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Total Antioxidant Capacity: a biomarker in biomedical and nutritional studies

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Abstract

When antioxidant defenses are weakened, body cells and tissues become more prone to develop dysfunction and/or disease. Then, the maintenance of adequate antioxidant levels, but not overdosage, is essential to prevent or even manage a great number of disease conditions. This review strongly describes and discusses the use of TAC, total antioxidant capacity test, as a biomarker of disease in biochemistry, medicine, food and nutritional sciences. In many different pathophysiological conditions (heart and vascular diseases, diabetes mellitus, neurological and psychiatric disorders, renal disorders and lung diseases), TAC could be a reliable biomarker of diagnostics and prognostics, although several cautions for its use should be carefully done (choice of apropriate method, use of other antioxidant biomarkers such as cell antioxidants, genetic antioxidant-response elements (ARE) or antioxidant vitamins, and use of valuable oxidative/nitrosative biomarkers). TAC could be useful to evaluate nutritional interventions with TAC-rich foods on disease risk and prevention, including anti-aging strategies.

Key Words**:** Total antioxidant capacity, cardiovascular, kidney and respiratory diseases, diabetes mellitus, neurological disorders, nutrition.

Total Antioksidan Kapasitesi: biyomedikal ve besinsel çalışmalarda bir biyomarkör

Özet

Antioksidan savunmalar zayıfladığında vücut hücreleri ve dokuları disfonksiyon ve/veya hastalık geliştirmeye daha yatkın hale gelirler. Böylece, yeterli antioksidan düzeylerinin doz aşılmadan sürdürülmesi, çok sayıda hastalık durumunu önlemek ve hatta control altına almak için gereklidir. Bu derleme makale biyokimyada, tıpta, gıda ve beslenme bilimlerinde bir hastalık biyomarkörü olarak TAC, total antioksidan kapasite testi, kullanımını anlatmakta ve ve tartışmaktadır. Birçok farklı patofizyolojik durumda (kalp hastalıkları ve vasküler hastalıklar, diyabet, nörolojik ve psikiyatrik hastalıklar, renal hastalıklar ve akciğer hastalıkları) kullanımı için çeşitli uyarıların dikkatlice yapılmasının gerekliliğine rağmen (uygun metodun seçilmesi, hücresel antioksidanlar gibi diğer antioksidanların kullanımı, genetik antioksidan cevap elementleri (ARE) veya antioksidan vitaminler ve değerli oksidatif/nitrozatif biyomarkörlerin kullanımı) TAC teşhis ve prognozda kullanılacak güvenilir bir biyomarkör olabilir. TAC, hastalık risklerinin ve hastalıkların önlenmesi için anti yaşlanma stratejileri de dahil olmak üzere, TAC açısından zengin yiyeceklerle besinsel müdahaleler gerçekleştirmek üzere kullanılabilir.

Anahtar Sözcükler**:** Total antioksidan kapasitesi, kardiyovasküler, böbrek ve solunum hastalıkları, diyabet, nörolojik hastalıklar, beslenme.

Introduction

Exceptional advances in biomedical sciences since the past century gives opportunities to understand the molecular basis of disease that could result in new strategies for treatment and for prevention of pathologies. The involvement of reactive oxygen, nitrogen and chlorine species in disease states is strongly consolidated. Today, more than 70 pathologies are intrinsically associated with oxidative stress and its biochemical consequences, like peroxidation of lipids (measured by its markers, such as malonaldehyde, MDA, and 4-hydroxynonenal, 4-HNE, between others), proteins (assessed by protein carbonyls), nucleic acids (evaluated by oxidative DNA bases) and carbohydrates (evaluated by glycosilation products) (Halliwell, 1994; Ferrari, 2000; Ferrari, 2001).

Into the origin of these pathophysiologies there is a mitochondrial dysfunction and subsequent imbalance between releasing of reactive oxygen, nitrogen or chlorine species and synthesis of defensive antioxidant capacity systems from nuclear DNA, resulting in oxidative stress. Serious consequences of the oxidative stress include from DNA damage and mutations to cell death by necrosis or apoptosis (Ferrari, 2000; Ferrari, 2001).

For many decades researchers have studied many markers of oxidative stress-associated tissue damage and antioxidant defense, including measurement of antioxidant enzymes–superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR), glutathione peroxidase (GPx), ceruloplasmin, and proteins such as metalothionins (Ferrari, 2001). In the beginning of 1990's, Miller et al. (1993) had created a new test to measure the total antioxidant status, which has been designated as total antioxidant capacity (TAC). The major advantage of this test is to measure the antioxidant capacity of all antioxidants in a biological sample and not just the antioxidant capacity of a single compound.

This review will focus on recent applications of the TAC test in medical and nutritional studies as well as future possible uses of TAC as a biomarker for diagnosis, prognosis and prevention of diseases.

Understanding the TAC methods

The most common total antioxidant capacity tests were summarized by Rice-Evans (2000).

In 1996, the research group led by Benzie described the "ferric reducing–antioxidant power" (FRAP) method, which is very widely used today (Szeto et al., 2002). The FRAP assay is based on the reduction of ferric ions to ferrous ions by the effect of the reducing power of the plasma (or a sample) constituents measured spectrophotometrically at 593nm.

Another important TAC method is the ORAC (oxygen radical absorbance capacity). ORAC assay was developed by Cao's research team (Cao et al., 1998). The ORAC method is based on the ability of plasma constituents to trap peroxyl radicals formed from thermal decomposition of azo initiators (AB-AP-2,2'-azobis[2-amidino propane]) and measurement of fluorescence decay of ß-phycoerythrin (ß-PE) (excitation wavelength of 540nm and emission wavelength of 565nm).

Miller et al. (1993) described the "Trolox-equivalent antioxidant capacity" (TEAC) method which was transformed in a commercial kit by Randox Laboratories Ltd. (UK). The method is based on formation of the $ABTS^{\bullet+}$ cation [2,2'-azinobis (3-ethylbenzothiazoline-6-sulfonic acid)] and its scavenging by antioxidant sample constituents (e. g., serum or food) measured by spectrophotometry (decay of green/blue chromophore absorbance is inversely associated with antioxidant sample content and the control antioxidant is Trolox, a hydrophilic vitamin E analog). For its relative simplicity and high analytical quality, TEAC kit (Randox) is world wide.

These TAC tests are now widely used in the analysis of serum, foodstuffs and biological tissues (Rice-Evans, 2000; Szeto et al., 2002; Paganga et al., 1999; Percário, 2000; Koch et al., 2002).

When uric acid is present, it strongly influences the TAC of the sample. To solve this problem, Erel (2004) reported a new TAC method in which uric acid influence is much lower. His method is based on a Fenton-drived reaction where Fe^{2+}-*o*-

dianisidine + *o*-dianisidine reacts with H_2O_2 yielding Fe^{3+}-*o*-dianisidine + $OH^{\bullet}$ (hydoxyl radical) + *o*-dianisidine. Subsequently, the hydroxyl radical reacts with *o*-dianisidine to form dianisidyl radicals and, in termination step, the complex non-radical molecules. Total antioxidant response (TAR) is then measured by spectrophotometry at 444 nm (Erel, 2004). Adom and Liu (2005) developed the peroxyl radical scavenging capacity (PSC) method that is based on the thermal degradation of 2,2'-Azobis (amidinopropane) yielding peroxyl radicals ($ROO^{\bullet}$) which oxidize dichlorofluorescein into a fluorescent form. The degree of fluorescence inhibition by the sample is measured at 485nm (excitation) and 538nm (emission) by fluorescent spectrophotometry. A variant of this method, called cellular antioxidant activity (CAA), uses the same reagents and measures fluorescence degree in a cell line (HepG2) in response to both lypophilic and hydrophilic antioxidants (Wolfe and Liu, 2007).

TAC in respiratory physiology and pathology

In many pulmonary pathophysiological states (acute bronchospasm, chronic bronchitis, pulmonary emphysema, asthma) there occurs an intense oxidative stress that is characterized not just by the presence of oxygen free radicals (superoxide anion [$O_2^{\bullet}$], hydroxyl radical [$OH^{\bullet}$], peroxyl radical [$ROO^{\bullet}$], peroxynitrite [$ONOO^-$], etc), but also by nitrogen and chlorine reactive species (Hatch, 1995; Percário, 2000; Stanner, 2000). This stronger oxidative stress induces depletion of thiol-rich antioxidants, which in turns causes apoptosis of pulmonary fibroblasts, a phenomenon that could be suppressed by addition of ascorbic acid and the antioxidant enzyme catalase (Aoshiba et al., 1999). Following this approach, it has been suggested that the use of thiol-rich substances constitute a promise perspective for the treatment of chronic asthma (Percário, 2000). Following this approach, N-acetyl-L-cysteine (NAC), a GSH precursor, N-acystelyn (NAL), an antioxidant and mucolytic agent, GSH-esters, with an ethyl group esterified to the glicine of GSH, and thiazolidines, cysteine-donor compounds, constitute promissory drugs to treat inflammatory oxidant lung diseases (Rahman and McNee, 2000). In the same manner, higher apple consumption, independently of its vitamin C and E levels, has been associated with an increasing pulmonary function, even in patients with chronic obstructive pulmonary disease (COPD), and these positive effects have been attributable to the rich polyphenolic content of this fruit, especially the quercetin, which is also found in onions, teas (green and black), grapes and red wines (Stanner, 2000). COPD patients and smokers had lower plasma values of TAC, but this change did not correlate with respiratory impairment (Rahman et al., 2000). Passive smoking children had lower values of TAC, thiols and vitamin C in plasma (Aycicek et al., 2005). Compared to non-smokers, healthy smokers had reduced salivary glutathione (3.3 μM *versus* 1.2 μM), although uric acid and TAC levels were normal (Zappacosta et al., 2001). This GSH depletion could reflect that it constitutes the first line of defense in respiratory mucosae (Kelly, 1999) that preserves uric acid and TAC for a long-term consumption. This explains, as a defense antioxidant mechanism against smoking, why the other study reported a slightly higher plasma TAC in smokers in compared to non-smokers, as well as the positive association between TAC and DNA oxidation (Nia et al., 2001).

In an experimental bronchospasm model with guinea-pigs lower lung and serum levels of TAC, CAT, lower lung levels of SOD and nitric oxide, and increased lung levels of uric acid has been observed compared to the controls (Percário, 2000). Asthma, a chronic inflammatory lung disease, characterized by higher levels of protanoids, leukotrienes, ROS, HOCl and NOS (Ryrfeldt et al., 1993), also induces alterations in antioxidant enzymes (SOD, GPX, GR) (Matés et al., 2000), although red blood cell CAT activity and TAC could not be altered in asthmatic patients (Nadeem et al., 2003). In contrast, a small but significant decrease in plasma TAC was found in asthma patients with chronic evolution (Pinto et al., 2006). This could be explained by the fact that severe asthma is associated with low plasma levels of vitamin C and billirubin, and high plasma levels of cholesterol (Misso et al., 2005).

Other acute and chronic lung diseases can present changes in total antioxidant defenses. Lower levels of TAC, vitamin A, and E have been found in patients with obstructive sleep apnoea syndrome (Barceló et al., 2006). Luzir lung capacity was associated with decreased plasma total antioxidant capacity in welding workers (Fidan et al., 2005). Untreated tuberculosis patients had decreased blood levels of vitamins C, E and A and

thiols when compared to healthy subjects (Madebo et al., 2003). Total antioxidant capacity was also found to be diminished in active tuberculosis patients, although antiobiotic therapy has reversed that decline (Wiid et al., 2004). Cystic fibrosis patients frequently have higher oxidative stress, as assessed by increasing levels of thiobarbituric acid reactive substances (TBARS), and decreasing retinol, alpha-tocopherol, beta-carotene (Benabdeslam et al., 1999), GSH (Gao et al., 1999), and TEAC values (Lands et al., 2000). Still considering cystic fibrosis, it is important to remember that GSH depletion occurs through a failure in its transport by airway epithelia (Gao et al., 1999), and that GSH aerosol administration inhibits ROS releasing by inflammatory cells in respiratory mucosae (Roum et al., 1999). The kinetics of lung antioxidant defense in the presence of free radical sources (cigarette smoke, environmental/occupational toxic vapors, diseases, etc) and possible protective roles of synthetic (N-acetyl-cystein) or natural antioxidants should be studied by using TAC.

TAC and diabetes diagnostics, prognostics and prevention

Although the relationships between oxidative stress, antioxidant defense and diabetes mellitus pathophysiology are too much complex and not fully resolved, the involvement of free radical mechanisms is well proved (Ferrari, 2001). It has been reported that insulin-dependent diabetes mellitus (IDMM) patients presented significantly higher levels of oxidized DNA than control subjects (Dandiona et al., 1996). Is there some relationship between DNA oxidation and TAC in diabetes and other diseases? The question remains to be determined.

Diabetes mellitus patients with or without proteinuria had much lower serum TAC values than control subjects (1.7 mmol/L and 1.4 mmol/L *versus* 2.7 mmol/L) (Opara et al., 1999). This was further confirmed by Shin et al. (2006) who reported an inverse association between insulin resistance and plasma levels of TAC, β-carotene and γ-tocopherol in non-diabetic hypercholesterolemic patients. A previous study revealed an inverse correlation between TAC and glycated hemoglobin, a relationship sustained by uric acid and vitamin A concentrations (Maxwell et al., 1997). Non-IDDM patients in Ghana presented lower values of TAC and these were inversely associated with fasting plasma glucose (Dosso et al., 2001).

A 75 year old male ketoacidosis IDDM insulin-dependent diabetic patient presented vomiting, thirst and polyuria at day of hospital admission. Serum biochemical analysis revealed mild α–tocopherol and β–carotene deficiencies, but normal TAC values as a consequence of higher blood urate levels (Johnston and Miller, 1998).

In 47 elderly non-IDDM, lipid hydroperoxide levels were higher than those observed in healthy elderly and young subjects (7.02 ± 2.29 μmol/L vs. 3.14 ± 1.50 μmol/L and 2.14 ± 1.38 μmol/L, respectively), GSH values were decreased compared to healthy young subjects (0.29± 0.09 μmol/L vs. 0.54 ± 0.19 μmol/L), and decreased values of TAC was also observed compared with the young group (386.4 ± 99.8 vs. 471.47± 94.29 μmol/L trolox equivalents) (Nutall et al., 1999). Higher lipid peroxidation and SOD levels and lower TAC and antioxidant enzyme levels (CAT and GPX) were observed in type 2 diabetic patients (Jandric-Balen et al., 2004; Rani et al., 2005). Plasma TAC was inversely associated with thrombosis markers (fibrinogen and prothrombins) in non-insulin-dependent diabetic patients (Ceriello et al., 1997). In diabetic patients with peripheral artery disease there were increased levels of lipid peroxidation and advanced glycation end products and decreased values of plasma TAC (Lapolla et al., 2007).

Type I diabetes mellitus patients with coronary artery calcification had lower TAC values than those observed in blood samples from type 1 diabetes patients without vascular damage (Valabhji et al., 2001). In the same manner, type 1 diabetic children presented lower levels of total antioxidant capacity and GSH, whereas blood lipid peroxidation was found to be increased (Varvarokská et al., 2003).

Pancreatic protection depends on higher levels of antioxidant enzymes, since cytoplasmic values of GPX, SOD and CAT were reduced in chronic pancreatitis and pancreatic carcinoma cells as compared to normal pancreatic tissue (Cullen et al., 2003).

Gliclazide (a sulfonylurea derivative) administration, during 12 weeks, decreased plasma lipid peroxides, increased plasmatic TAC and reduced both systolic and diastolic blood pressure in type 2 diabetes mellitus patients (De Mattia et al., 2003).

In a cohort study with a sample population of 9,665 people, the group that consumed five or more portions of fruits and vegetables had 27% reduced risk of develop diabetes mellitus than people who did not consume; and this decreasing of diabetes mellitus risk got 46%, considering just women (Ford et al., 2001). The next step in research is to incorporate TAC as a marker of dietary antioxidant, weight loss and exercise interventions to better evaluate preventive strategies for diabetes.

TAC in heart and vascular system

Evaluating TAC by total reactive antioxidant potential (TRAP) test, authors observed that liver homogenates (3900 μM Trolox-Equivalent/Kg of tissue) had better TAC than kidney (2700 μMTE/Kg), followed by brain (1700 μMTE/Kg) and heart (320 μMTE/Kg), which was the most vulnerable tissue to antioxidants (Evelson et al., 2001). Among all determined antioxidants in tissue homogenates, GSH presented the highest concentrations and accounted for the most TRAP values (Evelson et al., 2001). Then, patients with cardiomiopathy had decreased TAC by 17% composed to control subjects (Sofic et al., 2002).

Atherosclerosis patients had decreased erythrocyte glutathione (2.80 *versus* 5.82 μmolGSH/g Hb), serum vitamin C (1.00 *versus* 1.62 mg/dL), TAC (0.86 *versus* 1.43 mmol/L) and increased MDA concentrations (4.26 *versus* 1.02 nmol/mL) (Tamer et al., 2002). Coronary artery disease patients had lower serum levels of TAC, retinol, HDL, albumin and total protein, whereas α-tocopherol and α/γ-tocopherol ratio was higher than in control subjects (Nojiri et al., 2001). These authors also observed an inverse association between TAC and the number of damaged vessels, in logistic regression analysis only low levels of HDL were significantly associated with CAD risk. Other research reported increased DNA damage in the nucleus of coronary cells and decreased plasma TAC in coronary artery disease patients (Demirbag et al., 2003), confirming previous data from patients submmitted to coronary angioplasty which had presented lower TAC and higher lipid peroxidation plasma levels (Buffon et al., 2000).

The pathological role oxidative stress in vascular diseases is well recognized (Madamanchi et al., 2005). Hypertensive patients were found to have increased blood lipid peroxidation values and lower TAC levels (Kashyap et al., 2005). In the same study, TAC was negatively associated with diastolic blood pressure. The same results were reproduced spontaneously in hypertensive rats, where TAC values of brain, heart, liver and kidney were found to be lower than in normal rats (Sun et al., 2006). In salt-sensitive renal hypertensive rats the increased oxidative stress is associated with decreased plasma nitric oxide and TAC bioavailability (Manning Jr et al., 2003). An interesting approach to treat hypertension is represented by a low-sodium, high fruit/vegetable and low-calorie diet, the so-called Dietary Approaches to Stop Hypertension (DASH diet) (Appel, 2003). In obese hypertensive patients the DASH diet decreased the blood pressure and lipid peroxidation, and increased TAC of plasma (Lopes et al., 2003). Pharmacological use of atorvastatin (10 mg/kg) to slow down blood lipids significantly decreased autoantibodies against oxidized LDL (18.7%) and enhanced the lag time of LDL (time that precedes LDL oxidation) (31.3%) and the TAC (7.6%) (Orem et al., 2002).

TAC in chronic renal injury

When kidney suffers from ischemic-reperfusion injury, there is significant depression of antioxidant enzyme levels (SOD, CAT and GPX) (Dobashi et al., 2000). In rats with acute renal failure, severe decline in total antioxidant capacity was observed which was reversed spontaneuosly after 72h (Fernández-Fúnez et al., 2003).

Chronic renal disease patients which were admitted to hemodialysis, presented enhanced levels of MDA and oxidized glutathione (GSSG), and decreased concentrations of GSH and GPx, without any changes in plasma levels of TAC, vitamins A and E (Drai et al., 2001). A possible explanation for the maintenance of CAT levels in these patients is that, vitamin A and E concentrations remain stable, once oxidative stress would first deplete endogen or intracellular antioxidants to a further consumption of extracellular substances. But another clinical study reported that TAC measured even by TEAC, than FRAP was higher in hemodialysis patients compared with control group. Although MDA and 4-HNE levels were also increased, plasma thiols were lower and α–tocopherol was not altered (Gerardi et al., 2002). After hemodialysis, plasma levels of thiols, MDA,

4-HNE and TAC were normalized. Similar results were found by Samouilidou and Grapsa (2003). These agree with the observations that TAC was higher in patients with chronic renal injury, as a result of serum urea accumulation (Bergesio et al., 1998).

These studies confirm previous findings associating significantly increasing serum TAC levels with progression of chronic renal failure and this elevated TAC levels were strongly correlated to both serum creatinine and uric acid levels (Sofic et al., 2002). However, lipid peroxidation was not associated with TAC. Because of these facts, authors concluded that increased TAC was related to uric acid accumulation (uremia) resulted from chronic renal failure. In 37 chronic renal failure patients endothelial vasodilatation was positively associated with serum total antioxidant capacity and negatively correlated with lipid peroxidation markers (Annuk et al., 2001). Children with nephrotic syndrome presented lower blood levels of both total antioxidant capacity and GSH which were associated with increased rates of T lymphocyte apoptosis (Zachwieja et al., 2003). In kidney transplantation, insulin administration can partially recover the decay of plasma TAC (Monge et al., 2007).

TAC in neurological and psychiatric diseases

The role of free radicals in neurological diseases are well established (Halliwell, 1994; Ferrari, 2000). A clear inverse association between plasma TAC and degree of neurological damages induced by ischemic-reperfusion injury is well-established (Leinonen et al., 2000). Ischemic stroke patients had lower levels of blood TAC (Gariballa et al., 2002). Plasma TAC in schizophrenic patients was lower compared to control subjects, and significantly inversely correlated with the severity of symptoms (Yao et al., 1998).

In 1998, it was reported that psychological stress increases oxidative stress, measured by MDA, a lipid peroxidation marker (Schneider et al., 1998). Could psychological stress decrease TAC and reduce the antioxidants in the brain? In this sense, Sivonová et al. (2004) reported that the stress of tests caused increase of DNA oxidation and lipid peroxidation as well as decrease of total antioxidant capacity of plasma in university students. The stress induced by shift work was associated with decreased total antioxidant capacity in night shift working (Sharifian et al., 2005).

Decreased levels of TAC were observed in anorexia nervosa (24%), AIDS-associated encephalopathy (20%), cardiomyopathy (17%) and diabetic polyneuropathy (13%). However, plasma TAC levels of patients with Alzheimer's disease, Parkinson's disease, depression, and schizophrenia were all unchanged (Sofic et al., 2002). These results confirm previous findings that Alzheimer's disease and vascular dementia patients did not have TAC changes in comparison to control groups, although vitamin C and vitamin E deficiencies were observed in vascular dementia and Alzheimer's disease patients, respectively (Sinclair, 1998). However, Yanik et al (2004) reported decreased TAC and increased peroxidation in the blood of depressive patients; the severity of disease was positively associated with oxidative stress levels.

Contradicting the results presented above, authors reported decreased levels of TAC, SOD and GPx in Parkinson's disease patients compared to controls, whereas no changes were observed in the plasma levels of vitamins A, C and E between two groups (Yuan et al., 2000). These remarkable divergences could be attributable to the differences in clinical stages and/or genetic and environmental factors (mainly diet) between the Parkinson's disease patients and re-enforce the importance of new studies that could evaluate TAC in all clinical stages of disease.

Although TAC was not evaluated, it was reported that epilepsy patients had lower erythrocyte glutathione reductase and plasma vitamins A and C levels than the control group (Shuda et al., 2001). Epileptic patients presented higher levels of erythrocyte MDA, ceruloplasmin and hemolysis than control subjects. TAC could be useful in future studies of epilepsy. It should be emphasized that TAC could not be applied for the diagnosis of all neurological diseases (Alam et al., 2000).

TAC and cancer

The role of oxidative damage in cancer is well established, with a great number of pathobiochemical pathways that lead to free radical DNA damage and cellular neoplastic transformation (Ferrari, 2001). An interesting example was a study that observed an increase in TAC after surgical removal of lung cancer (Erhola et al., 1998). Notwithstand-

ing there is not a homogenous manifestation of oxidative damage among different types of cancer.

Pleural effusion culture of lymphocytes from carcinoma patients presented lower levels of TAC and higher degree of DNA oxidative damage (Liu et al., 2003). Children with bone cancer, Burkitt's lymphoma and large cell lymphoma, but not acute myelogenous leukemia, had higher plasma levels of MDA (Yazdanpanah et al., 1997), as well as in mammographic dysplastic women in comparison to cancer-free groups (Boyd and McGuire, 1991). Patients with fibroadenoma and adenocarcinoma of the breast had increased levels of plasma and erythrocyte MDA and decreased concentrations of GSH and vitamins C and E (Kumaraguruparan et al., 2002). In a recent study, it was observed that breast cancer patients had higher lipid peroxidation levels and lower blood TAC (Sener et al., 2006). Another female cancer, the cervical intraepithelial neoplasia, was also associated with lower blood antioxidant capacity levels (Chung et al., 2004). However, a study revealed that both control and childhood cancer patients have the same blood TAC levels, whereas chemotherapy has deteriorated antioxidant capacity of plasma (Papageorgiou et al., 2005).

In contrast to those studies, patients with oral squamous cell carcinoma had lower levels of MDA, catalase and SOD, and higher concentrations of GSH and GPx (Nagini et al., 1998). It reflects that in this cancer type, an antioxidant

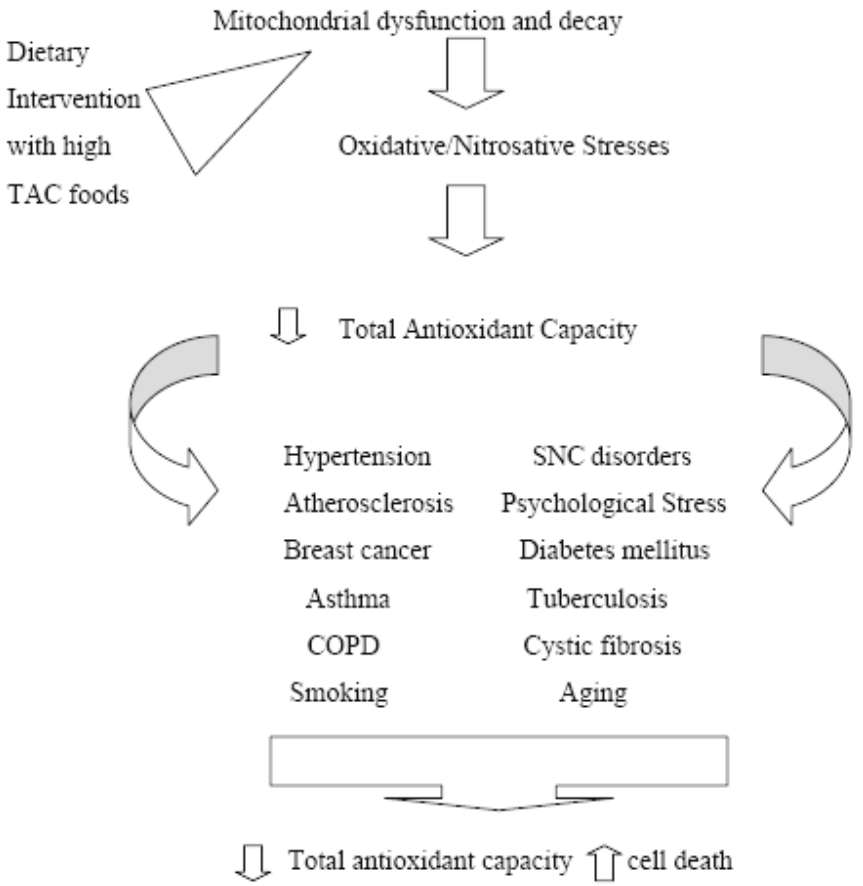

Figure 1. Pathophysiology and prevention of Total Antioxidant Capacity decay. (Arrows: stimulation, Head arrow: inhibition)

environment is crucial for neoplastic development. In the same manner, it is well recognized that high antioxidant capacity is essential for tumor survival against paclitaxel chemotherapy (Ramanathan et al., 2005).

In a case-control study (Ching et al., 2002) that evaluated possible breast cancer risk factors, the comparison of the higher against the lower quartiles of serum β-carotene, retinol, bilirubin and TAC revealed the following odds ratios, respectively: 0.47; 0.53; 0.50; and 0.47. This means that women with high TAC had 53% lesser risk to develop breast cancer.

In both poor and well-differentiated gastric adenocarcinomes, TAC levels were found to be decreased. On the other hand, DNA oxidation, measured by 8-hydroxy-deoxyguanosine (8-OH-dG), was increased in relation to the control group (Su et al., 2001).

Recently, it was observed that TAC was 2.45-fold lower in the brain of patients with glioblastoma compared to normal controls, whereas oxidative damage to cell DNA was remarkably higher (2.15-fold) than the control group (Tuzgen et al., 2007). Thus, TAC could be useful for better understanding the possible roles of antioxidant-oxidant involvement in cancers.

TAC in other pathophysiologies

In chronic inflammatory enteropathies (Crohn's disease), histologic levels of TAC were decreased in relation to control subjects (Koch et al., 2002; Koutroubakis et al. 2004). In patients with periodontal diseases it was observed that TAC of saliva is 40% lower compared to healthy controls (Diab-Ladki et al., 2003). Analysis of oxidative stress multiple sclerosis patients revealed increased oxidation to LDL and decreased levels of TAC (Besler and Çornoglu, 2003). Studying the oxidative stress in male infertility, its was found that seminal levels of reactive oxygen species in infertile males were significantly higher than in controls. Control subjects had seminal TAC values at least 1,41 fold higher than that found in infertile males; and sperm concentration was negatively associated with reactive oxygen species, with exception of idiopathic infertility (Pasqualotto et al., 2000). Figure 1 sum-

Table 1. Total Antioxidant Capacity in foods (μmol Trolox-Equivalent/100g or 100ml). ¯just one mean available; *μmol gallic acid equivalents/100mL (Paganga et al.,1999; Halvorsen et al., 2002; Proteggente et al., 2002; Szeto et al., 2002; Ishimoto et al., 2006)

Food	Minimum mean values for TAC	Maximum mean values for TAC
apple (green)	630	630
apple (red)	150	640
banana	181	420
butter cabagge	90	492
carrot	40	166
common beans	330	410
eggplant	170	490
lemon	1020	1040
lettuce	88	340
onion	432	670
orange	849	1140
papaya	-	620
red beet	-	1980
onion	432	670
orange	849	1140
red pepper	-	40
red wine (dry)*	-	247800*
tomato	160	310
watermelon	-	620

marizes the importance of TAC in many pathophysiological states, aging and the prospects for nutritional prevention of diseases.

Nutritional interventions to improve total antioxidant capacity

The role of antioxidant nutrients in fighting against oxidative stress is well-established in a great number of diseases including cancer, cardiovascular and neurological pathologies (Ferrari and Torres, 2003; Ferrari, 2004). In this sense, researchers had materially proved that following consumption of diets rich in fruits and vegetables there was an increase in serum TAC (Cao et al., 1998). For example, high tomato consumption potentially increased total antioxidant capacity of healthy subjects (Tyssandier et al., 2004). In a similar concern, adherence to Mediterranean dietary practices was positively associated with TAC levels and negatively associated with oxidation of the atherogenic LDL-cholesterol (Pitsavos et al., 2005). These higher TAC values of foods in Mediterranean diet could in part explain why adherence to this diet reduces mortality risk by 8% according to EPIC multicenter cohort study (Trichopoulou et al., 2005). However, depending on the type of food, duration of nutritional intervention and antioxidant concentration of foods the nutritional administration can not be sufficient to impact total antioxidant capacity of plasma (Pellegrini et al., 2000; van der Berg et al., 2001). Then, there is an increased interest of many research groups to evaluate TAC of foods (Paganga et al., 1999; Halvorsen et al., 2001; Proteggente et al., 2002; Szeto et al., 2002). TAC of Brazilian red wine, rich in polyphenolics, is very high (Ishimoto et al., 2006) when compared with other foods summarized in Table 1.

It should be emphasized that the roles of new antioxidants (mainly poyphenolics, such as quercetin, luteolin, kaempferol, anthocyanins, tea catechins, tomato licopene) in decreasing disease risk and maintenance of a healthy adequate physiological status have been recognized from the early age until aging (Ferrari and Torres, 2003; Ferrari, 2004). Apple extracts (rich in polyphenolics), with have higher TAC, were able to suppress proliferation of colon cancer cells (Eberhardt et al., 2000). Dietary supplementation with lyophilized apples decreased total plasma cholesterol, as well as hepatic cholesterol and urinary MDA, and increased serum TAC (Aprikian et al., 2001).

Its important to remember that a minimum of oxidant stress is necessary to maintain the integrity of biological systems, with a physiologic concentration of superoxide (Clément and Pervaiz, 1999) once the normal cellular environment is reduced (Gutteridge, 1999). This explains why high antioxidant supplementation have failed to improve health and is not recommended (McCall and Frei, 1999; Falsini et al., 2003; Jialal and Devaraj, 2003; Kris-Etherton et al., 2004; Yaffe et al., 2004). Excessive amounts of vitamin antioxidants can trigger oxidative stress damaging the cell DNA (Donnelly et al., 1999). In the same direction, excessive vitamin E supplementation can increase human mortality (Miller et al., 2005). Further, excessive total antioxidant status can have serious consequences. For example, failure of ovulation in polycyistic ovarian syndrome patients was positively associated with TAC levels (Verit et al., 2007). Then, although it is important to improve body TAC by means of a healthy diet, pharmaceutical supplementation should be avoided.

Perspectives and conclusions

Besides the consolidated role of oxidative stress in AIDS, malaria infection, chemical and physical intoxications (metals, pollutants, etc), mitochondrial aging processes and many other pathophysiological states (Ferrari, 1998; Fukagawa, 1999; Shankar et al., 1999; Ferrari, 2004; Barja et al., 2005; Pamplona et al., 2005), the beneficial roles of antioxidant protection on TAC and disease progression were not completely measured. In renal injury research, the kinetics of oxidative injury and antioxidant defense should be better studied.

Then, TAC evaluation, used with other oxidative stress and antioxidant defense biomarkers, constitutes the first step in search for a healthy body status.

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