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Dietary antioxidants and oxidative stress in predialysis chronic kidney disease patients

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ABSTRACT

Context: Dietary antioxidants are important in protecting against human diseases. Oxidative stress, a non-traditional risk factor of cardio-vascular disease is far more prevalent in chronic kidney disease (CKD) patients than in normal subjects. **Evidence Acquisitions:** Directory of Open Access Journals (DOAJ), Google Scholar, Pubmed (NLM), LISTA (EBSCO) and Web of Science have been searched. **Results:** Oxidative stress could be a consequence of an increase in reactive oxygen species as well as a decrease in antioxidant defenses. Among the important factors that can be involved in triggering oxidative stress is insufficient dietary intake of antioxidants. Malnourished CKD patients are reported to have more oxidative stress than well nourished ones. **Conclusions:** Moving beyond the importance of assessment of dietary protein and energy in pre dialysis CKD patients to the assessment of dietary antioxidants is of utmost importance to help combat enhanced oxidative stress levels in such patients.

Implication for health policy/practice/research/medical education:

Oxidative stress is far more prevalent in chronic kidney disease (CKD) patients than in normal subjects. Malnourished CKD patients are reported to have more oxidative stress than well nourished ones. Moving beyond the importance of assessment of dietary protein and energy in pre dialysis CKD patients to the assessment of dietary antioxidants is of utmost importance to help combat enhanced oxidative stress levels in such patients. Unmonitored dietary restrictions and absence of nutritional intervention can be one of the reasons for low nutrient intake and poor antioxidant status of CKD patients.

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1. Context

Oxidative stress, a non-traditional risk factor of cardio-vascular disease is far more prevalent in chronic kidney disease (CKD) patients than in normal subjects. Malnourished CKD patients are reported to have more oxidative stress than well nourished ones. Moving beyond the importance of assessment of dietary protein and energy in pre dialysis CKD patients to the assessment of dietary antioxidants is of utmost importance to help combat enhanced oxidative stress levels in such patients.

2. Evidence Acquisition

Directory of Open Access Journals (DOAJ) Google Scholar, Pubmed (NLM), LISTA (EBSCO) and Web of Science were searched with key words relevant to dietary antioxidants, oxidative stress and chronic kidney disease.

3. Results

45 research and review articles relevant to this topic directly or indirectly have been found. From the information given in these papers, the following aspects were drawn out.

3.1 Oxidative stress and antioxidant defense mechanism

Oxidative stress defines an imbalance between formation of reactive oxygen species (ROS) and anti oxidative defense mechanisms. It occurs when there is excessive free radical production and / or low antioxidant defence and results in chemical alterations of bio-molecules, causing structural and functional modifications (1,2). ROS such as hydrogen peroxide (O_2) or hypochlorous acid (HOCl), and free radicals such as superoxide (H_2O_2), hydroxyl radical ($OH\bullet$), and nitric oxide ($NO\bullet$), are continuously formed in vivo. Thus, detection of ROS per se does not yet define oxidative stress, however, in a situation

where anti-oxidative defense mechanisms are attenuated, it is the imbalance between formation of ROS and defense mechanisms that creates oxidative stress. Although oxidation reactions are crucial for life, they can also be damaging, hence, plants and animals maintain complex systems of multiple types of antioxidants, such as glutathione, vitamin C, and vitamin E as well as enzymes such as catalase, superoxide dismutase and various peroxidases. The balance between formation of ROS and antioxidative defense mechanisms depends on the activity of enzymes such as superoxide dismutases (SOD), catalase and glutathione peroxidase. This balance, however, is rather fragile, difficult to predict, and strongly dependent on environmental conditions, for example, once O_2 is formed, the activity of SOD will transform it to hydrogen peroxide (H_2O_2) which in the presence of sufficient catalase activity, will be converted to harmless H_2O and O_2 . However, too much SOD relative to H_2O_2 -removing catalase can be deleterious, giving rise to the formation of the highly reactive hydroxyl radical in the presence of metal ions. On the other hand, when there is too little SOD activity, $OH\bullet$ also can be produced from O_2 via the Haber Weiss reaction. Several enzymatic systems can detoxify free radicals: copper/ zinc super-oxide dismutase (SOD) catalyzes the conversion of the superoxide anion to hydrogen peroxide and works concomitantly with hydro peroxide scavenging enzymes such as catalase and a selenoprotein, glutathione peroxidase (GPx) (1).

3.2 The link between oxidative stress and chronic kidney disease

Chronic kidney disease is a pro-oxidant state (3). Increased lipid peroxidation (LP) and reduced enzymatic antioxidant defense have been observed in predialysis patients (4, 5). In view of

the profound biological effects of ROS, in recent years numerous clinical and experimental studies focused on detection of signs of oxidative stress in renal patients. Renal dysfunction is frequently associated with oxidative stress, as levels of different oxidative stress markers like malondialdehyde (MDA) are increased in patients with varying degrees of renal function (6-8). Loss or deficiency of antioxidant activity could also contribute to enhanced oxidative stress in uremia. (9) and the degree of oxidative stress is correlated with degree of renal failure. In one of the recent studies done by us, predialysis patients were found to have reduced antioxidant defense mechanism measured by serum levels of SOD, catalase and glutathione (5) sealing the above mentioned fact.

Patients with chronic renal failure show elevated plasma lipid hydro-peroxides. In uremia per se there is an accumulation of advanced lipoxidation end-products. Undoubtedly there is enhanced oxidation of patient LDL before institution of hemodialysis (HD) (10-13). That means as the patient goes towards HD, oxidative stress increases and this is exactly we found in a recent study. We aimed to evaluate oxidative stress status in pre dialysis CKD patients. Patients with severe CKD showed higher malondialdehyde (LPO) levels as compared to their moderate counterparts (5) reinforcing the fact that degree of oxidative stress increases as the disease progresses. Table 1 gives the preview of some of the studies carried out in relation to oxidative stress and renal failure (14-18)

3.3 Nutrients from diet and their relation to antioxidants and oxidative stress levels in chronic kidney disease

Dietary antioxidants may be especially important in protecting against human diseases associated with free radical damage to cellular DNA,

lipids, and proteins (19). Antioxidants have differing solubility which partition across the phases of tissues, cells and macromolecular structures; water-soluble ascorbate, glutathione and urate, lipid-soluble tocopherols and carotenoids and intermediary-soluble flavonoids and hydroxycinnamic acids (20).

3.3.1 Macronutrients

Adequacy of most important macronutrient which is energy and protein is imperative to the maintenance of nitrogen balance. It has been documented that nitrogen balance becomes more positive as energy intake was increased and urea nitrogen appearance correlated inversely with energy intake (21). In our recent study done on predialysis CKD patients (5), energy intake from diet was found to be significantly lower than the control group comprising normal subjects and the group having least energy intake (severe CKD) exhibited maximum oxidative stress in terms of LPO and lower antioxidant levels in terms of GSH, SOD and catalase. Our study results can be supported by the observations by various researchers (1, 22) that predialysis patients having compromised nutritional status have biochemical evidence of more oxidative stress than well nourished ones. Energy requirements for CKD patients are same as that for healthy adults which are 35-45 Kcal/kg body weight depending on the present nutritional status of the subject.

Numerous studies have focused on the protein requirement of CKD patients at 0.6g/kg/day (23-25) as against 1g/kg/day for normal persons having mixed protein diet (26). This is because excess protein, unlike in healthy adult, will form nitrogenous waste products which the damaged kidney won't be able to filter out and they will be accumulated in the body. Usually renal failure patients are told to take less protein rich foods

Table 1: Oxidative stress of chronic kidney disease studies investigating the relationships among reactive oxidative species, antioxidants and the level of renal function.

Author ^{Ref.}	Patients	CKD stage	Variables Reactive species	Antioxidants	Results
Himmelfarb (2000) ¹³	10 healthy controls 10 ND-CKD patients 10 HD-CKD patients	1 5 5D	Carbonyl radicals	Thiols	Progressive increase in ROS and decline in AOx from normal GFR to dialysis
Annuk (2001) ¹⁰	37 ND-CKD	4-5	Lipid peroxidation end-products	Glutathione	ROS and AOx increased with GFR reduction Association ROS - endothelial dysfunction
Oberg (2004) ¹⁴	60 ND-CKD	4-5	Carbonyl radicals F2-ioprostanes	Thiols	No correlations among ROS, AOx and GFR
Wiko (2003) ¹¹	162 ND-CKD	1-5	AOPP Malondialdehyde Carbonyl radicals	Glutathione peroxidase	AOPP higher in CKD AOPP inversely correlated to GFR
Terawaki (2004) ¹⁵	55 ND-CKD	4	Oxidized albumin		Inverse correlation between ROS and GFR
Yilmaz (2006) ¹⁶	159 ND-CKD	1-5	Malondialdehyde OxLDL	Superoxide dismutase Glutathione peroxidase Se, Zn, Cu	Increase in ROS and decrease in AOx as GFR declines
Dounousi (2006) ¹⁷	87 ND-CKD	1-4	8-epiPG F2alfa	-	Inverse correlation between ROS and GFR
Mircescu (2006) ¹⁸	20ND-CKD 20 healthy controls	4-5	TBARS Reactive dicarbonyl	-	ROS higher in ND-CKD patients

ND- Non dialysed, HD- Haemodialysis, CKD- Chronic kidney disease, ROS- Reactive oxidative species, AOx- Antioxidant activity, AOPP- Advanced oxidation protein products, Ox LDL- Oxidized low density lipoprotein

in the diet as a general guideline. Since CKD is a frightening disease with a very low quality of life and fatal end, some patients in absence of clear dietary guidelines tend to be overcautious about their food habits, and thus the energy intake also becomes automatically low due to overall poor dietary intake. This was the study result of our recent research where it was found that protein intake by predialysis CKD patients was even lower than the advised 'low protein diet'(5) and their calorie intake was also very poor as compared to normal subjects .

A low intake of antioxidants is suggested (22) in the pre dialysis patients exhibiting lower nutritional status which was true in our study group also since the nutritional status measured by dietary intake and anthropometry [body mass index (BMI) and skinfold thickness] of CKD patients was found to be significantly less than the normal controls (5) which was directly proportional to their antioxidant status.

3.3.2 Micronutrients

Alteration of trace element metabolism in

renal failure has been frequently reported. Zinc (Zn), a trace element, which has a strong antioxidant potential, is available in protein rich foods (27-30). The richest dietary sources of Zn are the organs and the flesh of mammals, fowl, fish and crustaceans and Zn fortified foods. Organ and flesh meat and poultry do not contain any known specific anti-nutritional factors that hinder zinc absorption. Eggs and dairy products are also rich in Zn and free from phytates, but they have slightly lower zinc content that can be found in organ and flesh foods (31). Although most cereals and legumes have relatively high amount of Zn, they contain high concentration of phytates which reduce the amount of absorbable Zn from the food and therefore, they are poor sources of zinc (32). It is likely that other constituents of cereals and pulses, such as fiber and phytate, will greatly reduce the bioavailability of zinc in Indian vegetarian diets (33).

Since pre dialysis CKD diets are compromised in protein intake, especially in the Indian scenario, where most of the diets are of vegetarian origin with poor quality protein source, zinc availability from diet also gets jeopardized as in case of our study where zinc intake was found to be significantly less in CKD patients which was positively correlated to their low protein intake. Dietary zinc intake levels were also positively correlated to serum zinc levels as well as antioxidant enzyme levels and inversely correlated with LPO levels (5). Therefore, low protein Indian vegetarian CKD diet might further have lower zinc content and requires judicious planning on the part of renal dietician and might be supplementation with zinc to fulfill its requirements since zinc is a powerful antioxidant as it is required for the enzymes to catalyse vital oxidation reactions (34). Average daily intake of zinc was found to be less than recommended in CKD patients in a study

(28) which was also found to be true in the present study. Zinc requirement from diet remains same for predialysis CKD patients as that for normal persons.

3.3.3 Ascorbic acid or vitamin C

Ascorbic acid or vitamin C is an effective water-soluble antioxidant, and epidemiologic studies suggest that increased ascorbate nutrition is associated with reduced risk of some degenerative diseases. The low levels of plasma C might result in reduced activity of the non-enzymatic antioxidant defense system and might be responsible for increased oxidative stress occurring in CRF (19). Epidemiological studies indicate that fruit and vegetables are health-promoting and protective against diseases. Possible plant nutrients providing this protection also include antioxidants.

The health protection provided by fruit and vegetables could arise through an integrated reductive environment delivered by plant antioxidants of differing solubility in each of the tissue, cellular and macromolecular phases (20) but since the diets of renal failure patients are restricted for potassium intake, and fruits and vegetables being rich source of potassium, unmonitored restrictions might decrease the intake of antioxidants from diet.

The vitamin C intake was calculated at an average of 36 mg /day in CKD patients in a study (22) and it was also observed that Vitamin C deficiency may occur with restricted potassium diets recommended for CKD patients. The patients under our study group (5) had a poor intake of fruits showing a frequency of once in ten days. Since potassium rich fruits and vegetables are also rich in vitamin C, this might be one of the reasons for low vitamin C intake in our study subjects. The RDA'S for vitamin C for predialysis CKD patients stand same as that for normal adults.

The low levels of plasma vitamin A and E might result in reduced activity of the non-enzymatic antioxidant defense system and might be responsible for increased oxidative stress occurring in chronic renal failure patients (19).

The intake of vitamin A which is one of the fat soluble antioxidant was also found to be significantly less in severe renal failure group as compared to moderate renal failure group in our study (5) and the intake of this group was significantly less than the control group. The daily average vitamin A intake was calculated at 555 µg retinol and found it to be sufficient in a study (35), whereas the Indian counterparts in our study (5) were consuming it at a daily average of 208 µg retinol/ day and 190 µg retinol/day in moderate and severe renal failure groups respectively which was found to be quiet less than the recommendations for healthy controls which remain the same for CKD patients. This difference in intake levels can be due to the dietary habits as Indian diet is mostly vegetarian and people are little aware of the rich sources of the vitamin.

Treatment with vitamins decreases renal injury in chronic renal failure (36) was shown in a study in which malondialdehyde activity was significantly reduced in rats having chronic renal failure after supplementation with vitamin E.

Certain amino acids such as cystine which is a non-essential amino acid have antioxidant properties. It is formed from methionine. It is found in so many high protein foods, which are restricted for CKD patients. In patients with chronic diseases, the synthesis of cystine from methionine appears to be prevented and could result in a deficiency.

Insufficiencies of cystine can reduce the antioxidant potential of the individual and make the patient more susceptible to free radical pathology. As an essential amino acid, methionine is

not synthesized in humans, hence we must ingest methionine or methionine-containing proteins. High levels of methionine can be found in seeds, fish and meats which all are restricted in predialysis CKD patients. For cystine, deficiencies of methionine will result in poor metabolism of cystine and reduced antioxidant protection (37).

As mentioned earlier, Indian diets are basically vegetarian and if they are restricted in protein and that too unmonitored dietary restrictions as in case of our study subjects, this might lead to amino acid deficiency and in this case, cystine and methionine intake by our study subjects was found to be significantly lower in severe and moderate predialysis CKD patients as compared to the normal subjects (5).

Cystine's antioxidant properties are typically expressed in the tripeptide glutathione, which occurs in humans as well as other organisms. The actual activity of glutathione as an antioxidant is dependent upon the cystine residue, which serves as a free radical-protecting agent (38). The biochemical function of glutathione peroxidase is to reduce lipid hydroperoxides (39).

The systemic availability of oral glutathione (GSH) is negligible, so it must be biosynthesized from its constituent amino acids, cystine, glycine, and glutamic acid which are readily available in most Western diets. Glutathione is not an essential nutrient since it can be synthesized from the amino acids L-cystine, L-glutamic acid and glycine (38). Foods rich in cystine, glutamic acid and glycine should be selected when wishing to increase the dietary intake of this nutrient (40) which might not be so easy to achieve in renal diets without judicious planning an implementation.

Therefore, unmonitored dietary restrictions and absence of nutritional intervention, as also reported by various researchers (41-45), can be

one of the reasons for low nutrient intake and poor antioxidant status of CKD patients.

4. Conclusions

Nontraditional risk factors such as oxidative stress and inflammation are far more prevalent in chronic kidney disease (CKD) patients than in normal subjects. Malnourished predialysis patients have biochemical evidence of more oxidative stress than well-nourished ones. Therefore, assessing the nutritional intake of macro as well as micronutrients that have antioxidant properties or act as precursors of antioxidant enzymes should be given importance and efforts should be made to meet the RDA (recommended dietary allowance) through diet or supplementation if need arises to combat the antioxidant and other nutritional deficiencies, to minimize oxidative stress and improve the overall health status. Therefore, individualized and parametric counseling for dietary intake is mandatory in CKD patients to increase their awareness about the important nutrients related to their diseased state and how to get these nutrients from diet.

Authors' contributions

Main draft write up and editing by NS. Important intellectual content and critical revision by KLG.

Conflict of interest

The authors declared no competing interests.

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