite this article: Targher G. Livelli circolanti di vitamina D e rischio di insorgenza di diabete mellito tipo 2: c'è un legame?. Vitamin D – Updates 2024;7(3):44-46. https://doi.org/10.30455/2611-2876-2024-6

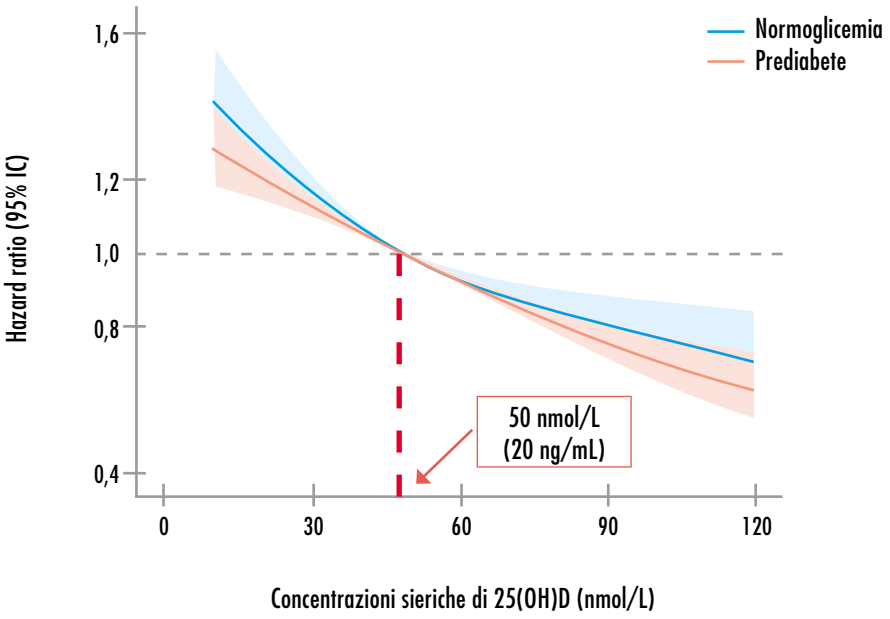

FIGURA 1.
Relazione tipo dose-risposta tra livelli circolanti di 25(OH)D e rischio di sviluppare diabete mellito tipo 2 durante il follow-up (mediana di circa 14 anni) in soggetti con normale tolleranza glucidica e soggetti con prediabete al baseline. In entrambi i gruppi di soggetti, il rischio di diabete si riduceva progressivamente nei soggetti che avevano valori di 25(OH)D ≥ 50 nmol/L (≥ 20 ng/mL) al baseline. Sull'asse y, i dati sono espressi come hazard ratio e intervallo di confidenza al 95% (95% IC, rappresentato come aree ombreggiate in blu e rosso) dopo aggiustamento statistico per le possibili variabili confondenti (tratta da Fu et al., 2024, mod.) [10].

questi quesiti. Per fare questo, gli autori hanno utilizzato i dati di un ampio studio di coorte osservazionale, lo *UK Biobank database*, che ha reclutato oltre 500.000 soggetti britannici adulti di età compresa fra 40 e 69 anni nel periodo compreso fra 2006 e 2010. Dallo studio sono stati esclusi i soggetti che erano affetti da diabete al baseline (in base alla loro storia clinica e/o i livelli di HbA_{1c}) e quelli che non avevano dati riguardanti il dosaggio sierico della 25(OH)D e la misurazione di quattro specifici polimorfismi genetici del VDR (rs7975232 *ApaI*; rs1544410 *BsmI*; rs2228570 *FokI*; rs731236 *TaqI*). Le informazioni riguardo alla diagnosi di diabete durante il periodo di follow-up sono state ottenute dall'analisi delle cartelle cliniche dei ricoveri ospedalieri e dai registri delle schede di morte.

Nello studio di Fu et. [10] sono stati pertanto complessivamente inclusi 379.699 individui adulti senza diabete al baseline (età media 56 anni, 54% donne); 86% di questi soggetti aveva una normale tolleranza glucidica (definita come HbA_{1c} < 5,7%), mentre il restante 14% (n = 53.886) aveva prediabete al baseline (definito come HbA_{1c} compresa tra 5,7% e 6,5%). I partecipanti con normale tolleranza glucidica al baseline avevano una mediana di 25(OH)D di 48 nmol/L (IQR: 33,5-63,4 nmol/L), mentre quelli con prediabete avevano una mediana di 25(OH)D di 45 nmol/L (IQR: 30,9-60,3 nmol/L). Complessivamente, nell'intera coorte dello studio il 53,4% dei soggetti aveva valori circolanti di 25(OH)D < 50 nmol/L. Durante il follow-up dello studio (mediana di 14 anni), 6.315 (1,9%) soggetti normoglicemici e 9.085 (16,9%) soggetti con prediabete hanno sviluppato diabete mellito tipo 2.

Quando i partecipanti dello studio venivano suddivisi in base ai loro valori circolanti di 25(OH)D al baseline in accordo ai cutoff proposti dalla *Endocrine Society* [25(OH)D < 25, 25-49,9, 50-74,9 e ≥ 75 nmol/L], gli autori hanno osservato una significativa associazione tra livelli circolanti più elevati di 25(OH)D e rischio ridotto di sviluppare diabete tipo 2. In particolare, confrontati con i soggetti che avevano livelli di 25(OH)D < 25 nmol/L, i soggetti con normoglicemia e valori di 25(OH)D ≥ 75 nmol/L al baseline avevano un rischio significativamente ridotto di sviluppare diabete tipo 2 (hazard ratio: 0,62, 95% IC: 0,56-0,70); analogamente, confrontati con i soggetti che avevano livelli di 25(OH)D < 25 nmol/L, i soggetti con prediabete e con valori di 25(OH)D ≥ 75 nmol/L al baseline avevano un rischio significativamente ridotto di sviluppare diabete (hazard ratio: 0,64, 95% IC: 0,58-0,70). Questi dati rimanevano significativi anche dopo aggiustamento statistico per sesso, età, razza, obesità, attività fisica, stato socioeconomico, uso di farmaci per dislipidemia ed ipertensione, uso di supplementi di vitamina D e molteplici altri possibili fattori confondenti. I risultati rimanevano significativi anche quando venivano esclusi dall'analisi statistica i casi di diabete che insorgevano nei primi 2 anni di follow-up dello studio. Gli autori hanno osservato che vi era una relazione inversa e lineare fra livelli di 25(OH)D e rischio di insorgenza di diabete nei soggetti con prediabete mentre tale relazione era significativa ma non lineare (ma polinomiale inversa) nei soggetti con normali valori di HbA_{1c} al baseline. Per ogni incremento di 10 nmol/L nei valori circolanti di 25(OH)D al baseline, vi era un decremento del rischio di insorgenza di diabete pari al 7%. Inoltre, sia nei soggetti con normale tolleranza glucidica che in quelli con prediabete al baseline, il rischio di sviluppare diabete nel corso del follow-up si riduceva progressivamente nei soggetti che avevano valori di 25(OH)D ≥ 50 nmol/L (Fig. 1). Gli autori hanno inoltre riportato la presenza di una significativa interazione statistica fra livelli di 25(OH)D e presenza di polimorfismi genetici del VDR nei soggetti con prediabete (ma non in quelli con normoglicemia al baseline); in tali soggetti l'effetto protettivo di elevati livelli di 25(OH)D sul rischio di sviluppare diabete era maggiore nei soggetti portatori dell'allele T (rs1544410) del gene *BsmI* (portatori di alleli TT: hazard ratio: 0,53, 95% IC: 0,38-0,73; alleli CT: hazard ratio: 0,65, 95% IC 0,55-0,77; alleli CC: hazard ratio: 0,75, 95% IC: 0,61-0,91). Infine, in un'analisi statistica di mediazione, gli autori hanno inoltre dimostrato che i lipidi plasmatici, in particolare i livelli di trigliceridi plasmatici, mediano una parte rilevante dell'associazione esistente fra livelli di 25(OH)D e rischio di diabete incidente, sia nei soggetti con normale tolleranza glucidica (26%) che in quelli con prediabete (34%) al baseline. In particolare, se un individuo aveva sia bassi

livelli di 25(OH)D che elevati livelli circolanti di trigliceridi il suo rischio di sviluppare diabete durante il follow-up era molto più elevato rispetto ai soggetti che avevano solo una alterazione isolata [10].

I principali punti di forza di questo studio di coorte sono il suo disegno prospettico, l'ampia numerosità del campione esaminato (circa 380.000 soggetti), la lunghezza del follow-up (mediana di circa 14 anni), l'aggiustamento statistico per comuni fattori di rischio e molteplici fattori confondenti. Tra i principali limiti dello studio vanno senz'altro menzionati il disegno osservazionale dello studio (infatti, è bene ricordare che questo non è uno studio di supplementazione/intervento farmacologico con vitamina D e, quindi, la presenza di una associazione significativa fra 25(OH)D e rischio di diabete non vuole dire automaticamente che esista una causalità!), la mancanza di misurazioni seriate dei livelli circolanti di 25(OH)D, l'inclusione di soggetti britannici di età compresa fra 40 e 69 anni e prevalentemente di razza caucasica, la mancanza di misurazione della glicemia a digiuno al baseline (essendo disponibili esclusivamente valori di HbA_{1c}) e il fatto che la diagnosi di diabete incidente durante il periodo di follow-up tosse basata sull'analisi delle cartelle cliniche dei ricoveri ospedalieri e dei registri delle schede di morte [10].

Pertanto, i risultati di questo studio di popolazione britannica (con soggetti di età compresa fra 40 e 69 anni) documentano come elevati livelli circolanti di 25(OH)D al baseline siano significativamente associati a un rischio ridotto di sviluppare diabete tipo 2 nel corso di un follow-up mediano di circa 14 anni, sia nei soggetti con normale tolleranza glucidica che in quelli con prediabete al baseline. In questa coorte di soggetti, il livello sierico di vitamina D dove si iniziavano ad osservare dei possibili effetti protettivi sul rischio di sviluppare diabete tipo 2 era ≥ 50 nmol/L (≥ 20 ng/mL). Nei soggetti con prediabete, l'associazione fra elevati livelli di 25(OH)D e ridotto rischio di diabete era inoltre modificata dalla presenza di varianti genetiche del VDR (rs1544410) del gene *Bsml*. Dai dati di questo studio, è possibile infine ipotizzare che il miglioramento del profilo lipidico (in particolare la riduzione dei livelli dei trigliceridi plasmatici) possa contribuire a spiegare almeno una parte dell'effetto protettivo dei livelli di 25(OH)D sul rischio di insorgenza del diabete mellito tipo 2 [10].

In conclusione, i risultati di questo ampio studio prospettico di coorte (che ha utilizzato l'*UK Biobank database*) forniscono un ulteriore e significativo supporto alla possibilità che adeguati livelli circolanti di vitamina D possano espletare dei benefici effetti sul rischio di sviluppare diabete mellito tipo 2 nella popolazione generale adulta.

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