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Oxidative stress and free radicals in liver and kidney diseases; an updated short-review

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ABSTRACT

Context: In normal conditions, liver and kidney act as a supply of internal antioxidants for neutralizing free radicals produced by viruses and internal/external compounds which were processed in the liver and kidney.

Evidence Acquisition: PubMed, EBSCO, Embase, Web of Science, directory of open access journals (DOAJ), Scopus, and Google Scholar were searched using keywords of oxidative stress, free radicals, liver diseases, kidney diseases and antioxidant therapy.

Results: When the antioxidants of the liver or kidney are low, or when the liver/kidney is under pressure through oxidative insults, the damages produced by free radicals would increase, leading to inflammation and fibrosis. In addition to cytotoxic effect of oxidative stress, it has also a substantial role in modulating of messengers in regulating the functions of cell membrane, with a vital factor for survival. However, there is also some benefits of oxidative stress such as inducing apoptosis to prepare birth canal for delivery or strengthening of biological defense mechanisms during ischemia and physical exercise.

Conclusions: There is an important association between diseases related to lifestyle and oxidative stress, as a condition that oxidation may exceed the antioxidant systems of the body with absence of balance between them. Oxidative stress is involved with many diseases such as kidney, liver and lung dysfunctions. Supplementation with vitamins C and E and selenium for four months could improve the balance between antioxidant-oxidant as well as potential slowing down of liver disease progression.

Short Review

Implication for health policy/practice/research/medical education:
Oxidative stress has an important effect on chronic kidney disease with a recommendation of treatment by antioxidants.

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1. Context

In normal conditions, the liver and kidney act as a supply of internal antioxidants for neutralizing free radicals produced by viruses and internal/external compounds which were processed in the liver and kidney (1). However, when the concentration of antioxidants in liver/kidney are low, or when the liver or kidney are under pressure through oxidative insults (due to alcohol or infections of hepatitis B and C virus or renal tubular cell damage), the damage produced by free radicals would increase, leading to inflammation and fibrosis (2). In fact, oxidative stress can be defined as an imbalance between producing of oxidants (reactive oxygen species or free radicals) and their eliminating through protective mechanisms like antioxidants (3). In fact, when reactive forms of oxygen would produce faster than they could be neutralized by antioxidants, resulting in oxidative stress (4). Moreover, increasing pro-oxidant formation, decreasing or lacking antioxidants may also lead to oxidative stress (5). In addition to the cytotoxic effect of oxidative stress, it has also a substantial role in modulating of messengers in regulating the functions of cell membrane, with a vital factor for survival (6). However, there is also some benefits of oxidative stress such as inducing apoptosis to prepare birth canal for delivery or strengthening of biological defense mechanisms during ischemia and physical exercise (6).

There is an important association between diseases

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related to lifestyle and oxidative stress, as a condition that oxidation may exceed the antioxidant systems of the body with the absence of balance between them (6). Lifestyle diseases, as multifactorial diseases, could have three important causal factors including genetic, habitual and environmental (6). Moreover, many associated genes with biological oxidative stress, many daily related habits leading to oxidative stress (such as smoking, drinking and irregular diet) and many environmental factors like oxygen radicals and carcinogenesis have been reported (6). Generally, oxidative stress can be caused by alcohol, drugs (anti-inflammation, anti-analgesic, anti-cancer and antidepressants), environmental pollutants (mercury chloride, lead, microcystin) and other factors (mobile phone-like radiofrequency radiation exposure, temperature (cold stress), benzoyl peroxide, ZnO_2, maternal high-fat diet and thyroid dysfunction (7). Moreover, alcohol consumption could be accounted for at least 3.8% of world mortality (7). In addition, it is believed that consumption of alcohol could have a positive action for oxidative stress as well as the promotion of inflammatory and fibrotic damage (8). In fact, chronic alcohol consumption may result in progressive liver damage, followed by inflammation and production of cytokine (9). Furthermore, it has been reported that antioxidant consumption could prevent the toxic effects of alcohol on liver or kidney (9). Because of inducing oxidative stress by alcohol, the antioxidant defense system would be compromised. Therefore, in addition to standard medical care, prescription of antioxidant supplements is recommended (10).

2. Evidence Acquisitions

PubMed/Medline, EBSCO, Embase Web of Science, directory of open access journals (DOAJ), Scopus, and Google Scholar were searched using keywords of oxidative stress, free radicals, liver diseases, antioxidant therapy, chronic kidney disease, reactive oxygen species, hypertension, diabetes mellitus, dyslipidemia, end-stage renal disease, liver dysfunction and antioxidant systems.

3. Oxidative stress

Oxidative stress is involved with many diseases including neurodegenerative diseases (Alzheimer's diseases [AD], Parkinson's disease [PD], amyotrophic lateral sclerosis [ALS], heart diseases (coronary hearth diseases [CHD], atherosclerosis, stroke/ischemia), obesity, kidney diseases (urolithiasis and diabetic nephropathy), lung diseases (asthma, pulmonary fibrosis and lung cancer), eye disease (cataract, age related macular degeneration [AMD], diabetic retinopathy [DR], autoimmune uveitis [AIU], retinitis pigmentosa [RP]), skin diseases, reproductive system, blood disorder (beta-thalassemia, acute lymphoblastic leukemia [ALL]), joint disorder (rheumatoid arthritis, temporomandibular [TMB] joint disorders, systemic lupus erythematosus [SLE]), liver and pancreatic diseases, diabetes, Wilson's diseases (11) and brain diseases (12).

The kidney is a susceptible organ to oxidative stress (13). There are many studies regarding oxidative stress and free radicals with kidney diseases (14). Oxidative stress may have an important impact on uremia, renal insufficiency and other kidney diseases (15). In fact, in the pathophysiology of many kidney diseases and related complications of these diseases, oxidative stress plays an important role in mediating oxidative stress alone, oxidative stress-related mediators and inflammation (14). In addition, there are many factors such as some diseases like hypertension, diabetes and hypercholesterolemia, some antibiotics, chemotherapeutics and radiocontrast agents, environmental toxins and occupational chemicals, radiation, smoking and alcohol which may induce oxidative stress in the kidney (14). Moreover, there is some evidence about the association between uremia (treated with hemodialysis or peritoneal dialysis) and enhanced oxidative stress which in turn would decline antioxidants levels in these patients (16,17). In fact, oxidative stress could play an important role in many renal diseases such as glomerulonephritis, acute or progressive renal failure, tubulointerstitial nephritis (18,19). In addition, the understanding sources and roles of oxidative stress regarding endothelial dysfunction, inflammation, atherosclerosis and glomerulosclerosis has been highly increased in recent decades. However, there is still no confirmed information about the effects of antioxidant therapy on hemodialysis patients, despite the primary benefits of antioxidants among these patients (20). Moreover, there is still no accepted explanation about the exact role of free radicals and oxidative stress in the pathogenesis of many acute and chronic kidney insufficiency, nephrological diseases, glomerulonephritis, gentamicin nephrotoxicity and ischemic- reperfusion injury (21). Oxidative stress has an important effect on chronic kidney disease (CKD) (22) with a recommendation of treatment by antioxidants (21).

CKD is a worldwide health problem with increasing incidence (22). In addition, low concentration of free radicals can play a vital role in many physiologic functions. However, their excess concentration could also lead to cellular damage and pathological processes

such as atherosclerosis (23). Moreover, CKD patients may be affected by many situations such as hypertension, diabetes and dyslipidemia which all are associating with oxidative stress (22). It has been reported that using antioxidant-based dialysis membranes, like vitamin E and vitamin C modified cellulose membranes, can reduce oxidative stress in dialysis patients (24, 25). Furthermore, excess consumption of dietary salt may modulate oxidative stress and target organ damage through angiotensin II (13). Moreover, increasing kidney disease and related end-stage renal disease (ESRD) may be associated to ageing of population' and high morbidity may be associated with lifestyle diseases like hypertension, diabetes and atherosclerosis (15).

There are many compounds for therapy of CKD patients including L-Carnitine, vitamin E, vitamin C, coenzyme Q10, α-lipoic acid, selenium, green tea, resveratrol, curcumin and omega-3 polyunsaturated fatty acids, which can administer alone or as a combination (26). However, these positive effects have not been confirmed everywhere (27).

In addition to kidney, the liver is also prone to oxidative stress-related damages. The liver is the principal organ for detoxifying of various compounds and its diseases are a substantial worldwide health problem (5). Oxidative stress could contribute to all conditions of liver dysfunction with different etiologies (28). Moreover, increasing oxidative stress in hepatocytes could indeed be one of the substantial mechanisms of liver dysfunction (9). In addition, the effect of oxidative stress in the pathogenesis of liver dysfunction has been studied (29). Moreover, cirrhosis patients are prone to oxidative stress which is related to the severity of liver cirrhosis (1). Although, because of the role of oxidative stress in initiating and progressing of liver damage, antioxidant therapy, by using natural and synthetic antioxidants, is mainly applying for preventing and treating of liver diseases as a potential extra-appropriate treatment. However, there is still a long way for applying antioxidants to all liver diseases (7). The exact mechanism of oxidative stress on the liver dysfunction is not well known (30). In addition, there is enough evidence about the association of oxidative stress and compromised antioxidant defense system (31). Measurement of oxidative stress could be through different methods such as "electron paramagnetic resonance (EPR)", determination of "peroxidation products" or "lipid peroxidation products" or "isoprostanes" or "protein carbonyl groups" or "DNA damage", measurement of glutathione (GSH) and determination of antioxidant enzymes or antioxidant molecules (30). Since oxidative stress can be considered as a pathogenetic phenomenon playing a substantial causal role in different liver diseases such as hepatitis, nonalcoholic steatohepatitis (NASH), fibrosis, cirrhosis and hepatitis type C. Therefore, monitoring endo-/exogenous enzymes and antioxidants to control free radicals level is very vital (30). Antioxidants could also be used for preventing and treating patients with alcoholic liver disease (ALD), nonalcoholic fatty liver disease (NAFLD) and other liver diseases (7).

During metabolic processes, many highly reactive compounds may produce named free radicals, which could participate in some physiological phenomena like immune response, inflammatory reaction and metabolism of fatty acids (unsaturated) (32). Excess amounts of free radicals may indeed lead to impairment of enzymes, membranes and DNA and further changes in the activity of immune system (29). When the generation of free radicals exceeds the ability of system for neutralizing and elimination them, oxidative stress may occur (33). In addition, the balance between antioxidants and free radicals is very important in many diseases (32). Furthermore, free radicals could result in an oxidation condition that may lead to injury in cellular membrane and related metabolic processes (34). They may also involve many degenerative diseases such as diabetes mellitus, lung and kidney damage, atherosclerosis, liver diseases and aging (35). Furthermore, free radicals could be released as a subsequence of hepatic detoxification of chemicals, drugs and toxic compounds in the liver (36). Moreover, due to the ability of antioxidants of cells and tissues to prevent the injury produced by free radicals, reactions of pathological free radicals do not necessarily lead to cell and tissue damage (37). In addition, due to very short half-lives of free radicals, oxidative stress is assessed by measuring of different stable oxidized productions of modified, lipids, proteins, nucleic acids and carbohydrates (2). In fact, free radicals or active oxygen species would be abnormally or excessively produced, the balance between forming and removing would be damaged and oxidative stress will initiate (6). Free radicals could also have a substantial role in the pathogenesis of tissue damage in many diseases such as kidney damage, inflammation, hepatic dysfunction and immune injury (38). Free radical might indeed lead to liver diseases which may induce by many situations such as alcohol abuse, fibrosis/cirrhosis of different etiologies, viral hepatitis and paracetamol overdose (39).

4. Antioxidants

Antioxidant level of blood could not reflect only the organ damaged by oxidative stress, but also their level

changes for responding to other organs' diseases (4). In fact, different antioxidants have different effects and their additive effect in plasma may protect against attacks of free radicals (40). For instance, daily consumption of *Rosmarinus officinalis*, as an antioxidant, hepatoprotective substance and a free radical scavenger, could limit the extent of histological damages as well as prevention of oxidative damage (34). In addition, supplementation with vitamins C and E and selenium for four months could improve the balance between antioxidant-oxidant as well as potential slowing down of disease progression (3). On the other hand, decreasing of vitamins E and C levels may indicate that antioxidant system breakdown might be the cause of developing and progressing of disease (41). In a study, antioxidant therapy (for four months) had a positive effect on antioxidant-oxidant balance as well as improving liver function test, but not reduced the systemic inflammation (42).

5. Conclusions

There is an important association between diseases related to lifestyle and oxidative stress, as a condition that oxidation may exceed the antioxidant systems of the body with the absence of balance between them. Oxidative stress is involved in many diseases such as kidney, liver and lung dysfunctions. Supplementation with vitamins C and E and selenium for four months could improve the balance between antioxidant-oxidant as well as potential slowing down of liver disease progression.

Author's contribution

MA wrote the paper lonely.

Conflicts of interest

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Ethical considerations

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