IN DEPTH REVIEW

Il consumo di proteine nell'insufficienza renale cronica rivisitato

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Introduzione

Dalla comparsa del lavoro di L.S Beale, più di 140 anni fa [1], la dieta ipoproteica viene proposta regolarmente ai pazienti affetti da malattia renale cronica (chronic kidney disease, CKD) e numerosi articoli sono stati pubblicati sui rischi, sui benefici e i limiti di tale dieta. Questi studi hanno portato alla conclusione che l'efficacia di tali diete sulla progressione dell'insufficienza renale è quantomeno discutibile mentre è molto significativa quando si consideri come outcome primario l'inizio della dialisi oppure la morte. Una riduzione nel consumo di proteine è associato a una diminuzione nei livelli plasmatici di fosfati, sodio e nell'acidosi. Pazienti con CKD che seguono una dieta ipoproteica migliorano i parametri biochimici e il loro outcome clinico [2] [3] [4] [5]; tuttavia, la sicurezza nutrizionale a lungo termine rimane incerta [6] (full text).

Recentemente, c'è stato un rinnovato interesse circa l'assunzione proteica con la dieta nella CKD in quanto è stato dimostrato che la tipica dieta del mondo occidentale, contenente alti livelli di grassi saturi, sodio, saccarosio , fruttosio e proteine derivanti da carni rosse, ma bassa in grassi insaturi, proteine vegetali e fibra alimentare, è associata allo sviluppo e alla progressione della CKD e degli eventi cardiovascolari, e che questi ultimi sono a loro volta la causa principale della morbilità e della mortalità nella CKD [7] (full text). Viceversa, altri studi hanno dimostrato l'effetto protettivo di una dieta vegetale sulla funzione renale e sui rischi cardiovascolari convenzionali e di nuova scoperta. Da questi studi è stata avanzata l'ipotesi che non sia soltanto la quantità di proteine consumata ma anche la loro origine che gioca un ruolo importante nella gestione dei pazienti affetti da CKD [8].

Il ruolo della quantità di proteine assunte con la dieta nella CKD

Dieta iperproteica

La tolleranza renale ad una dieta ad alto contenuto proteico è stata recentemente rivista alla luce del ruolo che tali diete hanno sulla popolazione generale per quanto riguarda il

calo ponderale. A livello sperimentale, la dieta iperproteica non nuoce la funzione renale nei ratti adulti sani [9] mentre nei ratti con una ridotta funzionalità renale, il declino del GFR è esacerbato se vengono alimentati con cibo iperproteico, ma migliora se viene somministrato cibo ipoproteico **[10]**.

Negli individui sani che consumano una dieta iperproteica a lungo termine, non viene osservato nessun peggioramento significativo della funzionalità renale [11]. Uno studio sulla salute generale condotto su una popolazione di infermiere, The Nurses' Health Study, ha confermato che, nelle donne con funzionalità renale normale seguite durante un periodo di 11 anni, il consumo di proteine nella dieta non esercitava nessun effetto sulla funzionalità renale. Viceversa, nelle donne affette da insufficienza renale iniziale o lieve, (stadio 1-2 CKD), una dieta iperproteica, soprattutto se di origine animale, (escludendo derivati del latte), poteva accelerare il declino della funzionalità renale già in atto [12]. Nei modelli sperimentali animali con uremia e nei pazienti affetti da CKD allo stadio 4-5, l'accumulo di tossine metaboliche peggiora la sindrome uremica mediante il peggioramento dello stress ossidativo, del funzionamento endoteliale e della resistenza insulinica [13]. Ciò accade con qualsiasi tipo di proteine [14], [15].

In sintesi, mentre non esistono chiare controindicazioni alla dieta iperproteica nei soggetti sani per quanto riguarda la funzionalità renale, un consumo eccessivo consumo proteico è da evitare nei soggetti affetti da CKD a rischio di progressione.

Dieta ipoproteica

L'effetto della dieta ipoproteica è conosciuto da molti decenni. In una CKD stabile, il fabbisogno del paziente può essere considerato sovrapponibile a quello di un soggetto sano ma, secondo le indicazioni del KDIGO, il consumo giornaliero dovrebbe essere ridotto a 0,8 g di proteine/kg/die per pazienti affetti da CKD allo stadio 4-5 [16], circa 50% del normale consumo proteico giornaliero per gli adulti occidentali. Uno studio recente che coinvolgeva 16872 adulti partecipanti al sondaggio National Health and Nutritional Examination Survey 2001-2008, ha dimostrato che il consumo proteico medio dei soggetti in vari stadi di CKD risultava abbondantemente superiore ai livelli raccomandati: 1,28, 1,25, 1,22 e 1,13 g/kg peso corporeo/die per gli stadi 1, 2, 3 e 4 rispettivamente [17]. Una dieta molto povera di proteine (supplemented very low protein diet o sVLPD), 0,3-0,4 g/kg/die, in aggiunta ad una miscela isomolare di alcuni aminoacidi essenziali (EAA) o analoghi privi di azoto, che fornisce equivalenti proteici ad alto valore biologico, potrebbe essere proposta ai pazienti affetti da CKD stadio 4-5 non affetti da severa co-morbidità, molto motivati e in grado di seguire dei regimi dietetici così stringenti. Si stima che circa 30% dei pazienti affetti da CKD stadio 4-5 potrebbe soddisfare tali criteri [18]. In ogni caso, il consumo di calorie dovrebbe mantenersi intorno a 30-35 kcal/kg per mantenere in equilibrio il bilancio azotato, sostituendo con una aumentata assunzione di carboidrati la perdita di calorie dovuta alla riduzione di proteine.

La dieta ipoproteica viene proposta da molto tempo ai pazienti affetti da CKD. Tale tipo di dieta esercita un effetto benefico sulla sindrome uremica, i cui sintomi sono in gran parte causati dall'accumulo del catabolismo proteico oltre che dall'accumulo di altre 'tossine uremiche' come fosfati ed acidi fissi.

L'interesse per la dieta ipoproteica si è acceso con la dimostrazione, in alcuni modelli animali di CKD, che una ridotta assunzione di proteine ha un effetto protettivo sulla funzionalità renale, in quanto previene l'aumento della pressione capillare e l'aumento del flusso glomerulare, che pur essendo entrambi meccanismi omeostatici, portano ad una progressiva glomerulosclerosi [19]. Purtroppo, i risultati degli studi clinici sono abbastanza deludenti: nello studio sulle modifiche della dieta nella CKD, *Modification of Diet in Renal Disease*

(MDRD), si è visto soltanto un trend non significativo nel declino della funzionalità renale dopo l'introduzione di una dieta ipoproteica [20]. Uno studio più recente non ha trovato nessuna differenza nella diminuzione del GFR in pazienti randomizzati affetti da CKD allo stadio 4-5 riguardo ad un regime ipoproteico oppure una dieta con moderata assunzione proteica [21]. Una meta-analisi che comprendeva 13 trial randomizzati controllati (n=1919 pazienti), ha confermato questi risultati: gli autori hanno osservato che l'effetto benefico della dieta ipoproteica (low protein diet, LPD) sul declino del GFR, se confrontato con una dieta qualsiasi, era solo del 7% (0,53 mL/min/anno) [22].

Tuttavia, se i risultati sulla perdita della funzione renale rimangano quantomeno discutibili, gli effetti della LPD diventano altamente significativi quando l'outcome primario da considerare è l'inizio del trattamento dialitico o la morte. Alcune meta-analisi hanno confermato una riduzione del 30-40% del numero di decessi per malattia renale in pazienti che seguono una LPD o una sVLPD [23], [24]. La sicurezza della dieta, più volte messa in questione, è stata viceversa confermata da altri studi, soprattutto da un recente studio prospettico multicentrico su 112 pazienti anziani non diabetici CKD-5 randomizzati in 2 gruppi: uno solo con dieta convenzionale sVLPD (0,3-0,4 g proteine/kg/die) e l'altro solo con l'inizio della dialisi regolare. Dopo un periodo di follow-up di 26,5 mesi, l'incidenza di mortalità era simile in entrambi i gruppi e l'incidenza di ospedalizzazione era più bassa nel gruppo sVLPD [25].

In effetti, quando i pazienti sono seguiti da un team composto da un dietologo e da un internista per garantire uno stretto controllo dell'adeguatezza proteica e calorica della dieta oltre che la compliance del paziente, si è visto che lo status nutrizionale del paziente rimane ben conservato. Nell'importante MDRD Study, dopo un follow-up medio di 2,2 anni, nonostante una piccola diminuzione di alcuni markers nutrizionali, non è stata osservata nessuna differenza tra i gruppi che seguivano diete diverse per quanto riguarda il tasso di mortalità, l'incidenza di prima ospedalizzazione e altri end points in entrambi i gruppi. Nessun paziente nel gruppo Study A e soltanto 2 pazienti nel gruppo Study B, (uno per ciascun gruppo dietetico), hanno raggiunto un end point per cachessia proteica [26]. In una serie di 203 pazienti con CKD 4-5 che hanno ricevuto una dieta sVLPD per una media di 33,1 mesi, non abbiamo osservato una correlazione tra l'incidenza di mortalità e la pregressa durata della dieta una volta iniziata la dialisi. Gli outcome dei pazienti erano simili a quelli registrati nel Registro Francese della Dialisi per quanto riguarda il gruppo in trattamento dialitico (n=101) e simile agli outcome del gruppo trapiantati (n=102) del centro di Bordeaux durante lo stesso periodo [27] **(full text)**. In contrasto con questi risultati, uno studio recente ha riportato che i pazienti appartenenti al MDRD Study B che avevano seguito la dieta sVLPD presentavano un aumento del tasso di mortalità a lungo termine una volta iniziata la terapia dialitica [28]. Inoltre, in contrasto con il protocollo rigoroso del MDRD Study, questo studio conteneva alcune falle: in particolare, nessuna informazione era stata fornita riguardo alla gestione medica e al decorso clinico durante il periodo trascorso tra la fine del MDRD Study fino all'analisi da parte del US Renal Data System database, avvenuta 7 anni più tardi [29]. Pare sorprendente che, nonostante questi evidenti problemi, i risultati di questa serie continuino ad essere utilizzati per giustificare il rifiuto o quantomeno la riluttanza da parte dei curanti a proporre la dieta sVLPD a pazienti CKD selezionati.

Il ruolo della fonte delle proteine assunte nei pazienti affetti da CKD

Il ruolo della fonte delle proteine assunte con la dieta sulla funzionalità renale è stato ben illustrato da studi sia a livello sperimentale che clinico. Nei ratti con massa renale ridotta, una dieta ricca di caseina riduce la funzionalità renale, mentre animali che ricevono una dieta

ricca di soia, contenente un identico livello di proteine, presentano una più lenta progressione di malattia [30].

Kontessis et al hanno dimostrato in alcuni studi su soggetti sani che, al pari contenuto di proteine, una dieta vegetariana con soia produceva una resistenza vascolare renale maggiore e una ridotta clearance dell'albumina frazionata se confrontata con una dieta con proteine di origine animale. Ciò potrebbe essere spiegato, almeno in parte, da differenze nella concentrazione plasmatica di aminoacidi e IGF-1 [31]. È generalmente accettato che i vegetariani presentano un GFR significativamente più basso rispetto ai non-vegetariani: tuttavia, uno studio recente non ha riscontrato nessuna differenza reale tra la funzionalità renale di 102 suore buddiste vegetariane quando confrontate con un gruppo di soggetti onnivori [32].

Mentre è relativamente facile valutare l'effetto della modifica di uno o più micronutrienti nella dieta in modelli animali, è decisamente più difficile negli esseri umani. Le diete vegetariane non sono sovrapponibili fra loro, variando da una dieta standard arricchita con frutta, verdura, cereali e latticini poveri in grassi, come, per esempio la dieta DASH (Dietary Approach to Stop Hypertension) [33] oppure la classica dieta mediterranea (Mediterranean diet) [34] (full text) alle diete vegetariane [35] (full text). Tuttavia, tutte queste diete presentano alcune caratteristiche in comune: forniscono grandi quantità di cereali integrali, frutta secca oleosa, frutta, legumi e verdure, permettendo al paziente di beneficiare di una vasta scelta di cibi gustosi. Queste diete sono ricche in acidi grassi n-6, fibre, acido folico, potassio, magnesio, vitamina C, vitamina E, carotenoidi e molte altre sostanze fitochimiche, mentre contengono pochi cibi processati e raffinati, fonte di proteine e di grassi di origine animale, di grassi saturi, sale e fosforo. Le diete vegetariane sono anche generalmente meno caloriche [35] (full text). I benefici potenziali di una dieta a base di vegetali nei pazienti affetti da CKD sono legati non solo alle differenze quantitative e qualitative delle fonti delle proteine, ma anche alla riduzione del rischio associato ad alcune componenti della dieta tipica 'occidentale', considerate fattori di rischio importanti nel peggioramento della funzionalità renale e nella progressione del CKD mediante le complicazioni indotte dalla dislipidemia, lo stress ossidativo e i processi di infiammazione [7] (full text).

Non abbiamo identificato nessuno studio sulla prevalenza o sull'outcome della CKD nelle popolazioni vegetariane. Tuttavia, ampi studi sui vegetariani hanno dimostrato che la prevalenza dell'ipertensione e del diabete mellito 2, le cause principali della CKD nei paesi industrializzati, è significativamente più bassa rispetto ai non vegetariani [36] [37] e, quindi, si può ipotizzare che anche la prevalenza della CKD sia ridotta in queste popolazioni.

Oltre all'assenza di alcune componenti dannose nella dieta tipica occidentale, esistono altri fattori che potrebbero spiegare un effetto protettivo renale diretto delle diete vegetariane. Tali fattori sono elencati nella **Tabella 1** [8], [38], [39] (full text), [40] (full text).

Tabella 1. Effetti benefici della dieta vegetariana sulla funzionalità renale.

Riduzione della biodisponibilità del fosforo
Miglioramento dell'insulinoresistenza
Migliore controllo dell'acidosi
Riduzione della produzione di tossine uremiche, compresi p-cresilsolfato ed indoxilsolfato, entrambi implicati nella progressione della CKD
La dieta ad alto contenuto di fibre alimentari è associata ad una riduzione dell'infiammazione ed un abbassamento della mortalità in pazienti con CKD
Miglioramento della disfunzione endoteliale, della proteinuria e del profilo lipidico (soprattutto con cibi contenenti soia)

In soggetti non CKD, la dieta vegetariana produce chiari benefici su quasi la totalità dei fattori di rischio cardiovascolari, compresi obesità, ipertensione arteriosa, diabete mellito 2, profilo lipidico, stress ossidativo. In grandi di avventisti del settimo giorno (Seventh-Day Adventists) e dello studio EPIC-Oxford, che studiavano soggetti vegetariani e non, con stile di vita e classe sociale molto simili, la mortalità per malattie coronariche era più bassa del 25-30% nei vegetariani [41] (full text). Ci si aspetterebbero analoghi benefici nelle popolazioni CKD, per cui le malattie cardiovascolari rappresentano la più comune causa di morte [42].

Infine, è evidente che anche altri fattori non legati alla dieta, ma che possono essere inclusi nello 'stile di vita vegetariano' come, per esempio, più attività fisica, meno obesità, assenza di tabagismo e basso consumo di alcool, possono facilmente contribuire a questi dati favorevoli.

Oltre agli effetti benefici sulle malattie cardiovascolari, la dieta vegetariana esercita altri benefici sulle complicanze metaboliche della CKD, che verranno esaminati nei seguenti paragrafi.

Contenuto dei fosfati nella dieta

L'iperfosfatemia rappresenta un fattore di rischio indipendente per la mortalità nei pazienti con CKD 3-4. L'iperfosfatemia è provocata dallo squilibrio tra una ridotta escrezione di fosfati e il consumo di cibi ricchi di fosfati, soprattutto carne bovina e latticini, comune nelle popolazioni occidentali. Tale squilibrio viene ulteriormente peggiorato dai conservanti a base di fosforo presenti nei cibi processati o 'fast food', risultando in un consumo di fosforo fino a 1000 mg/die [43] . La dieta vegetariana è stata proposta per mantenere l'omeostasi fosfatica nei pazienti con CKD [44] (full text) Inoltre, la dieta sVLPD è associata alla riduzione dei livelli di fosfatemia [45].

La biodisponibilità del fosforo varia molto: l'assorbimento intestinale è di circa 80% per fosforo proveniente dalla carne ma di circa 30-40% per quello proveniente da fonti vegetali, in quanto il fosforo vegetale è contenuto nei fitati e gli esseri umani non possiedono l'enzima intestinale fitasi. Se confrontata con una dieta normale, la dieta vegetariana è associata ad una riduzione significativa di fosfatemia, di livelli di FGF-23 e di fosfaturia nelle 24h, ad eguale contenuto di proteine e di fosforo [46]. Questo è un punto importante in quanto sia la fosfatemia che il livello di FGF-23 sono associati in modo indipendente agli eventi cardiovascolari e alla mortalità da qualsiasi causa in pazienti CKD. Recentemente, Di Ioro et al hanno dimostrato che il carico fosfatico attenua l'effetto antiproteinurico della VLPD [47]. Ciò conferma che la fonte proteica potrebbe essere un fattore importante e modificabile mediante la riduzione nella dieta dei cibi industriali, contenenti grandi quantità di fosfati.

L'insulinoresistenza

L'insulinoresistenza, strettamente associata all'aterosclerosi e alla mortalità cardiovascolare nella popolazione generale, è presente comunemente nei pazienti in vari stadi della CKD, ed è dovuta ad un deficit post-recettoriale della risposta muscolare [48] (full text). Inoltre, l'insulinoresistenza gioca un ruolo importante nella patogenesi della cachessia proteica nei pazienti con CKD, in relazione all'accelerazione del catabolismo delle proteine [49]. Altri fattori, come l'acidosi metabolica, l'infiammazione, l'iperparatiroidismo secondaria ed altri fattori associati probabilmente al metabolismo proteico sono presumibilmente coinvolti nel fenomeno dell'insulinoresistenza, tutti fattori soggetti a miglioramento dopo l'introduzione di una dieta vegetariana e la riduzione del consumo di proteine. Dopo 3 mesi

di una dieta vegetariana associata ad un ridotto consumo proteico nei pazienti con CKD, la sensitività insulinica migliorava, con una riduzione dell'insulinemia a digiuno, della glicemia e della produzione glucidica endogena, con una conseguente riduzione del fabbisogno giornaliero di insulina nei pazienti diabetici con insufficienza renale [50].

E' altrettanto vero che, anche nei soggetti vegetariani sani, si osserva un miglioramento della sensitività insulinica e tale miglioramento persiste anche dopo correzione di possibili fattori confondenti [51]. Inoltre, il grado di miglioramento della sensitività insulinica è correlato agli anni di dieta vegetariana [52].

L'acidosi metabolica

L'acidosi metabolica, abbastanza frequente nei pazienti con CKD, produce effetti negativi a livello endocrino, metabolico e muscoloscheletrico, grazie all'effetto di enzimi catabolici presenti nel muscolo.

Nei soggetti sani, la tipica dieta occidentale tende all'acidosi, con un carico acido presente nella dieta di circa 50-75 mEq/die, mentre le diete vegetariane o quelle arricchite con frutta, verdure, legumi e frutta secca oleosa, sono, in contrasto, ricche di proteine basiche e forniscono un carico acido non superiore a 30 mEq/die, nonostante un identico consumo proteico totale. Osservazioni simili sono state fatte per i pazienti affetti da CKD. In uno studio incrociato che comprendeva quasi 3000 pazienti con CKD allo stadio 2-4, l'introduzione di una maggiore quantità di proteine vegetali nella dieta era associata ad un aumento del bicarbonato plasmatico a prescindere dalla quantità di consumo proteico [46].

Recenti scoperte nell'uomo e anche in modelli animali suggeriscono che, nell'insufficienza renale, l'acidosi metabolica sia un fattore di rischio indipendente per la progressione di malattia [53]. Il peggioramento del GFR potrebbe essere favorito dall'aumento dei radicali liberi dell'ossigeno e dalla upregulation del gene endoteliale, provocando vasocostrizione e fibrosi [54] (full text). La somministrazione di supplementi alcalini a lungo termine esercita un effetto protettivo renale [55] (full text). Un recente studio ha dimostrato gli effetti favorevoli, simili a quelli prodotti dalla somministrazione di alcalini, di un aumento del consumo giornaliero di frutta e verdura in pazienti con nefropatia ipertensiva macroalbuminurica CKD-2. I fattori coinvolti includevano la proteinuria e il controllo pressorio [56].

Effetti benefici simili sulle stesse complicanze metaboliche sono state riportate per pazienti che seguivano la dieta sVLPD e ed attribuiti alla riduzione del consumo di proteine. La percentuale alta di proteine di origine vegetale in questo tipo di dieta gioca anche un ruolo. Siccome risulta difficile distinguere dissociare gli uni (riduzione del contenuto proteico) dagli altri (proteine di origine vegetale), pare logico consigliare ai pazienti con CKD di associare la riduzione 'ragionevole' del consumo di proteine (di circa 0,6–0,8g/kg/die) alla preferenza per le proteine di origine vegetale. E' sorprendente, quindi, che il recente KDIGO-CKD non faccia menzione di raccomandazioni riguardo al consumo di proteine [16].

C'è ancora posto per gli EAA ed analoghi?

Un punto importante nella gestione del CKD è il posto che occupano i supplementi con EAA (aminoacidi essenziali) o i loro analoghi privi di azoto. In effetti, se ci si propone di aumentare il consumo di proteine a circa 0,6-0,8 g/kg/die, la supplementazione con EAA diventa discutibile in quanto, almeno in teoria, il fabbisogno dei pazienti è già quantitativamente soddisfatto. In una recente revisione, Kovesdy et al [57] propongono che aggiungere proteine ad alto valore biologico (EAA o i loro analoghi privi di azoto), ad una dieta già contenente 0,6-0,8 g proteina/kg/die potrebbe essere utile in alcune condizioni ipercatabo-

liche, come, per esempio, la elevata proteinuria, il sanguinamento cronico o i disturbi gastrointestinali, che richiedono un aumentato consumo di energie e quindi anche di proteine. La dieta molto ipoproteica è anche associata ad un migliore controllo pressorio se fattori come il tipo di proteina, la riduzione del consumo di sale e la supplementazione con chetoanaloghi sono anche considerati [58].

Anche nei pazienti più anziani, molto rappresentati nella popolazione CKD non in dialisi, alla luce dello studio di Brunori et al [25] e dell'analisi medico-economica effettuata da Scalone et al [51], pare ragionevole proporre una dieta che fornisce 0,6-0,8 g proteina, soprattutto di origine vegetale, supplementata con EAA ed analoghi privi di azoto, per garantire un corretto equilibrio del bilancio azotato.

Conclusioni

La maggior parte degli autori consiglia di evitare un consumo troppo alto, incontrollato, di proteine nei pazienti affetti da CKD, e raccomanda una moderata riduzione della assunzione di proteine nei pazienti CKD allo stadio 4-5 per alleviare i sintomi uremici e ritardare il più possibile l'inizio del trattamento dialitico. I rischi e i limiti della dieta ipoproteica sono conosciuti da tempo, ma è importante ricordarsi che i pazienti, se sottoposti a regolare follow-up, non corrono il rischio della malnutrizione.

Un dato nuovo ed interessante è costituito dall'interesse recente per le diete basate su cibi vegetali per i pazienti affetti da CKD. Queste diete permettono una maggiore flessibilità dietetica e una scelta più varia dei cibi, favorendo la compliance da parte dei pazienti ma anche un maggiore apporto calorico. Inoltre, le diete vegetali esercitano effetti benefici anche a livello cardiovascolare e metabolico, entrambi problemi comuni che peggiorano gli outcome in questi pazienti.

Infine, l'uso degli EAA e i loro analoghi privi di azoto, unito ad una ridotta assunzione proteica, ed a una dieta contenente proteine di origine vegetale, è giustificato negli anziani o in situazioni di catabolismo per garantire la disponibilità di proteine di alto valore metabolico per l'aumentato fabbisogno del paziente.

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IN DEPTH REVIEW

Protein intake in chronic renal failure revisited

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Key words: chronic kidney disease, plant-based diet, protein intake

Introduction

Since the initial work by L.S Beale, over 140 years ago [1], *restricted protein diet has been widely proposed to patients with chronic kidney disease (CKD)* and numerous articles have been published on the benefits, risks and limits of *this dietary prescription*. The main conclusions which have been drawn from these studies are that efficacy of such diets on the progression of renal failure is at least questionable while effects are highly significant when onset of dialysis or death are the primary outcomes. Decrease in protein intake is associated with decrease in phosphate, sodium and acid load, CKD patients on such diets improve biochemical variables and clinical outcomes [2], [3], [4], [5], *nevertheless*, long-term nutritional safety remains questionable [6] (full text).

Recently, the interest for protein intake in CKD has been renewed when it has been shown that a Western-style dietary pattern and its different components (high in saturated fat, sucrose and fructose, proteins from red meat, sodium and low in polyunsaturated fat, plant-derived protein and fiber content) are associated with the development and progression of kidney disease and cardiovascular events, these latter being the main cause of morbidity and mortality in CKD [7] (full text). Conversely, several studies have reported protective effects of plant-based diets on renal function and on traditional and nontraditional cardiovascular risk factors. According to these different *findings*, it has been advanced that, apart from the amount of protein intake, the source of protein could also play an important role in the management of CKD patients [8].

Role of the amount of protein intake in CKD

High protein intake

The renal tolerance of high-protein diets has been recently questioned as they are currently proposed as weight-loss tools in the general population. Experimentally, long-term high-protein diet has no deleterious effect on renal function in healthy adult rats [9] while in rats with remnant kidney, GFR decline is exacerbated by increased amounts of standard rat chow protein and improved by its reduction [10].

No significant change in renal function or blood pressure was observed in healthy individuals on a long-term high protein diet [11]. The Nurses' Health Study confirmed that in women with normal renal function followed over an 11-yr period, there is no impact of protein intake on renal function. However, in women with beginning or mild renal insufficiency (stage 1-2 CKD) high protein intake, particularly of nondairy animal protein, may accelerate renal function decline [12]. In uremic animal models and in patients with stage 4-5 CKD, the accumulation of metabolic waste products aggravate uremic syndrome by worsening oxidative stress, endothelial function and insulin resistance [13]. Such findings are observed whatever the source of protein [14], [15].

To summarize, while there are no clear renal-related contraindications to high protein diets in healthy individuals, it is wise to avoid excessive protein intake in adults with CKD at risk of progression.

Reduced protein intake

As opposed to high protein intakes, effects of reduced protein intake in renal failure have been widely described for decades. In stable CKD patients, dietary protein requirements are similar to those of normal healthy individuals, but according to KDIGO recommendations, the daily allowance should be decreased to 0.8 g protein/kg/day of mixed biological value for stage 4-5 CKD patients [16], *which is approximately 50% of usual western adult protein intake. A recent study concerning 16872 adults participating in the National Health and Nutritional Examination Survey 2001-2008, has shown that average dietary protein intake in adults with different stages of CKD was well above recommended levels : 1.28, 1.25, 1.22 and 1.13 g/kg BW/d for stages 1, 2, 3 and 4 respectively [17].* A supplemented very low protein diet (sVLPD), 0.3-0.4 g/kg/day supplemented with an isomolar mixture of some essential amino acids (EAA) and nitrogen-free analogues, to provide equivalents of protein of high biological value, could be proposed to stage 4-5 CKD patients, without severe comorbid conditions, selected with regard to their motivation and ability to follow such dietary prescriptions. Thirty percent of stage 4-5 CKD populations could meet these criteria [18]. In any case energy intake should be in the range of 30-35 kcal/kg to ensure nitrogen balance, the loss in calories due to protein restriction should be compensated by an increase in the amount of ingested carbohydrates.

Restricted protein intake has been proposed for a long time to CKD patients because of its beneficial effects on uremic syndrome, most of the symptoms of which are caused by the accumulation of waste products of protein metabolism and also of phosphates and fixed acids which both behave as "uremic toxins".

The interest for low-protein diet was reinforced when it was shown, in some CKD animal models, that reduction in protein intake had protective effects on renal function, mainly through the prevention of the increase in capillary pressure and glomerular flow which are functionally adaptive but physically detrimental leading to progressive glomerulosclerosis [19]. Unfortunately results of clinical studies have been rather disappointing: only a non significant trend to a slower decline of kidney function in CKD patients on LPD was observed in *the Modification of Diet in Renal Disease* (MDRD) Study [20]. A more recent study found no difference over a 48-month follow-up, in the decline in GFR in 423 stage 4-5 CKD patients randomly assigned to a low- vs moderate-protein diet [21]. A meta-analysis including 13 randomized, controlled trials (n=1919 patients), confirmed these results, the authors observed that the beneficial effect of a low-protein diet (LPD) on the rate of decline in glomerular filtration rate (GFR) compared with no dietary prescription was only 7% (0.53 mL /min/yr) [22].

If results on the loss of renal function remain at least debatable, on the other hand, effects of LPD become highly significant when onset of dialysis or death is the primary outcome. Several meta-analyses have confirmed a 30-40% reduction in the number of renal deaths in patients on LPD or sVLPD [23], [24]. The safety of the diet, which has been frequently questioned, has been confirmed by several studies and is well illustrated by a recent prospective multicenter study concerning 112 elderly non diabetic patients stage 5-CKD who were randomly assigned to receive a conventional sVLPD (0.3-0.4 g protein/kg/d) or to start regular dialysis treatment. After a 26.5-month follow-up, all-cause mortality rates were similar in the two groups and hospitalization rates were lower in the sVLPD group [25].

In fact, when patients are regularly and jointly followed-up by a physician and a dietitian to survey the proteic and caloric adequacy of the diet and compliance with the dietary prescription, nutritional status of patients remains well preserved. In the landmark MDRD Study, after a mean follow-up of 2.2 years, despite a small decline in some nutritional markers over time, no difference *was observed* between diet groups in the rates of death, first hospitalizations or other « stop points » in either study. No patient in Study A and only two patients in Study B (one from each diet group) reached a stop point due to protein-energy wasting [26]. In a series of 203 *stage 4-5 CKD* patients who received a sVLPD for a mean duration of 33.1 months, we did not observe a correlation between death rate and previous duration of the diet once patients were on renal replacement therapy. Patient outcomes were similar to those of the French Dialysis Registry patients for the dialysis group (n=101) and similar to those of the patients who were transplanted in the same center in Bordeaux during the same period for the transplant group (n=102) [27] (full text). Contrasting with these results, a recent study has reported that patients of the MDRD Study B previously assigned to sVLPD presented an increased death rate on the long term, once on renal replacement therapy [28]). Contrary to the rigorous protocol of the MDRD Study, there were several flaws in this latter study; *in particular* no information was provided about medical management and clinical course during the period from the end of the MDRD Study until examination of the US Renal Data System database seven years later [29]. It is quite surprising that despite these glaring shortcomings, results of this series keep on being put forward to justify the reluctance or even the rejection to *propose* this diet to *selected* CKD patients.

Role of the sources of protein intake in CKD:

The consequences of the source of protein intake on renal function are well illustrated by both experimental and clinical studies. In rats with experimentally reduced nephron mass, casein diet has a deleterious effect on renal function while animals fed soy diet, with the same amount of protein, have much slower progression of renal disease [30].

Kontessis et al. have shown in several studies in healthy individuals that, for a similar amount of protein intake, vegetarian diet and soy diet induced greater renal vascular resistance and reduced fractional clearance of albumin compared with animal protein diet. This could be partly explained by differences in plasma concentrations of amino acids and IGF-1 [31]. As a consequence, it is generally admitted that GFR is significantly lower in vegetarians than in non-vegetarians, however a recent study did not find any difference in renal function between 102 Buddhist vegetarian nuns and a matched group of omnivores [32].

While it is easy to assess the effects of an alteration of one specific macro- or micronutriment in animal models, it is more difficult in humans. Plant-based diets are not unequivocal and range from a standard diet enriched with fruits, vegetables, low-fat dairy products and whole grains such as the Dietary Approach to Stop Hypertension (DASH) diet

[33] or the Mediterranean diet [34] (full text) to the different varieties of vegetarian diets [35] (full text). *However, all* these diets have some characteristics in common: they provide large amounts of whole-grain cereals, nuts, fruits, legumes and vegetables which allow the patient to benefit from a greater variety and better palatability of foods from which to choose. These diets are rich in n-6 fatty acids, dietary fibers, folic acid, K, Mg, vitamin C, vitamin E, carotenoids and many phytochemicals and relatively poor in highly processed and refined foods, in protein of animal origin, in animal fat, saturated fat, salt and phosphorus and are generally associated to a lower caloric intake [35] (full text). Thus potential benefits of plant-based diets in CKD patients are not only related to the quantitative and/or qualitative changes in protein supply but also to the associated reduction of some components of the Western-style diet which are considered as important risk factors for impaired kidney function and development and progression of CKD and its complications via the induction of dyslipidemia, oxidative stress and inflammation [7] (full text).

We could not identify studies on the prevalence of renal disease and their outcome in vegetarian populations, but as studies of large series of vegetarians have shown that hypertension and type 2 diabetes, which are the leading causes of CKD in industrialized countries, are significantly less prevalent than in non vegetarians [36], [37], it can be hypothesized that prevalence of CKD could also be reduced in vegetarians compared with non vegetarians.

Besides the withdrawal of some deleterious factors from the Western diet, several grounds, which could explain a direct renal protective effect of vegetarian diets, are listed in **Table 1** [8], [38], [39] (full text), [40] (full text).

In non-CKD individuals, there is a clear benefit of the vegetarian diets on most of the traditional risk factors of cardiovascular disease: obesity, hypertension, type 2 diabetes, lipid profile and oxidative stress. In the large cohorts of Seventh-Day Adventists and of the EPIC-Oxford Study which included vegetarians and non vegetarians of similar lifestyle and social class, coronary heart disease mortality was 25-30% lower in the vegetarians [41] (full text). Similar benefit of vegetarian diet could be expected in CKD populations whom cardiovascular diseases are the leading cause of death [42].

Lastly, it should also be stated that non-dietary lifestyle factors such as higher levels of physical activity and lower prevalence of obesity, smoking and alcohol consumption, which are generally reported in the cohort of vegetarians, may also contribute to these favorable data.

Besides its effect on *development of* cardiovascular disease, a beneficial effect of vegetarian-based diets has also been observed on some of the main metabolic complications, which hamper the outcome of CKD patients:

- ***Dietary Phosphate load***

Hyperphosphatemia is an independent risk factor for mortality in stage-3-4 CKD patients, which results from an imbalance between a reduced urinary excretion of phosphate and high intakes of phosphorus-rich foods in the western diets, which are usually rich in dairy products and protein sources. This imbalance is worsened by phosphorus-based additives added to processed and fast foods which may increase daily phosphorus load until 1000 mg/day [43]. It has been *proposed* that vegetarian-based diet should be recommended for the control of phosphorus homeostasis in CKD patients [44] (full text). It has been previously shown that sVLPD is associated to a lowering of serum phosphate levels [45].

Bioavailability of phosphorus varies widely according to sources from an intestinal absorption rate of 80% for phosphorus from a meat source to 30-40% for phosphorus from vegetal source which is mostly in the form of phytate and is poorly absorbed because lack

of phytase in humans. Compared with usual diet, the same amount of protein and phosphorus in vegetarian diet is associated with a significant reduction in serum phosphorus and FGF 23 levels and in urinary 24-h phosphorus excretion [46]. This is an important point since serum phosphorus and FGF-23 concentration are independently associated with CV events and all-cause deaths in CKD patients. Recently, Di Ioro et col. demonstrated that phosphate load attenuates the antiproteinuric effect of VLPD [47]. This confirms that the source of protein could be an important modifiable factor with the reduction of processed food, which contain high amount of phosphate salt.

- *Insulin resistance*

Insulin resistance, which is closely associated with atherosclerosis and CV mortality in the general population, is commonly observed in patients with various stages of CKD where it is due to a post-receptor defect in muscle responsiveness [48] (full text). Moreover, insulin resistance plays also a role in the pathogenesis of protein energy wasting of CKD patients, in relation with an accelerated protein catabolism [49]. Metabolic acidosis, *inflammation,* secondary hyperparathyroidism and putative factors deriving from protein metabolism have been put forward to explain insulin resistance, both of them are improved by vegetarian diet as also by a quantitative reduction in protein intake. In CKD patients, after 3 months of a vegetarian diet associated with a reduction in protein intake, insulin sensitivity improved: fasting serum insulin levels, blood glucose levels and endogenous glucose production were reduced, as a confirmation daily insulin requirements decreased in diabetic patients with renal failure [50].

It is noticeable that *improved* insulin sensitivity is also observed in vegetarians with normal renal function and persists after adjustment for possible confounding factors [51], moreover the degree of insulin sensitivity is correlated with years on vegetarian diet [52].

- *Metabolic acidosis*

Metabolic acidosis, which is quite common in CKD patients, has detrimental endocrine, metabolic and musculoskeletal consequences due to the increased activity of muscle catabolic enzymes.

In healthy subjects, contemporary westernized diets are largely acid-inducing with median estimates of dietary acid load of approximately 50-75 mEq/day, while vegetarian diets or diets that are enriched with plant foods (fruits, vegetables, nuts and legumes) are rich in base-inducing protein and yield a dietary acid load not exceeding 30 mEq/day despite identical protein intake. Similar statements have been made in CKD patients. In a cross-sectional study including nearly 3000 stage-2-4 CKD patients, a higher percentage of protein from plant sources was associated with a rise in plasma bicarbonate whatever the total protein intake [46].

Table 1. Effetti benefici della dieta vegetariana sulla funzionalità renale.

Riduzione della biodisponibilità del fosforo
Miglioramento dell'insulinoresistenza
Migliore controllo dell'acidosi
Riduzione della produzione di tossine uremiche, compresi p-cresilsolfato ed indoxilsolfato, entrambi implicati nella progressione della CKD
La dieta ad alto contenuto di fibre alimentari è associata ad una riduzione dell'infiammazione ed un abbassamento della mortalità in pazienti con CKD
Miglioramento della disfunzione endoteliale, della proteinuria e del profilo lipidico (soprattutto con cibi contenenti soia)

Recent findings in animals and humans suggest that, in chronic renal failure, metabolic acidosis is an independent risk factor for kidney disease progression [53]. GFR decline could be favored by increased production of reactive oxygen species and upregulation of the endothelin gene leading to vasoconstriction and fibrosis [54] (full text). Long-term alkali supplementation has an effective kidney-protective effect [55] (full text). A recent study has shown that increase in the daily intake of fruits and vegetables in patients with macroalbuminuric hypertensive nephropathy stage 2-CKD had favorable effects, similar to those of alkali supplementation, on some factors of progression of renal failure: proteinuria and blood pressure [56].

Similar beneficial effects on these metabolic complications have been previously reported in patients on sVLPD and fully attributed to the reduction of protein intake. The high percentage of protein of vegetal origin in this type of diet plays also a role. As it is quite uneasy to dissociate the peculiar effects of the reduced amount of dietary protein intake from those of the vegetarian source of protein, it seems logical to advise CKD patients to associate a reasonable reduction in protein intake (0.6–0.8 g/kg/d) with a predominance of proteins from vegetal origin. Surprisingly, there is no specific mention on the source of protein in the recent KDIGO-CKD recommendations concerning protein intake [16].

Is there still a place for EAAs and analogues?

One important point refers to the place of the supplementation with EAA and their nitrogen-free analogues in the management of CKD patients. As a matter of fact, if it is proposed to raise protein intake to 0.6-0.8 g/kg/d, supplementation with EAAs becomes questionable since, theoretically, such *quantitative* protein intake meets patients' nutritional requirements. In a recent review, Kovesdy et al [57] suggest that the addition of protein with high biological value (EAAs and/or nitrogen-free analogues) to a dietary protein intake of 0.6-0.8 g/kg/d may be beneficial in some hypercatabolic conditions such as infection, heavy proteinuria, chronic bleeding, gastro-intestinal disorders which all require increased energy and protein intake. Very low protein diet is also associated with a better control of blood pressure in relation with type of protein, ketoanalog supplementation and reduction of salt intake [58].

In older patients, who are overrepresented in the nondialyzed CKD population, in the light of the study of Brunori et al [25] and of the secondary medico-economic analysis by Scalone et al [51], it seems reasonable to propose a diet providing 0.6-0.8 g protein predominantly of vegetal origin/kg supplemented with EAAs and nitrogen-free analogues to ensure nitrogen balance.

Conclusion

Most authors advise to avoid uncontrolled high protein intake in CKD patients and recommend a moderate reduction in protein intake in stage 4-5 CKD patients to alleviate uremic symptoms and therefore to delay the initiation of renal replacement therapy. Risks and limits of restricted-protein diets are well known, but it is important to recall that there is no specific risk of malnutrition provided that patients are regularly followed and monitored.

The new fact comes from the recent interest for the plant-based diets in CKD patients which allows an increased variability and flexibility in the choice of foods favoring a higher energy intake and improving compliance to the diet. Moreover, plant-based diets have beneficial

effects on cardiovascular and metabolic complications, which worsen the outcome of CKD patients.

Lastly, EAAs and their nitrogen-free analogues in association with a reduced intake of protein, predominantly of vegetal origin, are justified in the elderly and in catabolic situations to provide adequate amount of protein of high biological value and so to meet patient's nutritional needs.

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