Original Article

Acquired Clinical Vulnerability Test - Appraising Utility and Significance of Measuring Total Antioxidant Capacity as a Public Health Tool

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Abstract: The prevalence of lifestyle diseases or the Non-Communicable Diseases (NCDs) are on the rise colossally as well as globally. The key contributors are understood to be the pollutants and contaminants present in local ambient environment that trigger the onset of cellular oxidative stress i.e. imbalance in levels of oxidants and antioxidants at cell level, and the pro-inflammatory changes. Reports in literature indicate a possibility of association between risk of increase in lifestyle-disease-incidences and the acquisition of clinical vulnerability (ACV) in subjects chronically exposed to pollutants. Occurrence of oxidative stress is known to be the first and foremost change for the onset of NCDs. Therefore a periodic assessment of imbalance in levels of oxidants and antioxidants is plausible that can be performed by determining levels of cellular oxidative damage and the Total Antioxidant Capacity (TAC) in blood or body fluids. Elucidation of subnormal TAC can provide an opportunity for protection from ACV or getting predisposed to diseases and disorders through evidence based timely supplementation of antioxidants. In this review, we hypothesize, and appraise, the utility and significance of TAC measurements as a public health tool for monitoring ACV. Its measurement at different levels of NCD prevention shall result in efficient implementation of global action program for control of NCDs burden. Points in approval are ease, reliability, specificity, reproducibility, and the inexpensiveness of the method. We also contend that further research could lead to development of a proper cocktail of antioxidants to be used as adjuvant therapeutic measures to delay or reverse existing NCDs and their impact in individuals. We propose TAC as an early indicator that can be used to detect and control ACV and related NCDs.
Keywords: diseases, disorders, clinical, vulnerability, toxicants, xenobiotics, pollutants

INTRODUCTION

The incidences of Non-Communicable Diseases (NCDs) or lifestyle diseases have increased colossally and have now become a global phenomenon. Solely in India, chronic diseases have accounted for 53% of all deaths in 2005. It is projected that mortality due to chronic diseases may increase from 40% of all deaths in 1990 to 67% of all deaths in 2020 [1]. This rise has been widely attributed to life style factors [2]. By and large, causal factors for the rise include a prolonged exposure to xenobiotics which can be chemical, biological and radiation-emitting agents present in ambient environment. Chemicals that are attributed to NCDs are alcohol, tobacco smoking, heavy metals and toxic elements, some pesticides, some occupational exposures; and the biological agents attributing to NCDs are active microorganisms and their remnants e.g. *lipopolysaccharide* with a potential to induce pro-inflammatory-changes.

Rise in NCDs incidences is mostly an outcome of free radical induced oxidative stress (OS); it occurs at cellular level after chronic exposures to xenobiotics and is followed usually by onset of pro-inflammatory changes at sub-clinical level that accumulate and help to develop pathophysiological changes in tissues. This interpretation is based on concept that the repeated insults or damages and their inadequate repair develop causal cellular and molecular changes in vital tissues or organs or systems in human subjects. It is thus perceptible that such molecular and cellular events promote acquisition of clinical vulnerability (ACV) and manifest clinical signs and symptoms subsequently. Literature on ACV vis-a-vis exposure to chemicals has been reviewed earlier and a relation between increase in incidences of NCDs (e.g. cancers, diabetes, obesity, infertility, respiratory diseases, allergies, cardiovascular diseases, and neurodegenerative disorders) and exposures to xenobiotics been observed [3]. We now intend to evaluate association of NCDs with systemic status of antioxidant capacity in humans with an aim to know utility and significance of Total Antioxidant Capacity (TAC) assay as a public health tool to assess ACV.

NCDs are difficult to detect and control in initial stages. Nevertheless, early detection of ACV is possible. This is considered so because most of NCDs are OS mediated and run parallel to changes in redox homeostasis [4]. A decrease in systemic TAC and rise in oxidative damage to cellular bio-molecules are seen frequently in NCDs. It can therefore be construed that an upset in oxidant and antioxidant or redox homeostasis may render subjects prone to oxidative and nitrosative injuries and hence vulnerable to diseases contributed by prolonged exposures to toxicants of ambient environment. Accordingly, measuring OS levels to detect ACV seems an attractive and important tool for public health monitoring. Though the measure of both TAC and the oxidized bio-molecules is important for assessing ACV, the TAC measurement alone is preferable for multiple reasons.

TAC assay measures potential of systemic antioxidants and their dynamism with respect to scavenging ROS; though it provides evidence for oxidative stress also. Further, it is a low cost and an easy-to-perform test [5]. Essentially, TAC level in systemic or in body fluids is largely a reflection of the amounts of antioxidants equilibrated between tissues and constituent cells. The measure of TAC showcases the cumulative and dynamic action of all the antioxidants present in plasma and body fluids rather than an integrated sum of measurable antioxidants. TAC assay reflects systemic preparedness of xenobiotic exposed subjects to (a) counter OS mediated inflammation and the linked morbidities, (b) delay, restrain, or prevent NCD epidemics, and (c) promote public good health by providing opportunity to supplement antioxidants as evidence based medicine. TAC levels in blood or body fluids can fluctuate following their utilization, intake, or intracellular generation. The concept of TAC has been applied to biology and medicine, and further to nutrition and epidemiology. However, it has never been proposed for use in public health monitoring. We believe that it needs to be appraised as a screening and preventive tool for ACV.

SIGNIFICANCE OF TAC IN DISEASES AND DISORDERS

Koracevic *et al* invented the TAC test in 2001; [6] and it was instantly endorsed by Young [7] as the test measuring status of antioxidants' competence in blood or body fluids, which (a) works as systemic defense mechanism, (b) counters the action of cellular ROS or other oxidants, and (c) protects the expected oxidative damage to cellular bio-molecules. TAC in blood or other body fluids remains in equilibrium with sheathing exudates of cell/ tissue [8] and works like a chest-of-currency ready to be spent for inactivation of ROS and protection of cells or tissue from damage and malfunction. Speculatively, TAC levels in humans can display status of ACV to protect them from OS, pro-

inflammatory changes, and inapt tissue homeostasis, and risk of diseases & disorders invisible clinically.

ROS are continuously generated in cells at tissue level and in a regulated manner. Dysregulation of ROS generation results either in OS and the associated morbidities (Figure 1A) or in reductive stress (RS) as shown in Figure 1B. OS is known for its pro-inflammatory actions and contribution to onset of chronic diseases; oxidative damage is an accompanying phenomenon causing an early consumption of antioxidants [9]. The antioxidant capacity is an adaptable response of organism to prevent irreversible oxidative damage or the derived risks from a chronic exposure to causative agents. Eventually, the prolonged low level exposure to oxidants sparks cellular responses setting up pro-inflammatory conditions, tissue damage, organ dysfunction, and disease such as diabetes and cancer.
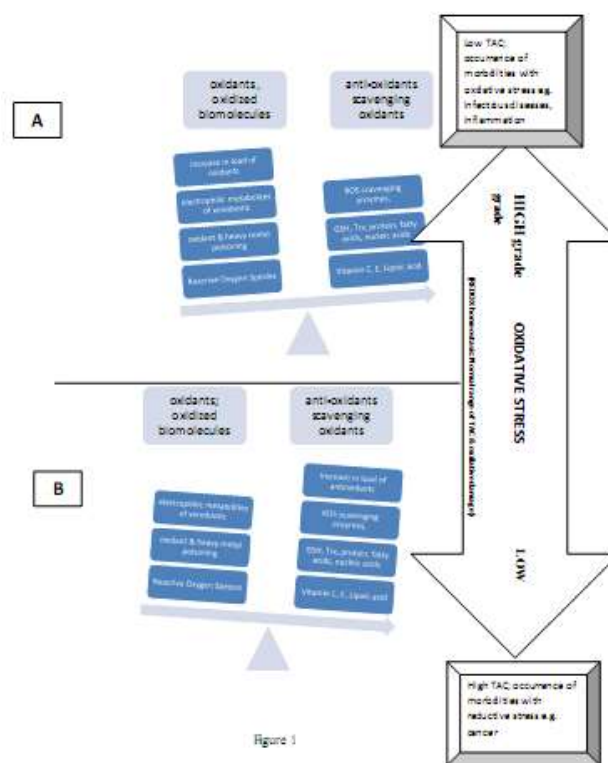

Fig-1: Relation between levels of oxidants, antioxidants, TAC, and the morbidities

On the other hand, RS may happen due to undue over-generation of the endogenous antioxidants [10, 11] and changes in ROS homeostasis [12] seen in cancer tissues; significance of RS in cancer is evident from the fact that it is being targeted for cancer chemotherapy [13-16]. RS is defined as a condition wherein excessive amount of reducing equivalents are present in the form of NAD(P)H, GSH, thioredoxin & glutaredoxin system. RS is known for inducing vulnerability to inheritable cardiomyopathy [17, 18] and growth of microorganisms like Mycobacterium tuberculosis in humans [19-20].

In redox homeostasis, equilibrium is maintained between generation of oxidants (e.g. oxygen free radicals, ROS, electrophilic metabolites of xenobiotics etc) and their evenhanded scavenging by antioxidants (enzymatic and non-enzymatic). TAC tones down OS and maintains redox equilibrium to allow the balanced rate of redox reactions in cell physiology [21]. Basically, redox homeostasis controls several functions e.g. gene expression and cell regulatory pathways ensuring least destruction of functionally differentiated cell. Cellular redox homeostasis is known to regulate also the cell-cycle progression to and fro quiescent state to proliferation state[22-23]. The prolonged disruptions in redox homeostasis thus can result into (a) incongruity in cell growth and differentiation, (b) disruptions in homeostasis of cells in tissues, (c) display of clinical manifestations, and (d) malfunctioning of organs or systems eventually.

An escalation of oxidants' generation and the consequential decrease in TAC creates an abnormal physiology in cell, which if not rectified timely can damage vital molecules of cells at tissue level. Oxygen free radical generation occurs commonly during aerobic cellular metabolism, activation of innate immune cell function of inflammatory cells (neutrophil, eosinophils, monocytes, and macrophages), and in epithelial cells. Induction in level of oxidant generation occurs also during the xenobiotics metabolism. ROS function as 'second messenger' and regulate various cell functions including proliferation and differentiation [24, 25]. Ultimately, either the apoptosis or uncontrolled proliferation commences in the affected cells. The inaptness of cellular redox homeostasis may form basis of antioxidant-poor-environment (i.e. OS) or antioxidant-rich-environment (i.e. RS) and be the axis-of-evil interceding chronic disease conditions like cancer, disrupted wound healing, fibrosis, cardiovascular diseases, diabetes, and neuro-degenerative diseases in humans. This hypothesis is in consonance with implications of OS or RS in pathologies and related diseases or disorders.

The extremes of redox spectrum in cells upset several key functions and as a consequence play crucial roles in disease pathogenesis. In fact, an array of diseases and disorders are known in literature that involves crucial participation of the significant imbalances between TAC and ROS levels. An enhanced status of the damaged and dysfunctional macromolecules like increased level of protein carbonyl groups, 8-hydroxy guanosine, MDA, isoprostanes, protein glycation are reported in chronic disease conditions that include Diabetes Mellitus, neuro-degenerative diseases, cardiovascular diseases, pulmonary diseases, cancer, and expectedly in many more type of diseases that involve prolonged inflammation [26].

In OS, the capability of countering ROS production or accumulation and their inactivation solely depends upon steady-state levels of antioxidants that are administered exogenously and the levels of enzymatic or non-enzymatic antioxidants generated endogenously. Among exogenous type, a large group of hydrophilic and lipophilic antioxidants are active and include glutathione, arginine, citrulline, taurine, creatine, uric acid, vitamin C, vitamin E (alpha-tocopherol), zinc, selenium, carotenes, and lipoic acid. These function mostly by two mechanisms namely inhibition of chain reaction of free radical formation, or limiting the increased ROS production or accumulation. Among the endogenous antioxidants, both non-enzymatic and enzymatic are highly efficient and include glutathione, cysteine, methionine, Co-Q, ceruloplasmin, superoxide dismutase, catalase, peroxidases, and hydroperoxidases. The bio-molecules like cytochromes, albumin, polyunsaturated fatty acids, and nucleic acids are also effective due to their nucleophilic potential; but these biomolecules lose their required function during the counter of oxidants.

The proposal of measuring TAC for public health monitoring therefore appears prudent. The suggestion finds strength from the reports elucidating link between occurrence of a disease/ disorder and altered TAC status. Change in TAC levels is known to recover to their normal status during the course of scheduled treatment; the prescribed treatment regimens have been found to normalize TAC levels during the course or the ramification of treatment. We reviewed the relevant literature to elucidate involvement of TAC in oxidative stress mediated pathologies and their clinical manifestations. The endeavor was more to illustrate penchant of investigators for TAC monitoring in chronic conditions and to think about topping up of the prescribed clinical management with antioxidants.

TAC LEVELS IN DISEASES AND DISORDERS

A spectrum of ailments showing changes in TAC levels is described in literature (Table 1). These studies have assessed the correlation between changes in TAC level of blood or saliva and alteration in clinical characteristics and/or relevant biomarkers chronic disease conditions. In general, a trend of decrease in TAC is seen as compared to normal counterparts. This trend is notable in study population of all age groups i.e. children, adolescents, middle-aged or older adults. Studies have found even a recovery from the observed decrease in TAC to normal levels during the course of clinical management or after the standard treatment [44]. Conversely, an increase is also reported in morbid subjects; salivary TAC increased in subjects carrying active dental caries compared to that in saliva of caries free subjects. The changes and the trend were found to be statistically significant in Pearson's Correlation Coefficient analysis. In most of these studies, TAC was determined as described by Koracevic *et al*; [6] FRAP

method described by Benzie and Strain [57] was also used measuring ultimately TBARS for TAC assay. In essence, the referred studies measured status of the collective potential of antioxidants available in body fluids for controlling OS in human pathologies.

Table 1: TAC levels in blood and saliva in human diseases

S No	Disease/disorder	Characterization / diagnosis by analyses of	Trend of Change in TAC level	Reference
1	Insulin-dependent diabetes mellitus (IDDM)	Islet cell antibodies	↓	[27]
2	Uncomplicated IDDM	Criteria of EURODIAB IDDM complications	↓	[28]
3	NIDDM	Oral Glucose Tolerance Test and HbA1c	↓	[29]
4	Pre-eclampsia	Angiotensin Converting Enzyme and Angiotensin II type-1 receptor	↓	[30]
5	Premenstrual syndrome	PMS questionnaire	↓	[31]
6	Periodontitis	Clinical periodontal indices	↓	[32]
7	Periodontitis	Clinical examination, presence of at least two non-adjacent sites per quadrant with probing pocket depths of ≥5mm that bled upon gentle probing	↓	[33]
8	Dental caries	As per WHO criteria, at least five decayed tooth surfaces	↑	[34]
9	Dental caries	Oral examination, as per WHO criteria of decayed/missing/ filled teeth (DMFT) score	↑	[35]
10	chronic periodontitis	Clinical examination	↓	[36]
11	Periodontal disease susceptibility in obese subjects	Body mass index	↓	[37]
12	Temporomandibular joint disorders and pain	Clinical examination by means of a questionnaire, the Research Diagnostic Criteria for Temporomandibular Disorders, validated for research and diagnosis of temporomandibular disorder	↓	[38]
13	Androgenic alopecia	Pattern of increased hair thinning on the fronto-temporal area and vertex in men; and on the frontal/ parietal scalp with retention of frontal hairline in women; family history of androgenetic alopecia; the presence of miniaturized hairs and diversity of hair diameter on dermoscopic examination	↓	[39]
14	Acute rheumatic fever	Clinical examination	↓	[40]
15	Essential hypertension	Daytime systolic and diastolic blood pressures	↓	[41]
16	Unstable Angina	Clinical and Paraclinical	↓	[42]

	pectoris	protocol, physical examination, medical history, electrocardiography,		
17	Acute myocardial infarction	History of prolonged ischemic chest pain, characteristic electrocardiogram, changes and elevated creatine kinase iso-enzyme, troponin-T within 12h after the pain	↓	[43]
18	Acute coronary syndrome	Clinical examination, ECG, ST-segment elevation sub-type, cardiac biomarkers	↓	[44]
19	Eales disease, uveitis, chronic cataract	Fundus examination by ophthalmoscope	↓	[45]
20	Chronic obstructive pulmonary disease	Clinical examination, smoking habits, forced expiratory volume in one second, duration of disease.	↓	[46, 47]
21	Acute Liver Failure	Criteria of International Association for the study of liver, occurrence of encephalopathy within 4 weeks of onset of symptoms in absence of any preexisting liver disease, presence of massive/sub-massive necrosis in post mortem liver biopsy specimens	↓	[48]
22	HIV-1 seropositive, asymptomatic / symptomatic	Numerical and functional decline in CD4 cells which results in progressive immunodeficiency	↓	[49]
23	HIV	Clinical diagnosis	↕	[50]
24	Infertile men	Sperm concentration, motility, morphology	↓	[51]
25	Sickle cell disease	Sickled erythrocyte and Hb content	↓	[52]
26	Paranoid schizophrenia	DSM-IV criteria	↓	[53]
27	Attention deficit hyperactivity disorder	DSM IV-TR criteria	↓	[54]
28	Alcoholism	Patients suffering from alcoholism	↓	[55]
29	Psoriasis	Inflammation biomarkers e.g. CRP, IL-6, IL-8, ESR	↓	[56]

Interest in importance of measuring TAC in medicine and health spans last two decades [58, 59]. The issue however continues to be still under debate for its applicability in epidemiology and public health monitoring [60, 61]. Nevertheless, utility of TAC determination for these applications finds support from studies showing increased generation of ROS, low levels of systemic antioxidant capacity, and empirical effect of antioxidants' supplementation that has been observed in a variety of human diseases or disorders like diabetes, atherogenesis, reperfusion injury, hemodialysis, male infertility, rheumatoid arthritis, premature neonates, septic shock [58, 62].

Currently, TAC test is being included frequently in studies on human pathologies. Whereas, it is mostly due to need of elucidating the role of OS in human diseases or disorders, however notion of using TAC as new biomarker is also becoming popular to provide anticipated benefits and improve clinical

management of chronic conditions. In last two decades, the advent of new methods has facilitated immense use of TAC determination in blood or saliva [63]. The potential of TAC measurement for applications in clinic and public health is still awaited and is largely unexplored.

CHEMICALS, NCDS AND TAC

The role of toxicants in development of human disease is well known. Exposure to these through air, water, food, and soil at home or at work affects all organ-systems. They may be causal or contributory factors for a variety of human sickness, like CVDs, asthma and other respiratory diseases, reproductive outcomes, altered neurological and immune functions, dermal pathologies, as well as many type of cancers. Significant increase in chemical exposure is related to their increased use. It is, therefore, essential that the health care professionals have access to resources and information to assist them in the prevention, diagnosis, and treatment of disorders attributable to such exposures. Safe use and disposal of such chemicals may be indicative of their impact on public health.

Chatham-Stephens et al have estimated in 2010 that more than 8 million persons in India, Indonesia, and the Philippines have suffered disease, disability, or death from exposures to industrial contaminants [64]. This information is derived from a survey of toxic waste sites in 2010, resulting in 828,722 DALYs. The investigators concluded that 'toxic waste sites are responsible for a significant burden of disease in low- and middle-income countries. These figures may be an underestimate of the actual burden of disease due to the factors like unidentified and unscreened sites. Extrapolation of environmental sampling to the entire exposed population could have resulted in a higher estimate of the burden of disease attributable to these sites. However, we feel that the poor state of waste disposal and inappropriate use of chemicals in these countries may have even larger disease burdens due to chemical exposures.

There is no dearth of toxicological studies that demonstrate exposure to toxic chemicals cause OS. However, there are few studies in humans that prove the corollary i.e. depleted TAC levels in parallel to diseases and disorders. A few of these chemical are listed in Table 2 though it is not based on a comprehensive review of literature.

Table 2: NCDs, Chemicals, and TAC levels

Heavy Metals	Blood TAC levels	Remarks	Reference
Arsenic	Decrease in TAC	Population using contaminated water in Lanyang Basin, Taiwan	[65]
Lead + Mercury + Cadmium	Decrease in TAC	Gasoline workers	[66]
Organic Solvents			
Toluene	Decrease in TAS	Exposed workers	[67]
Benzene	Decrease in TAC	Workers in Fuel stations	[68]
Pesticides			
Organophosphates and Carbamates	Decrease in TAC	Pesticide sprayers	[69]

Effects of xenobiotics on total antioxidant capacity have been reviewed by Ferrari [70]; it is concluded that measurement of TAC is appropriate for evaluation of the total antioxidant defenses of blood, cells, and different kinds of tissues and organs. TAC is lowered by alcoholism, smoking, and exposure to radiation, herbicides, carbon monoxide, carbon tetra-chloride, lead, arsenic, mercury, cadmium, aluminum, and other toxic elements. Antioxidant status is suggested to influence vulnerability to oxidative damage, and thereafter the inception and succession of OS mediated disease [71]. TAC test, an important tool, could evaluate ACV in individuals incessantly exposed to physicochemical and biological factors in the environmental and occupational environment. There is enough scientific evidence that chemical exposures cause or contribute to current epidemic of NCDs. It is our contention that estimation of TAC in serum should be used as a screening tool in public health monitoring and clinical medicine for early diagnosis of OS mediated pathologies and treatment of such diseases accordingly. More public health basic research is warranted on this issue.

Measuring TAC

Several methods are available for TAC determination. In general, the assay of Trolox equivalent antioxidant capacity (TEAC), ferric reducing ability of plasma (FRAP), and cupric reducing antioxidant capacity (CUPRAC) has been used. These have been reviewed for use in clinical studies [63,72]. For measuring TAC, a battery of 2-3 types of tests is recommended [7, 60]. Nevertheless, method developed by Koracevic *et al* [6] has been used quite often for testing TAC in blood and other body fluids. It is mostly due to the ease, low cost, affordability, and availability of the common instruments in a laboratory.

A SIMPLISTIC MODEL DESCRIBING ROLE OF ACV AND TAC IN PUBLIC HEALTH

WHO Global action plan for the prevention and control of NCD lays stress on the need of strategies that are based on latest scientific evidence and/or best practice, cost-effectiveness, affordability and public health principles, taking social and cultural considerations into account [73].

The action plan is essentially built around bringing a change in behavioral patterns like tobacco use, unhealthy diet, physical inactivity, and the harmful use of alcohol. The biochemical basis of these is maintenance of healthy oxidative radical homeostasis (Figure 2).
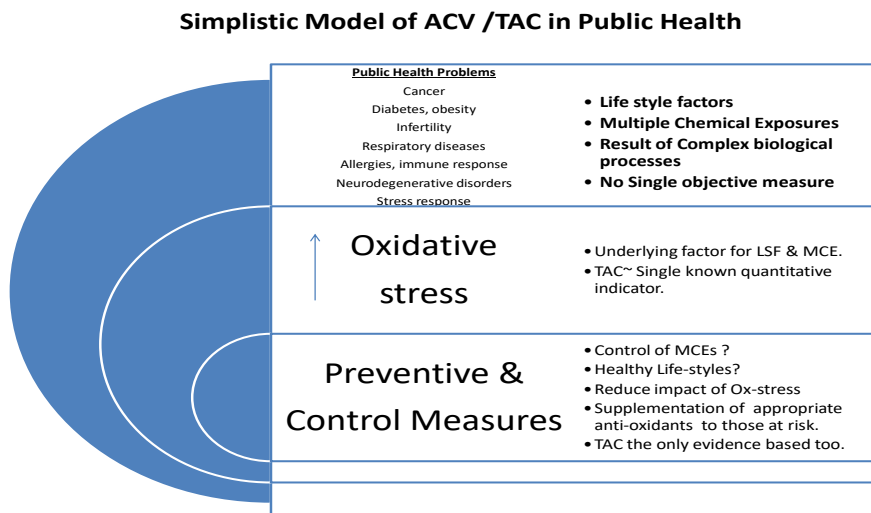
Simplistic Model of ACV /TAC in Public Health

Public Health Problems
Cancer
Diabetes, obesity
Infertility
Respiratory diseases
Allergies, immune response
Neurodegenerative disorders
Stress response

- **Life style factors**
- **Multiple Chemical Exposures**
- **Result of Complex biological processes**
- **No Single objective measure**

Oxidative stress

- Underlying factor for LSF & MCE.
- TAC~ Single known quantitative indicator.

Preventive & Control Measures

- Control of MCEs ?
- Healthy Life-styles?
- Reduce impact of Ox-stress
- Supplementation of appropriate anti-oxidants to those at risk.
- TAC the only evidence based too.

Fig-2: Simplistic model of ACV / TAC in public health

Unfortunately, such measures require massive logistic inputs, especially in absence of a measurable evidence based reliable and scientifically valid indicator. The above diagram is an effort to depict this graphically and shows TAC as the tool that may prove to be the crux of control strategy for NCDs.

THE WAY FORWARD

TAC measurement seems a logical tool to monitor antioxidant status of individuals. The susceptibility to OS and proneness to OS mediated diseases & disorders can be checked by TAC status in disease free individuals and the subsequent follow up till the development of morbid conditions. A periodic testing plan of TAC test may be of use in social and preventive medicine. Essentially, this endeavor will assay the preparedness of individuals for preventing possibility of ACV that is risked by repeated and prolonged exposures to damaging oxidants or electrophilic metabolites formed in cells from oxidative metabolism of environmental pollutants which is now being considered globally as the major cause of mortality and morbidity.

TAC evaluations will be of use for evidence based medicine to supplement anti-oxidants for improved clinical management of patients with chronic illnesses or keeping the populations by and large free of diseases. Besides, secondary complications and exacerbations of diseases or disorders involving oxidative damage can be suppressed and curbed in

ailing subjects by supplementing antioxidants. This exploratory attempt will keep TAC levels in normal range and could promote early recovery and prevent the recurrences.

Determining plasma TAC may help to identify conditions affecting oxidative status in vivo (e.g., exposure to reactive oxygen species and antioxidant supplementation). Measuring TAC may also help in the evaluation of physiological, micro-environmental, and nutritional status of the redox state in humans. In test of TAC, since the capacity of systemic antioxidants and their synergistic interaction is assessed, it gives an insight into the delicate balance in vivo between oxidants and antioxidants.

TAC measurement and appropriate strategies may provide appropriate opportunities for supplementation of antioxidants for therapeutic, preventive and health promoting reasons as a worldwide feasible solution to combat diseases. Identifying TAC in human body fluids is important also for developing strong tools in health promotion and disease prevention towards outpatient clinics, bedside monitoring, and providing home medical care.

Antioxidants are emerging as prophylactic and therapeutic agents. Several antioxidants like SOD, CAT, epigallocatechin-3-*O*-gallate, lycopene, ellagic acid, coenzyme Q_{10}, indole-3-carbinol, genistein, quercetin, vitamin C and vitamin E have been found to

be pharmacologically active as prophylactic and therapeutic agents for diseases like cancer, diabetes, cardiovascular diseases, autoimmune diseases, neurodegenerative disorders and are implicated in aging. These need to be pharmacologically explored for their therapeutic and health protective role and developed as drugs and health supplements. Further, low levels of TAC should be considered as a risk factor for ACV and related NCDs. Monitoring of TAC and supplementation of right mix of antioxidants could be the sheet anchor for prevention and control of such diseases.

CONCLUSIONS

Based on relevant literature reports, we identify and propose TAC as an early indicator to monitor and control ACV and related NCDs. It is easily measureable, reliable, reproducible and affordable. Its use in public health at different levels of prevention shall result in efficient implementation of global action program for control of NCDs.

We also contend that further research could lead to the development of cocktail of antioxidants that may delay or reverse the existing NCDs in individuals or can be used as co-therapeutic measures. Elucidation of the subnormal TAC status can provide an opportunity for protection from acquiring clinical vulnerability or getting predisposed to diseases and disorders through evidence based timely supplementation of antioxidants.

Acknowledgement

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