IN DEPTH REVIEW

Supplementi dietetici di calcio nei soggetti sani: rischi e benefici

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Abstract

Recentemente sono stati sollevati dubbi sulla sicurezza cardiovascolare delle terapie orali con supplemento di calcio assunte da milioni di persone quotidianamente. Nonostante sia esile l'evidenza che il calcio eserciti un effetto positivo sulla riduzione del rischio di frattura, le linee guida sull'osteoporosi continuano a promuovere la terapia orale con calcio, presumendo che 'male non fa'. Ma una più attenta analisi dei trial randomizzati controllati (RCT) e degli studi osservazionali evidenzia la presenza di un aumento significativo, seppure modesto, del rischio cardiovascolare nei soggetti sani che assumono supplementi di calcio. L'obiettivo di questo articolo è di sintetizzare i dati più recenti per evidenziare che questo aumento del rischio cardiovascolare potrebbe essere causato proprio dal supplemento di calcio nei soggetti sani.

Parole chiave: malattie cardiovascolari, supplementi di calcio

Introduzione

Il calcio è un elemento essenziale per la vita. Nel corpo umano, il 99% del calcio è immagazzinato all'interno dello scheletro. Tuttavia, come catione bivalente, il calcio possiede anche altre funzioni fisiologiche, che comprendono: la comunicazione a livello inter ed intracellulare, la coagulazione del sangue e la conversione dell'attività elettrica a quella meccanica, come accade durante la contrazione muscolare. Il calcio viene ricavato dai prodotti alimentari caseari e il deficit di calcio risulta assai raro.

Il calcio viene prescritto a varie categorie di pazienti, compresi quelli affetti da insufficienza renale, per normalizzare la fosfatemia, per quelli affetti da ipoparatiroidismo per prevenire l'iperparatiroidismo, per tutti i pazienti con apporto di calcio inadeguato nella dieta, (come i pazienti istituzionalizzati, per esempio), ma soprattutto per i pazienti con diagnosi di osteoporosi o ritenuti a rischio di osteoporosi. Le linee guida per la cura dell'osteoporosi consigliano la somministrazione di supplementi di calcio (fino a 1 g al giorno), nonostante manchi l'evidenza dai grandi trial randomizzati che tale terapia produca una riduzione del rischio di frattura e sempre seguendo l'ipotesi che il calcio non faccia del male.

Osteoporosi

L'osteoporosi è una malattia cronica caratterizzata dal riassorbimento dell'osso con decalcificazione e una conseguente riduzione della densità minerale ossea (bone mineral density o

BMD), comportando una diminuzione nella resistenza dell'osso ed un aumento del rischio di frattura. L'osteoporosi è un disturbo soprattutto delle persone anziane con conseguente aumento della prevalenza di pazienti osteoporotici con l'aumentare dell'età media della popolazione [1] (full text) [2]. La conseguenza più grave è la frattura del femore, associata ad una mortalità del 30% a un anno [3] (full text), e, sebbene l'incidenza di frattura sia collegata alla BMD, ciò si verifica soltanto con un apporto giornaliero di calcio molto basso, di <700mg/day [4] (full text). Pertanto, in assenza di un chiaro rapporto tra dosaggio di calcio e rischio di frattura non c'è nessuna evidenza che si abbia una maggiore protezione con dosaggi più alti.

La prevenzione e il trattamento dell'osteoporosi con calcio e vitamina D

I supplementi di calcio possono migliorare la BMD [5] [6] [7] [8] [9], e potrebbero attenuare il riassorbimento osseo [10]. Tuttavia, i dati non sono completamente attendibili e non è ancora stato dimostrato che un aumento della BMD riduca l'incidenza delle fratture. I primi studi in merito sembravano dimostrare che il rischio di frattura diminuiva dopo l'introduzione di supplementi di calcio e vitamina D nella dieta [6] [11] (full text) [12] (full text) [13], ma RCT più estesi sull'effetto della supplementazione di calcio, con o senza vitamina D, non hanno confermato tale riduzione nell'incidenza di fratture (tabella 1) e, ancora più importante, non hanno evidenziato alcun effetto sulla morbilità o sulla mortalità [14] [15] (full text) [16] [17] [18] [19] (full text) [20]. Revisioni sistematiche e meta-analisi hanno dimostrato che ci potrebbe essere una riduzione marginale nell'incidenza di fratture dopo introduzione di monoterapia con calcio e co-supplementazione con vitamina D [21] [22] [23] [24] [25] (figura 1). Il gruppo che sembra beneficiare di più da queste misure è quello di donne che vivono nelle strutture residenziali per anziani.

L'applicazione pratica dell'evidenza che ci arriva dai trial risulta difficile. In primo luogo, i soggetti coinvolti nei trial non potevano presentare comorbidità, escludendo quindi pazienti con insufficienza renale anche lieve, malattie delle vie respiratorie e malattie cardiovascolari. Pertanto, soggetti normali potrebbero essere sia più a rischio di fratture osteoporotiche, e quindi potenzialmente avere più da guadagnare dalla somministrazione dei supplementi di calcio, sia a più ad alto rischio dagli effetti collaterali di tali supplementi. In secondo luogo, tutti gli studi mostravano una scarsa aderenza terapeutica da parte dei

Tabella 1. Study characteristics and results of recent randomised control trials of calcium and vitamin D with fracture risk reduction.

			Mean age	Intervention		Fracture risk reduction	
Study	**Year**	**Participants**	**(years)†**	**Calcium mg/day**	**Vitamin IU/day**	**Hip**	**Nonvertebral**
Larsen (14)	2004	9605	74 (65-103)	1000	400	x	-16%*
Harwood(15)	2004	150	81 (67-92)	1000	800	x	NS
RECORD (16)	2005	5292	77 (6)	1000	800	NS	NS
Porthouse (17)	2005	3454	77 (5)	1000	800	NS	NS
Flicker (18)	2005	625	83.4	600	1000	NS	x
Jackson (19)	2006	36282	62 (7)	1000	400	NS	NS§
Pfeifer (20)	2009	242	77 (4)	1000	800	NS	x

NS: nonsignificant; x:not available
†The SD or range of age is presented for studies with the information available
§Total fracture
*p<0,05

Reproduced with permission [21].

partecipanti [26]. Sebbene i soggetti con una ottima aderenza terapeutica avessero dimostrato una riduzione di rischio di fratture, le analisi pre-protocollo introducevano dei bias e pertanto non potevano evidenziare alcun beneficio per l'intera popolazione.

Effetti collaterali cardiovascolari della calcio-supplementazione: l'evidenza

La sicurezza è un fattore di fondamentale importanza per una terapia applicata in modo così universale come il calcio. Persino gli effetti negativi minori, difficili da quantificare negli RCT, potrebbero avere delle conseguenze importanti, a livello economico e in termini di sofferenza, quando venissero amplificati milioni di volte all'interno di una intera popolazione. Tutto ciò risulta particolarmente importante per la popolazione che assume regolarmente supplementi di calcio, in quanto un aumento modesto dell'incidenza di malattie cardiovascolari per esempio, potrebbe non essere facilmente evidenziabile. Pertanto, si continua a prescrivere la calcio-supplementazione nonostante non ci sia abbastanza evidenza dei benefici di tale terapia, perché persiste nel tempo l'idea che almeno non faccia del male. Inoltre, i sistemi di monitoraggio non sono riusciti a rilevare tutti i potenziali rischi della terapia con il calcio perché molte persone si automedicano, comprando i supplementi come 'farmaci da banco'. In questo modo, si riduce la differenza osservabile tra pazienti a cui il calcio è stato prescritto e quelli ai quali non è stato prescritto.

È insolito osservare come i dati che evidenziano gli effetti cardiovascolari negativi della calcio-supplementazione siano stati raccolti in modo opposto rispetto a quello che si fa di solito per i fattori di rischio cardiovascolari: cioè dagli RCT che studiavano l'osteoporosi piuttosto che dai dataset osservazionali. Tutto ciò riflette l'entusiasmo generale che ha da sempre accompagnato l'uso dei supplementi di calcio. I primi dati osservazionali comprendevano l'osservazione che livelli maggiori di calcio nell'acqua potabile erano associati ad un minore rischio cardiovascolare [27]. Questi dati piuttosto rassicuranti hanno rallentato notevolmente il riconoscimento del maggiore rischio cardiovascolare associato all'uso dei supplementi di calcio nei trial.

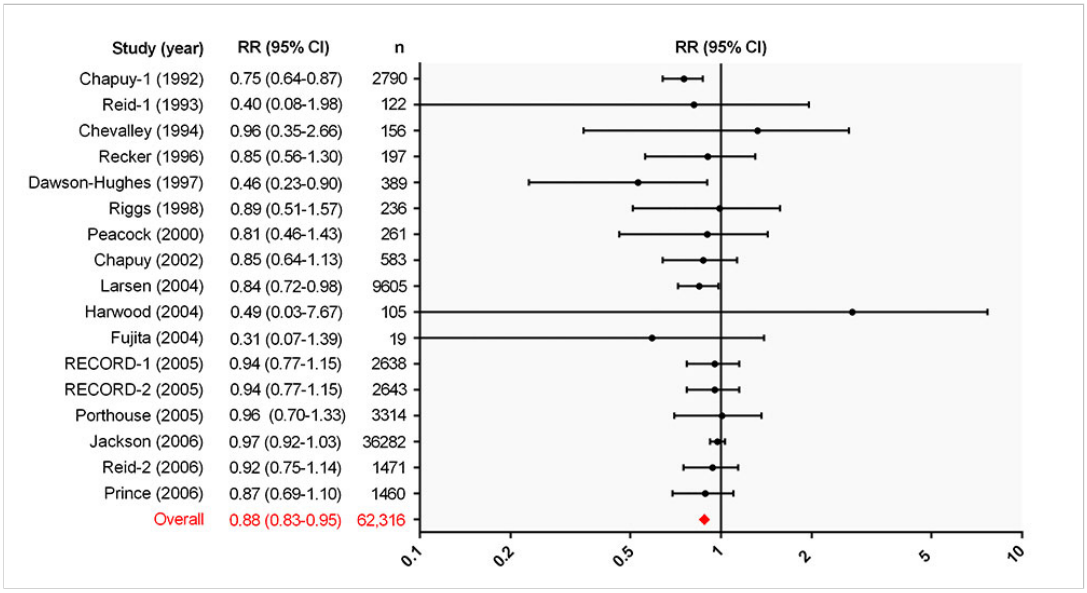

Figura 1.
Meta-analysis of the effects of calcium monotherapy and co-supplementation with vitamin D on fracture risk [21]. Reproduced with permission.

Dati dai trial

Il dataset cruciale, che evidenziava un aumento del rischio cardiovascolare dopo somministrazione di supplementi con calcio, dimostrava un aumento significativo di infarto del miocardio (RR 2.12; 95%CI 1.01-4.47) in donne sane in post-menopausa con età media di 74 anni, quando venivano confrontate con donne che assumevano placebo [28] (full text)(figura 2).

Una successiva meta-analisi [29] (full text) degli RCT (11.921 pazienti) che confrontava la monoterapia con calcio con quella con placebo, dimostrava un maggiore rischio di infarto del miocardio per l'assunzione di calcio (RR 1.27; 95% CI 1.01-1.59), con NNT di 69 a cinque anni per provocare un infarto miocardico. Questa meta-analisi non comprendeva co-supplementazione di calcio con vitamina D e utilizzava auto-documentazioni, cartelle cliniche e certificati di morte per identificare gli eventi cardiovascolari, in quanto, non essendoci end-point di studio prespecificati, i dati sugli eventi cardiovascolari non erano stati raccolti in modo sistematico.

D'altro canto, lo studio Calcium Intake Fracture Outcome Study (CAIFOS), completato dopo la pubblicazione dei due studi discussi sopra, non evidenziava un effetto negativo né su ricoveri ospedalieri in seguito ad eventi vascolari aterosclerotici né sull'incidenza di mortalità nell'arco di cinque anni [30]. Tuttavia, sebbene in questo studio gli eventi cardiovascolari fossero stati formalmente monitorati, i risultati non potevano essere confrontati direttamente con i precedenti studi, in quanto lo studio CAIFOS esaminava le malattie aterosclerotiche vascolari in generale, e non specificamente degli end-point cardiovascolari, come l'infarto del miocardio, per esempio.

La vitamina D potrebbe possedere delle proprietà cardioprottetive [31]: è quindi plausibile che la co-somministrazione di calcio con vitamina D possa produrre meno effetti avversi. In effetti, un'analisi del dataset proveniente dalla Woman's Health Initiative (WHI),non evidenziava un aumento di eventi cardiovascolari o di eventi cerebrovascolari dopo somminis-

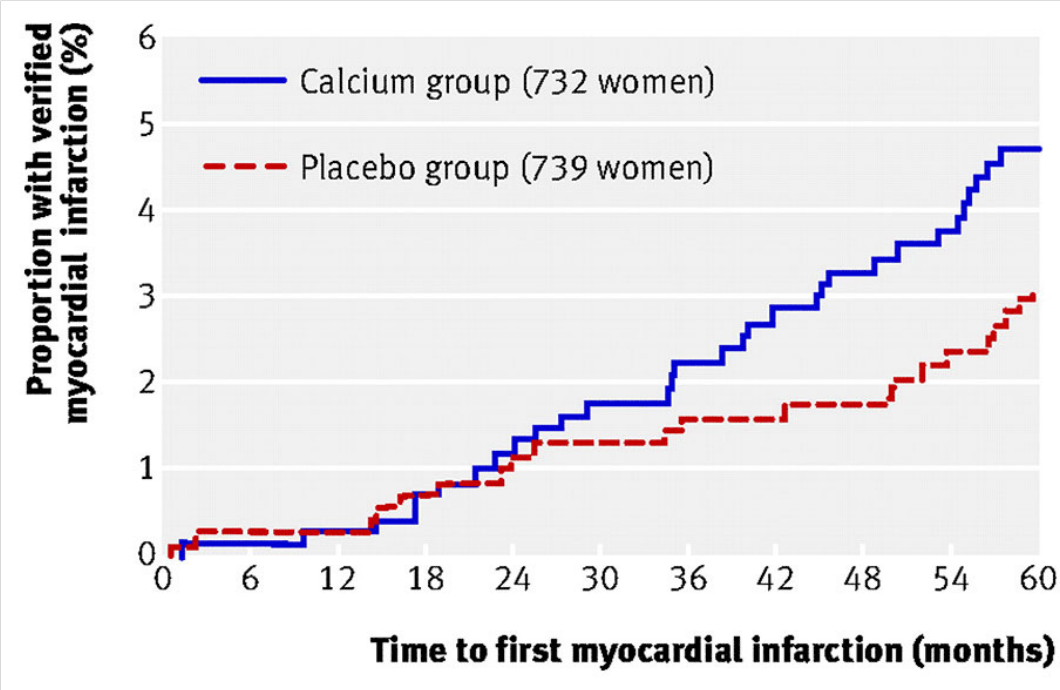

Figura 2.
Kaplan Meier curve showing adverse outcomes with calcium supplementation in 1471 healthy women [28] (full text). Reproduced with permission.

strazione di supplementi di calcio con o senza vitamina D [32] (full text), ma è importante considerare che, durante la randomizzazione, è emerso che molte delle partecipanti assumevano già supplementi di calcio (54%) e di vitamina D (47%), un fatto che poteva inficiare l'identificazione di eventi avversi. Inoltre, questo studio evidenziava una scarsa aderenza terapeutica con l'assunzione dei supplementi e un'alta frequenza di altra terapia farmacologica, per esempio estrogeni. Una seconda analisi studiando soltanto le 16.000 donne che non assumevano calcio o vitamina D acquistati come farmaci da banco, mostrava un aumento del rischio di infarto del miocardio (HR 1.22; 95%CI 1.0-1.5) e di ictus cerebrale (HR 1.17; 95%CI 0.95-1.44) dopo supplementazione di calcio e vitamina D [33] (full text), di simile entità rispetto agli studi precedenti [29] (full text). Se, a questi dati, aggiungiamo i risultati dello studio RECORD [16], e un RCT che studiava l'incidenza di tumori in donne che prendevano calcio e vitamina D (Calcium and Vitamin D Malnutrition in Elderly Women) [34] (full text) troviamo un aumento significativo dell'incidenza di infarto del miocardio (RR 1.24; 95% CI 1.07-1.45). Se adoperiamo i dati provenienti da questi studi, il trattamento di 1000 pazienti con calcio, con o senza vitamina D, provocherebbe 6 infarti del miocardio o ictus cerebrali, mentre preverrebbe soltanto 3 fratture senza alcuna riduzione di mortalità. Come già per la meta-analisi sulla calcio-supplementazione, questi dati erano anch'essi limitati dalla mancanza di omogeneità nei trial e nei dosaggi dei supplementi ed inoltre vi era l'assenza di predefinizione degli endpoint cardiovascolari a livello dei singoli trial. Per esempio, è possibile che alcuni sintomi gastro-intestinali fossero stati classificati come sintomi cardiovascolari, anche se questo è poco probabile, dato che l'aumento del rischio cardiovascolare risultava essere della stessa entità in tutti gli studi.

Dati osservazionali

Sono stati pubblicati recentemente i dataset di quattro grandi studi osservazionali [35] [36] [37] [38] (full text). Lo studio sull'osteoporosi, The Kuopio Osteoporosis Study [35], è uno

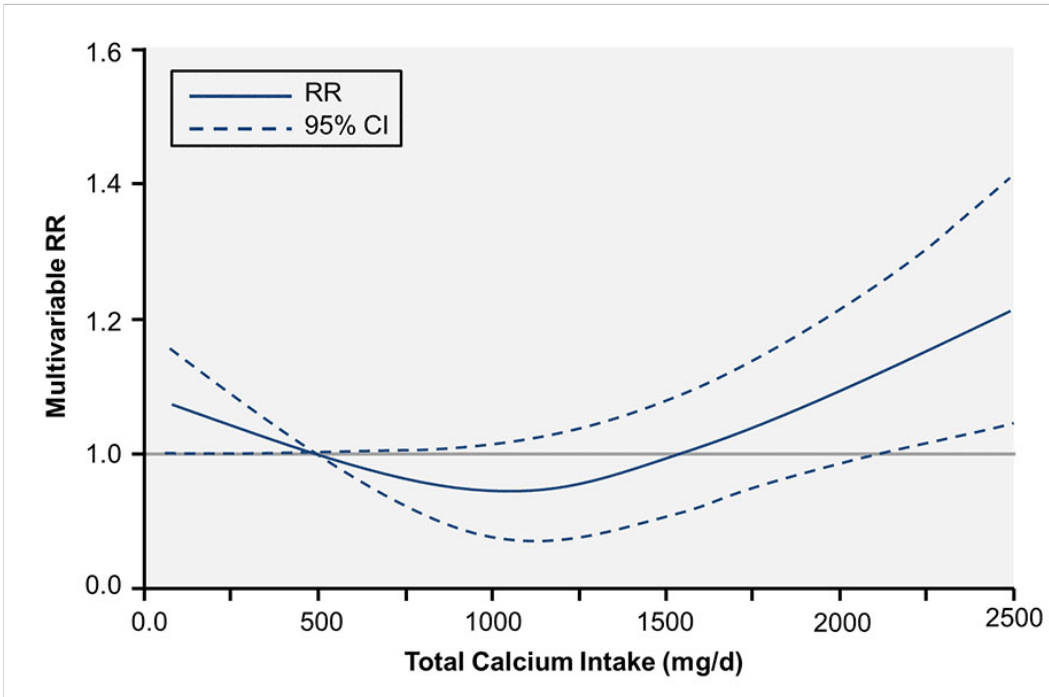

Figura 3.
Nonparametric regression curve displaying adjusted multivariate relative risks (RRs) and 95% CIs for the relationship between total calcium intake and total cardiovascular disease mortality in men [37]. Adapted with permission.

studio prospettico di coorte che coinvolgeva 10.555 donne, di età compresa tra 52 e 62 anni, seguite per un periodo di 7 anni con l'obiettivo di valutare prospetticamente l'effetto di supplementi di calcio, con o senza vitamina D, sulla cardiopatia ischemica (CHD). Se confrontate con pazienti che non assumevano né calcio né vitamina D, queste donne presentavano un aumento del rischio di eventi coronarici statisticamente significativo (HR 1.24; 95%CI 1.02-1.52). Nella coorte EPIC-Heidelberg [36], 23.390 soggetti sani, di età compresa tra 35 e 64 anni, sono stati seguiti per una media di 11 anni. I supplementi di calcio aumentavano il rischio di infarto del miocardio sia associati a vitamina D (HR 1.86; 95%CI 1.17-2.96) che senza (HR 2.39; 95%CI 1.15-5.12). In compenso, il calcio proveniente da latticini riduceva viceversa il rischio di infarto del miocardio (HR 0.69; 95%CI 0.5-0.94). Nello studio svedese sulle mammografie, [38] (full text) che comprendeva 61.433 donne, il calcio era associato ad un aumento di mortalità da qualsiasi causa se il calcio nella dieta era maggiore a 1400 mg/giorno (HR 2.57; 95%CI 1.19-5.55). Questo risultato sembra indicare che i soggetti sani che consumano una dieta con livelli adeguati di calcio naturale si sottopongano ad un maggiore rischio se associano supplementi di calcio alla dieta. E' possibile, tuttavia, che i soggetti anziani fragili con una dieta contenente livelli inadeguati di calcio naturale siano l'unico gruppo per cui i supplementi di calcio non solo prevengono le fratture ma non provocano un aumento del rischio cardiovascolare [21]. I dati più recenti, provenienti dallo studio NIH-AARH [37] che coinvolgeva californiani sani, suggeriscono che il rischio associato ai supplementi di calcio rimane piccolo per le donne che non presentano co-morbidità e che hanno un rischio cardiovascolare molto basso, ma è invece alto negli uomini, con un effetto dose-risposta molto chiaro, (figura 3), e nelle donne che presentano fattori di rischio, tabagismo o tabagismo pregresso, ipertensione arteriosa o ipercolesterolemia.

I fattori confondenti sono sempre difficili da scovare nei trial osservazionali. Negli studi sul calcio si deve considerare che chi usa supplementi di calcio possiede già per definizione un profilo cardiovascolare migliore rispetto a chi non li assume, proprio perché più conscio della propria salute: ciò si deduce anche da fatto che un soggetto del genere si arruola più volentieri in uno studio dietetico [33] (full text). Un'attenta correzione statistica per fattori socio-economici è stata effettuata per tutti questi studi ma, ciononostante, il rischio avverso proveniente dall'uso di supplementi di calcio potrebbe essere comunque maggiore nella popolazione normale.

Una possibile eziologia del rischio cardiovascolare provocato dall'uso di supplementi di calcio

I supplementi di calcio non sono molto buoni al palato ma possibili complicazioni immediate sono piuttosto rare; l'effetto collaterale più comune è la stipsi [39]. Nel medio termine, i consumatori di calcio presentano un maggiore rischio di calcolosi renale [19] (full text). Il monitoraggio di tale terapia rimane difficile e costoso in quanto gli effetti clinici di una terapia a lungo termine potrebbero comparire solo dopo alcuni decenni, Inoltre, i supplementi costano poco, e all'inizio, si riteneva che potessero abbassare la pressione arteriosa [40] [41] (full text), e migliorare il profilo lipidico, [28] (full text) [42], portando ad un uso molto diffuso e ad una certa nonchalance riguardo agli effettivi cambiamenti fisiologici che provocavano. Dati più recenti indicano invece che l'ipercalcemia provoca uno stato di ipercoaguabilità [43] [44], indurimento arterioso e deficit della vasodilatazione [45] (full text) [46] [47] [48]. Provoca inoltre l'aumento dose-correlato della pressione sistolica mediante cambiamenti nel meccanismo vasodilatatorio dell'endotelio [47]. Anche livelli di calcio al limite superiore della norma possono provocare un aumento della calcificazione vascolare [49] [50] (full text) l'ateroma carotideo, ed eventi cardiovascolari, in

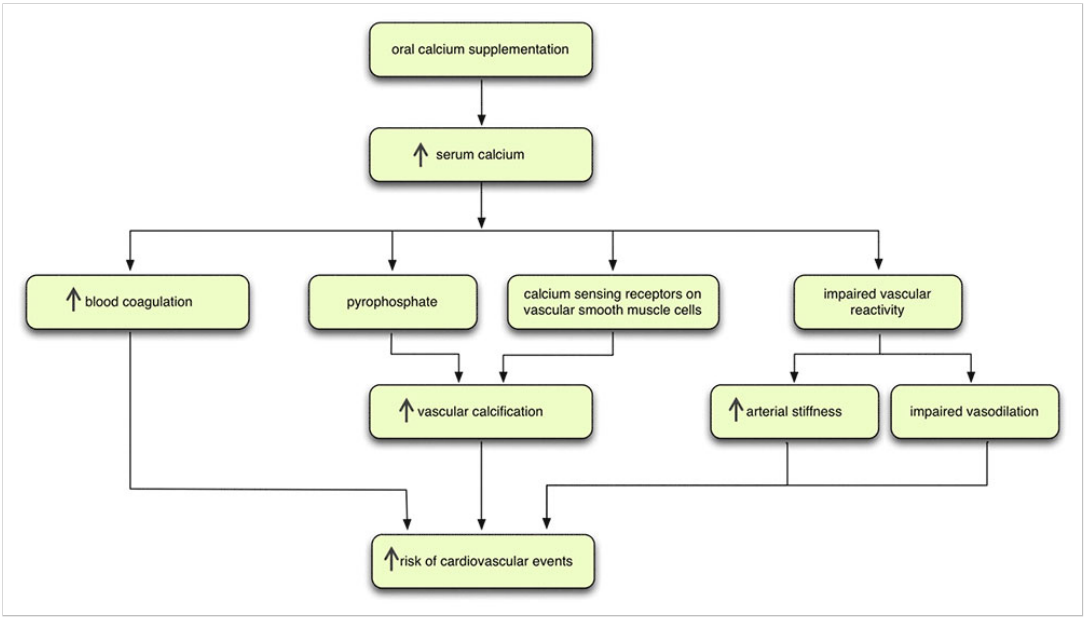

Figura 4.
Potential mechanisms that oral calcium supplementation may be associated with an increased risk of cardiovascular events.

generale con aumento della mortalità, [51], soprattutto se sono presenti altre comorbilità vascolari come l'insufficienza renale [52], [53] (full text). Non sorprende, quindi, che livelli di calcio superiori alla norma possano provocare un aumento del rischio cardiovascolare (CHD) [54] [55] [56] (full text) e dello stroke [54]. Dopo l'assunzione di calcio orale, i livelli sierici sfiorano l'ipercalcemia fino a sei ore consecutive [57] [58] [59], un fenomeno che non viene osservato con l'assunzione di calcio già presente nella dieta spontaneamente, in quanto viene assorbito in modo più lento [60] [61]. Questo aumento dei livelli sierici del calcio potrebbe causare la calcificazione vascolare mediante un effetto sul pirofosfato e sul legame con i recettori sensibili al calcio presenti nelle cellule del muscolo liscio. È quindi possibile che l'assunzione regolare di supplementi di calcio possa contribuire allo sviluppo e alla progressione di patologie vascolari che, a loro volta, aumentano il rischio di eventi cardiovascolari (figura 4).

I supplementi di calcio e le malattie cardiovascolari pre-esistenti

Gli studi sull'uso di supplementi di calcio hanno arruolato soggetti anziani sani, escludendo quei soggetti già affetti da patologie cardiovascolari preesistenti, e ciò ha limitato la possibilità di chiarire l'effetto del calcio sul rischio cardiovascolare globale. Gli studi osservazionali pubblicati dimostrano anch'essi un bias verso i soggetti a basso rischio. È quindi possibile che i soggetti già a più alto rischio di eventi cardiovascolari che assumono anche il calcio, un gruppo che comprende fumatori, ipertesi, diabetici, soggetti con ipercolesterolemia e quelli con anamnesi di infarto del miocardio, potrebbero presentare un rischio ancora maggiore di quello attualmente riconosciuto. È anche possibile, naturalmente, che l'effetto benefico sulle fratture sia maggiore in questi soggetti con comorbilità significative, dato il rischio maggiore di fratture che presentano. Tuttavia, i supplementi di calcio vengono prescritti abitualmente anche per soggetti per i quali non esiste alcuna indicazione di beneficio.

Conclusione

Il calcio presente nella dieta è essenziale alla vita. I supplementi di calcio e di vitamina D a basso dosaggio vengono prescritti abitualmente a soggetti ritenuti a rischio di osteoporosi o a rischio potenziale di osteoporosi, nonostante che i dati di ricerca indichino che questi supplementi aumentano la BMD ma non riducono l'incidenza di fratture né abbassano la mortalità e la morbidità associate alle fratture. Inoltre, non esistono dati che sostengono un largo uso di supplementi di calcio in soggetti con comorbidità. È vero invece, che si stanno accumulando dei dati che dimostrano come i supplementi di calcio a lungo termine potrebbero avere un effetto avverso sugli eventi cardiovascolari, soprattutto in quei soggetti già ad alto rischio. Riteniamo che ci sia un urgente bisogno di studi sulla sicurezza dell'uso dei supplementi di calcio nella popolazione generale.

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Key words: calcium supplementation, cardiovascular diseases

IN DEPTH REVIEW

Calcium supplementation in healthy subjects: benefits and risks

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Abstract

Over recent years the cardiovascular safety of calcium supplementation, taken by millions on a daily basis, has raised concerns. Despite the borderline benefit of calcium supplementation in regards to fracture risk reduction, osteoporosis guidelines continue to advocate daily calcium supplementation assuming that calcium does no harm. However, reanalysis of large randomised controlled trials (RCTs) and observational studies consistently show a modest, but significant increased cardiovascular risk in healthy individuals taking calcium supplementation. The aim of this review is summarise recent data demonstrating elevated cardiovascular risk possibly attributable to oral calcium supplementation in healthy individuals.

Key words: calcium supplementation, cardiovascular diseases

Introduction

Calcium is an essential nutrient necessary for life. In the human body 99% of calcium is stored in the skeleton. However, as a bivalent cation it also has widespread functions throughout the body in inter- and intracellular communication, blood coagulation and the conversion of electrical to mechanical activity such as in muscle contraction. The main source of calcium is from dairy products, and calcium deficiency is very rare.

Prescribed calcium supplementation is used to lower phosphate in patients with renal failure, in patients with hypoparathyroidism, to suppress hyperparathyroidism, and in patients thought.

to have an inadequate calcium intake (most commonly institutionalised patients), but the most frequent recipients of daily calcium supplementation are those thought to be at risk of or proven to have osteoporosis. Osteoporosis guidelines advocate daily calcium supplementation (up to 1g daily) despite little evidence of a reduction in fracture risk from large randomised studies and no evidence of benefit on health utility, assuming that calcium does no harm. However, reanalysis of large randomised controlled trials (RCTs) and observational studies consistently show a modest, but significant increased cardiovascular risk in patients taking calcium supplementation. The aim of this review is summarise recent data demonstrating elevated cardiovascular risk possibly attributable to oral calcium supplements.

Osteoporosis

Osteoporosis is a chronic disease characterised by net bone resorption with a loss of calcification and a reduction in bone mineral density (BMD) leading to decreased bone strength and an increased fracture risk. The condition is mainly seen in older persons and consequent upon the ageing population, its prevalence and numbers of people at risk is increasing [1] (full text) [2]. The most serious complication is hip fracture, which is associated with a 30% one year mortality [3] (full text), and although fracture rates are related to BMD, this seems to be only seen in those with a markedly low calcium intake of <700 mg/day [4] (full text), with no dose response relationship in terms of risk, and no additional protection from higher daily calcium intakes.

Prevention or treatment of osteoporosis with calcium and vitamin D

Calcium supplementation can improve BMD [5] [6] [7] [8] [9], and may attenuate the increase in bone resorption [10]. However, the data are not consistent and increased BMD is not related to fewer fractures. Despite early studies showing reduced fracture risk with calcium and vitamin D supplements [6] [11] (full text) [12] (full text) [13], larger RCTs assessing the effects of calcium supplementation, with or without vitamin D, have demonstrated no reduction in fracture rate (tabella 1) or, more importantly, no benefit on morbidity or mortality [14] [15] (full text) [16] [17] [18] [19] (full text) [20]. Systematic reviews and meta-analyses have been performed demonstrating that there might be marginal benefits on fracture rates of calcium monotherapy and co-supplementation with vitamin D [21] [22] [23] [24] [25] (figura 1). Preventative effects seem to be greatest in women living in nursing homes.

Translating the evidence from these studies into real life is difficult. Firstly, subjects in the studies were required to have no important co-morbidity, so there are no data in people with even mild renal dysfunction, airways disease or heart disease. Hence, although normal people might be at higher risk of osteoporotic fractures and potentially more to gain from calcium supplementation, these might also be at higher risk of any side effects of calcium supplementation. Secondly, the studies all suffered from poor compliance by the subjects

Tabella 1. Study characteristics and results of recent randomised control trials of calcium and vitamin D with fracture risk reduction.

			Mean age	Intervention		Fracture risk reduction	
Study	**Year**	**Participants**	**(years)†**	**Calcium mg/day**	**Vitamin IU/day**	**Hip**	**Nonvertebral**
Larsen (14)	2004	9605	74 (65-103)	1000	400	x	-16%*
Harwood(15)	2004	150	81 (67-92)	1000	800	x	NS
RECORD (16)	2005	5292	77 (6)	1000	800	NS	NS
Porthouse (17)	2005	3454	77 (5)	1000	800	NS	NS
Flicker (18)	2005	625	83.4	600	1000	NS	x
Jackson (19)	2006	36282	62 (7)	1000	400	NS	NS§
Pfeifer (20)	2009	242	77 (4)	1000	800	NS	x

NS: nonsignificant; x:not available
†The SD or range of age is presented for studies with the information available
§Total fracture
*p<0,05

Reproduced with permission [21].

[26]. Although those with excellent compliance benefitted from a reduced fracture risk, per-protocol analyses introduce biases and do not reflect what benefit a population might gain.

Evidence of cardiovascular side effects of calcium supplementation

A critical feature for any treatment applied as widely as calcium supplementation is safety. Even small adverse effects, difficult to measure in RCTs, when amplified millions of times within a population can have health utility and health economic consequences. This is especially true for calcium supplementation, where a modest increase in a condition of high prevalence in the calcium-exposed population, such as cardiovascular disease, may go unnoticed. Hence despite awareness that calcium supplementation may be pointless, prescribing has continued unabated in the belief that at least it does no harm. In addition, monitoring systems have failed to identify potential risks since many people take calcium supplements over the counter, thereby reducing the observed difference in risk between patients prescribed and not prescribed calcium.

Unusually, the published data on the adverse effects of calcium supplementation starts with the RCTs for osteoporosis, and only recently have observational datasets been collected. This is a reverse of the usual pattern of evidence collection for a cardiovascular risk factor and is a reflection of the widespread enthusiasm for calcium supplementation. Very early observational data based upon the calcium content of drinking water suggested that higher calcium intake was associated with lower rates of cardiovascular disease [27]. It was these reassuring data that led to the slow recognition of the cardiovascular effects of calcium supplementation in the trials.

Trial data

The seminal dataset demonstrating increased cardiovascular risk with calcium supplementation a significantly higher risk of myocardial infarction (RR 2.12; 95%CI 1.01-4.47) in

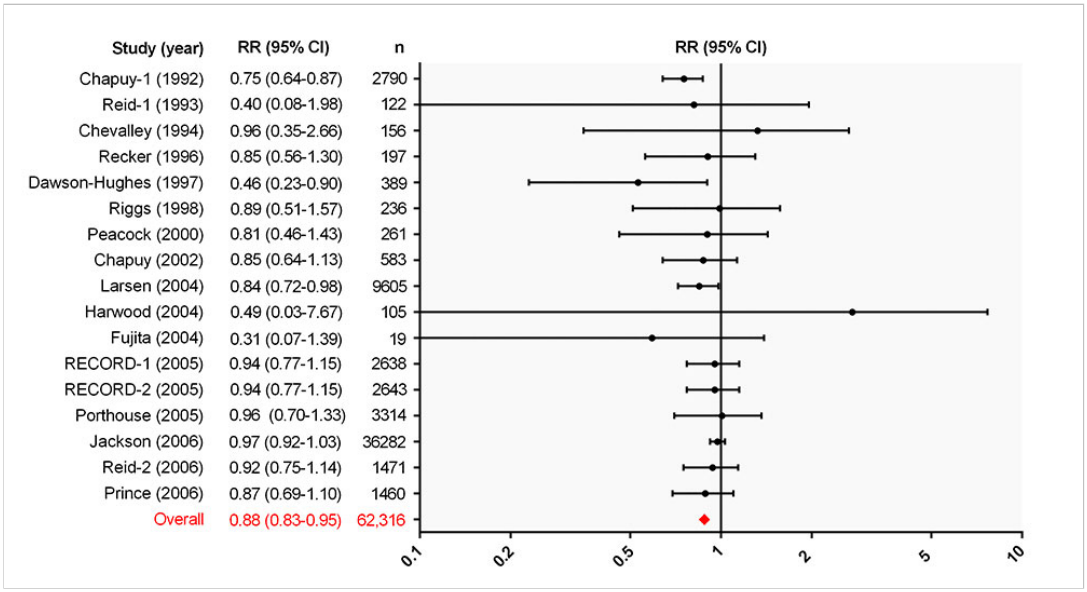

Figura 1.
Meta-analysis of the effects of calcium monotherapy and co-supplementation with vitamin D on fracture risk [21]. Reproduced with permission.

healthy postmenopausal women (mean age 74 years) taking calcium than in those taking placebo [28] (full text)(figura 2).

Subsequent meta-analysis [29] (full text) from the RCTs (11,921 patients) comparing calcium supplementation monotherapy with placebo showed a higher risk of myocardial infarction with calcium supplementation (RR 1.27; 95% CI 1.01-1.59), giving a number needed to treat for five years to cause one myocardial infarction of 69. This particular meta-analysis, excluded studies of co-supplementation of calcium and vitamin D and used self-reports, death certificates and medical records since cardiovascular events, not being prespecified study endpoints, were not systematically collected.

On the other hand, the Calcium Intake Fracture Outcome Study (CAIFOS), completed following the publication of the two papers discussed above, did not show an adverse effect on verified atherosclerotic vascular hospitalisation and mortality rates over 5 years [30]. Although, these events were formally monitored in this study, the results are not directly comparable to previous work, as the study did not look at specific cardiovascular endpoints like myocardial infarction, rather the broader composite endpoint of atherosclerotic vascular disease.

Vitamin D may be cardio-protective [31], so it is plausible that co-supplementation of calcium and vitamin D may have fewer adverse effects. Indeed a review of the Woman's Health Initiative (WHI) dataset revealed no increase in coronary or cerebrovascular risk with calcium supplementation with or without vitamin D [32] (full text), but many participants were already taking their own calcium (54%) and vitamin D (47%) supplements at randomisation which may have obscured any adverse effects. There was also poor compliance with the supplementation and high frequency of use of other agents such as oestrogen. A reanalysis including only the 16,000 women not taking any over the counter calcium or vitamin D supplements at randomisation, showed an increased the risk of myocardial in-

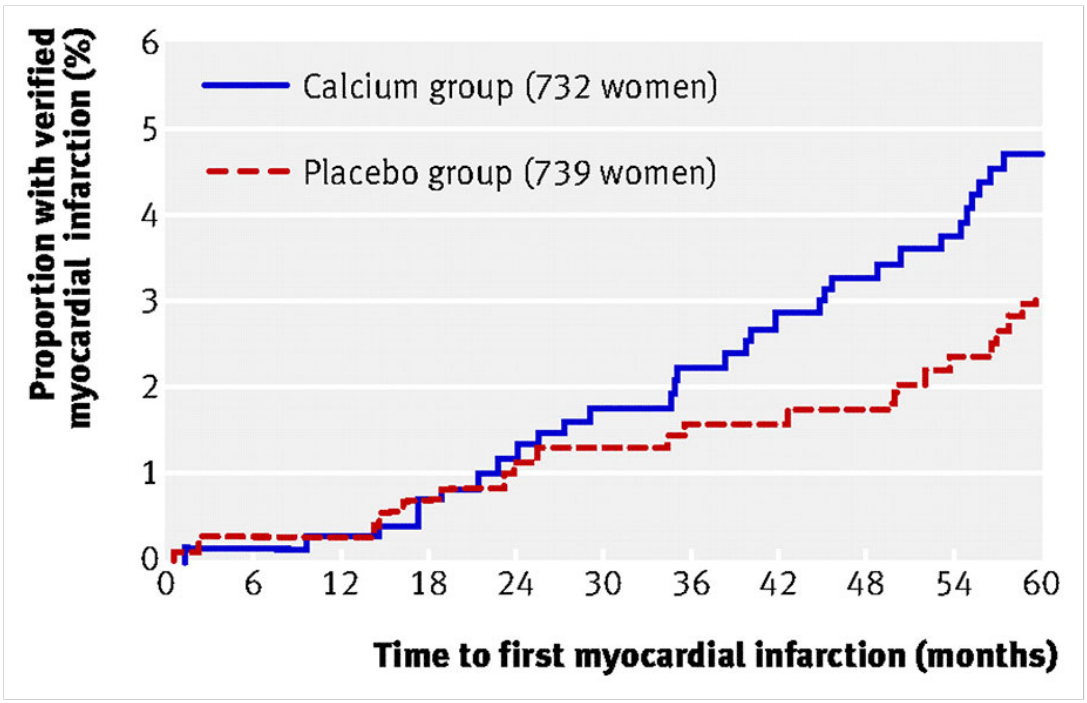

Figura 2.
Kaplan Meier curve showing adverse outcomes with calcium supplementation in 1471 healthy women [28] (full text). Reproduced with permission.

farction (HR 1.22; 95%CI 1.0-1.5) and stroke (HR 1.17; 95%CI 0.95-1.44) with calcium and vitamin D supplementation [33] (full text), of similar magnitude to that of previous work [29] (full text). Adding these data to the RECORD study [16], and a RCT of vitamin D and calcium on the incidence of cancer (Calcium and Vitamin D Malnutrition in Elderly Women) [34] (full text) led to the finding of a significant increase in myocardial infarction (RR 1.24; 95% CI 1.07-1.45). Using these data, treating 1000 patients with calcium, with or without vitamin D, for five years would cause an additional six myocardial infarctions or strokes and only prevent three fractures with no change in mortality. As with the calcium meta-analysis, these data are also limited by the inclusion of trials using different doses of the supplements, and the lack of prespecification of cardiovascular endpoints in the individual trials. For example, it is possible that in some people gastroinstestinal symptoms could have been misclassified as cardiovascular events, although this is less likely given that the increased risk is of a similar magnitude across all trials.

Observational data

Four large observational datasets have recently been published [35] [36] [37] [38] (full text). The Kuopio Osteoporosis Study [35] was a prospective cohort study of 10,555 women from the ages of 52-62 followed for seven years with the aim of prospectively assessing the effect of calcium supplementation, with or without vitamin D, on coronary heart disease (CHD). Compared with non-users of any supplement the authors found a statistically significant increased risk of incident CHD (HR 1.24; 95%CI 1.02-1.52) in users of calcium supplementation. In the EPIC-Heidelberg cohort [36], 23,390 healthy individuals between the ages of 35-64 were followed for an average eleven years. Calcium supplementation increased the risk of myocardial infarction both with vitamin D (HR 1.86; 95%CI 1.17-2.96) and without (HR 2.39; 95%CI 1.15-5.12). On the other hand, dairy calcium reduced the risk of myocardial infarction (HR 0.69; 95%CI 0.5-0.94). In the Swedish mammography cohort [38] (full text) of 61, 433 women, calcium supplements were observed to be associated with increased all-cause mortality when combined with dietary calcium intake above 1400 mg/day (HR 2.57; 95%CI 1.19-5.55). This emphasises that healthy individuals with adequate dietary calcium intake are exposing themselves to increased risk by taking unnecessary calcium supplements. Perhaps frail elderly patients with low dietary calcium intake, the only group in whom a reduced fracture rate has been clearly documented [21], may not be at increased cardiovascular risk from additional calcium The most recent data from the NIH-AARH study [37] in healthy Californians suggest that the risk of calcium supplementation is small in women with no co-morbidities, and a very low cardiovascular risk, but is elevated in men (in whom there is a clear dose-response, figura 3), and women with risk factors; previous or current smoking, hypertension or hypercholesterolaemia.

In any observational study it is difficult to counter confounding especially, when calcium supplement users typically have favourable cardiovascular risk factor profiles than non-users and are already more health conscious than peers, having volunteered for an observational dietary study [33] (full text). Careful correction for socio-economic factors was undertaken in these studies but nevertheless, the adverse risk from calcium supplementation might be greater in a truly normal population.

Aetiology of possible cardiovascular risk with calcium supplementation

Calcium supplements are not particularly palatable, and immediate complications are rare, mainly constipation [39]. In the medium term, users have a higher risk of renal calculi

[19] (full text). Early reports of reductions in blood pressure [40] [41] (full text), and improved lipid profile [28] (full text) [42], have led to complacency around the physiological effects of calcium supplementation and since calcium supplements are cheap to buy, and the clinical effects may only appear after decades, in the form of common diseases, monitoring is difficult and expensive. More recent data have demonstrated that acute hypercalcaemia causes increased blood coagulation [43] [44], arterial stiffness and impaired vasodilation [45] (full text) [46] [47] [48], raising systolic blood pressure through a dose-related impairment in endothelium vasodilator function [47]. Even a high-normal serum calcium level is associated with higher rates of vascular calcification [49] [50] (full text) carotid artery atheroma, cardiovascular events and mortality [51], especially if there are other cardiovascular co-morbidities such as renal disease [52], [53] (full text). Hence, it is not surprising that frankly high serum calcium levels are also associated with increased risks of CHD [54] [55] [56] (full text) and stroke [54]. Oral calcium supplementation acutely raises serum calcium levels into the borderline hypercalcaemic range for up to six hours [57] [58] [59]. This is not observed with dietary calcium due to slower absorption [60] [61]. Increased serum calcium levels could be causing vascular calcification by influencing pyrophosphate and binding to calcium-sensing receptors on vascular smooth muscle cells. It is therefore conceivable that regular dosing with calcium supplements could contribute to the development and progression of vascular disease increasing the risk of cardiovascular events (figura 4).

Calcium supplementation and existing cardiovascular disease

Studies of calcium supplementation have recruited healthy older people excluding those with existing cardiovascular disease limiting the breadth of the analyses possible in clarifying whether calcium supplementation represents an increased cardiovascular risk. The published observational studies are also biased towards individuals at overall lower risk.

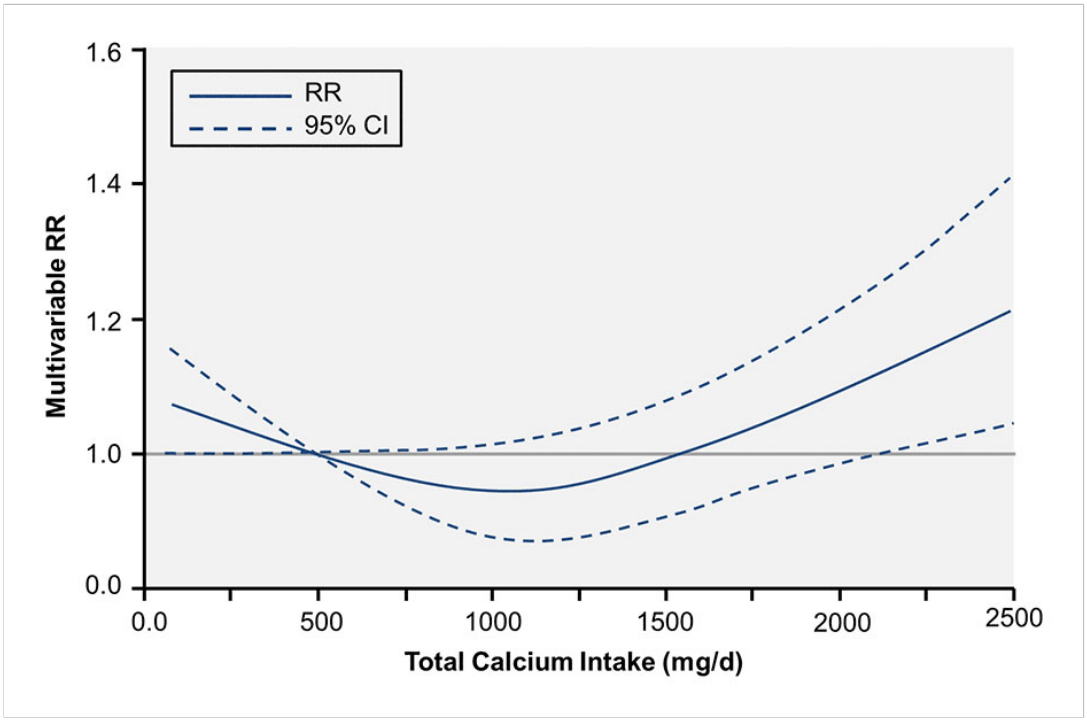

Figura 3.
Nonparametric regression curve displaying adjusted multivariate relative risks (RRs) and 95% CIs for the relationship between total calcium intake and total cardiovascular disease mortality in men [37]. Adapted with permission.

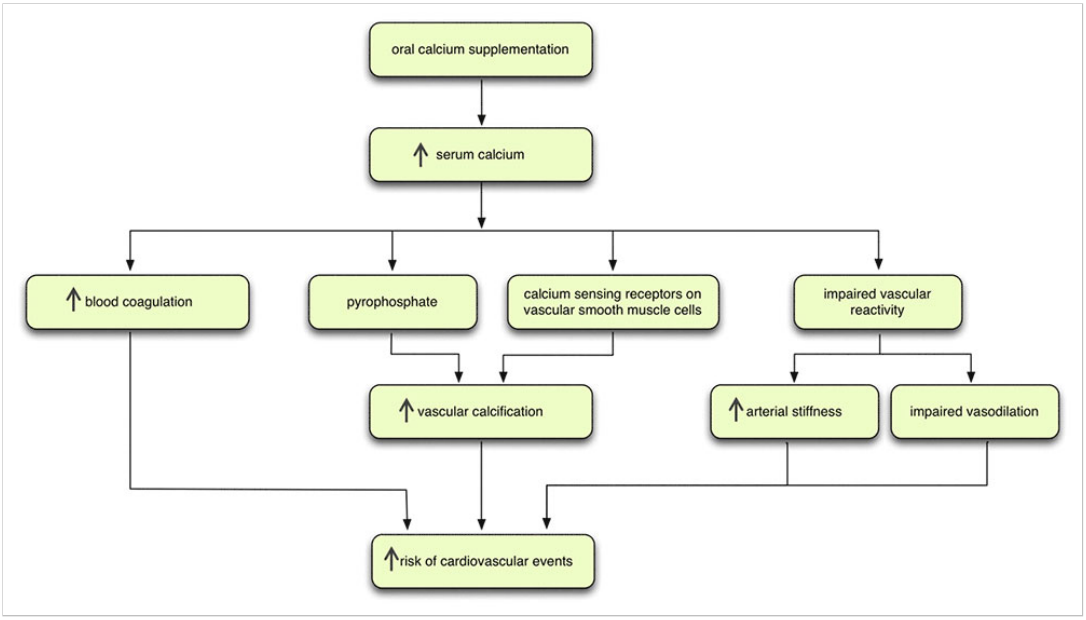

Figura 4.
Potential mechanisms that oral calcium supplementation may be associated with an increased risk of cardiovascular events.

Hence calcium supplementation in patients with an elevated cardiovascular risk profile such as smokers, hypertensive patients, and those with hypercholesterolaemia, diabetic patients, those with a previous myocardial infarction, might have a greater adverse effect than currently recognized. It is of course equally possible that calcium supplementation has a greater fracture prevention effect in these people with significant co-morbidities due to their higher overall risk of fractures. However, calcium supplements are currently widely prescribed to patients for whom there are no data at all.

Conclusion

Dietary calcium is an essential part of a balanced diet. Calcium supplements and low dose vitamin D are widely prescribed to individuals at risk of or with proven osteoporosis despite data demonstrating that although calcium supplementation might improve BMD, they do not prevent fractures or reduce the associated morbidity or mortality. Furthermore, there are no data supporting their widespread use in people with co-morbidities. On the other hand, there is gathering evidence that long term calcium supplementation might have an adverse effect on cardiovascular events especially in those at higher risk. Data are urgently needed to confirm the safety of calcium supplements in normal populations.

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