Oxidative Stress Index: Disease Onset Prediction and Prevention

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Abstract

The Oxidative Stress Index (OSI), a measure of the probability of disease onset in people who are clinically ill as well as those without prevalent disease, has been described. OSI has also been applied to predict which disease causing parameters are more contributory to the onset of Alzheimer's disease and how it may be applied as a public health survey instrument to evaluate the likelihood of disease onset with residence proximity to points of environmental pollutant releases. These applications, as well as other proposed applications of the OSI are discussed.

Keywords: Oxidative Stress; Oxidative Stress Index; Alzheimer's Disease; Disease Causes; Disease Prevention

Introduction

The Oxidative Stress Index (OSI) has been proposed as both a measure of an individual's level of oxidative stress (OS) and a predicator of the probability of disease onset in those with prevalent disease as well as those without symptoms of illness [1]. OSI has also been hypothesized to demonstrate which parameters are more contributory to the onset Alzheimer's disease [2]. It has also been shown to be applicable as a public health survey instrument to evaluate the likelihood of disease onset as a function of residence proximities to points of environmental pollutant releases [3].

All disease is both a cause of and a consequence of oxidative stress [4,5]. OS and disease onset are caused by a combination of genetic load, environmental toxic chemical and radiation exposures, lifestyle, psychological stress, the prevalence of other diseases and their symptoms, medications regularly taken and chronic inflammation. It is well established that total oxidative stress, the sum of all contributory OS sources, is related to increased likelihood of disease onset in a dose-response relationship ([5] and the references contained in it).

OS may be measured by its biomarkers, including serum malondialdehyde (MDA), F2-Isoprostanes, lipid hydroxides, hydroperoxides, hydrocholesterols, aldehydes and ketones [1]. Of these, malondialdehyde (MDA), is the most widely used [6]. Biomarkers, however, can vary widely in concentrations depending upon food eaten, environmental exposures, state of one's health or even the time of day when serum is drawn [6]. The OSI, shown in table 1, is determined via a multi-item questionnaire, that reduces such uncertainty by addressing all OS inducing factors in one's life [1]. The total of all the items checked on the questionnaire equals the OSI.

The OSI, as originally formatted, does not predict which disease will more likely develop with increasing OS, only the extend to which further disease onset is likely. That said, however, it has been shown that the OSI can be used to be an indicator of which parameters elevate the likelihood of onset of Alzheimer's disease and can likewise be used to similarly evaluate the onset of other diseases [2].

Another application of the OSI has also been demonstrated. People living proximate to sources of environmental pollution are well known to develop disease in higher numbers than cohorts not so exposed. An example of this phenomenon is the increased prevalence of

asthma among children living near heavily trafficked highways and the falling off of asthma incidence with distances removed from such roads [7]. As exposures to chemical pollutants are associated with increases in oxidative stress disease levels and OSI, it has been postulated that OSI public health surveys can be valuable for determining increased disease risk as functions of distances from emission points of chemical pollutants emanating from chemical and petroleum storage and transfer sites, power plant and other industrial stacks, leaking toxic landfills, mining and smelting sites, heavy metal recycling operations and electromagnetic radiation sources [3].

In addition to the three applications of the OSI that were identified above, it is proposed here that additional ones also exist. These include: identifying specific causes of other late onset diseases, health pre-screening, rural and limited medical care area screening and longitudinal studies of disease patterns and causes.

Methods

The results presented here are based upon a literature review of the causes of oxidative stress, OS measurement, disease causing exposures, empirical and mechanistic associations between OS and disease onset and the use of patient or surrogate answered questionnaires. The questionnaire developed for measuring OSI contains items that address all OS raising factors; genetic, environmental, lifestyle, health status and medications taken at the time of measurement.

Results and Discussion

The first three of the following sections address published uses for the OSI. The three that follow suggest additional applications. The OSI has been modified from its original form and the current form of the OSI is presented in table 1.

Table 1: Oxidative stress index questionnaire.

Family History
Family History Put one check for each parent, sibling (sister or brother) or grandparent who has or had each of the diseases or conditions identified: • Parent with neurological disease - Alzheimer's, Parkinson's, Lou Gehrig, ADHD or Autism • Parent with diabetes • Parent with heart disease, heart attack or stroke • Parent with asthma or COPD • Parent with allergies - hay fever, animals, food or chemicals • Parent with cancer • Siblings with neurological disease - Alzheimer's, Parkinson's or Lou Gehrig, ADHD or Autism • Siblings with diabetes • Siblings with heart disease, heart attack or stroke • Siblings with asthma or COPD • Siblings with allergies - hay fever, animals, food or chemicals • Siblings with cancer • Grandparents with neurological disease - Alzheimer's, Parkinson's or Lou Gehrig, ADHD or Autism • Grandparents with diabetes • Grandparents with heart disease, heart attack or stroke • Grandparents with asthma or COPD • Grandparent with allergies - hay fever, animals, food or chemicals • Grandparent with cancer **Total Family History Checks ____** • **Gender** Female ___   Male ___ • **Age**

Check all age boxes that apply. If, for example, you are 55 years old check the first two boxes. If you're 82, check all 5 of these boxes

- 40 or older
- 50 or older
- 60 or older
- 70 or older
- 80 or older

Weight

If you are overweight from your recommended weight, check all the weight boxes that apply. If, for example you are 40 pounds over your recommended weight, check the first three boxes and add three checks to the total. Find your recommended weight on the weight chart at the end of the OSI checklist.

- 10 - 20 pounds overweight
- 21 - 40 pounds overweight
- 31 - 60 pounds overweight
- 61 - 80 pounds overweight
- 81 or more pounds overweight

Total age and weight checks ____

Illnesses and conditions

Check all illnesses or conditions that you have been diagnosed with and currently have.

- Acne
- ADHD (Attention Deficit Hyperactivity Disorder)
- AIDS or HIV
- Alcohol addiction
- Allergic rhinitis (sinus inflammation)
- ALS (Lou Gehrig's disease)
- Anemia
- Anorexia
- Anxiety disorder
- Appetite loss
- Arthritis
- Asthma
- Autism and ASD
- Autism or autism spectrum disorder (ASD)
- Benign prostate hyperplasia (enlargement - BPH)
- Bipolar disorder
- Bronchitis (chronic)
- Bulimia
- Bulging or herniated disc
- Carpal tunnel syndrome

Cancer - Check all that apply. If stage three, for example, check first three

- Cancer - stage 1
- Cancer - stage 1 or 2
- Cancer - stage 1, 2 or 3
- Cancer - stage 1, 2, 3 or 4
- Cardiovascular disease
- Chronic Fatigue Syndrome (CFS)
- Crohn's disease

- Common cold (frequent)
- COPD (chronic obstructive pulmonary disease)
- Crohn's disease
- Dementia
- Dengue fever
- Dental abscess (frequent)
- Depression
- Diabetes (type 1 or type 2)
- Diarrhea (frequent)
- Diverticulitis
- Drug addiction
- Eczema
- Emphysema
- Endometriosis
- Epilepsy
- Fibromyalgia (FM)
- Flu
- Frequent common colds
- Frequent headaches
- Frequent indigestion
- Frequent infection
- Frequent itching
- Frequent rashes
- Frequent sinus infections (sinusitis)
- Glaucoma
- Gout
- Gum disease
- Heart attack
- Heart Disease or heart problems
- Hemorrhoids
- Hepatitis B (chronic)
- High blood pressure (hypertension)
- High cholesterol
- Herpes
- Inflammatory bowel disease
- Irritable bowel syndrome (IBS)
- Kidney disease
- Leukemia
- Liver cirrhosis
- Liver disease
- Lupus
- Lyme disease
- Macular degeneration
- Malaria
- Metabolic syndrome (pre-diabetes)
- Middle ear infection (frequent)
- Migraine headaches
- Multiple chemical sensitivity (MCS)
- Multiple sclerosis

- Obesity
- Osteoarthritis
- Osteoporosis
- Parkinson's disease
- Periodontal disease (swollen or bleeding gums)
- Post-traumatic stress disorder (PTSD)
- Rocky Mountain spotted fever
- Psoriasis
- Rosacea
- Schizophrenia
- Seizures
- Sexually transmitted disease (STD)
- Shingles
- Sjogren's syndrome
- Sleep apnea
- Stroke
- TB (Tuberculosis)
- Thyroid disease
- Tourette syndrome
- Tremors
- Ulcers
- Varicose veins
- West Nile Fever
- Yellow fever
- Zika

Write in the names of any other illnesses you have that were not listed above and check those.

- _____
- _____
- _____

Total Disease Checks ___

Disease Start

- How many of the diseases checked above started in
- The past 2 years?
- The past 5 years?
- The past 10 years?

Symptoms

Check all the symptoms that you currently experience.

- Abdominal pain (frequent)
- Allergic reactions to chemicals
- Allergic reactions to any foods
- Allergic reactions to insects
- Allergic reactions to medications
- Allergic reactions to plants (Hay fever)
- Ankle pain
- Attention span decline
- Anxiety often

- Bleeding gums
- Blood in stool
- Blood in urine
- Blurred or cloudy vision
- Bruise easily
- Burning when urinating
- Butterflies in your stomach often
- Change in skin color
- Chest pain
- Constant chills
- Constipation
- Cough that is persistent
- Coughing or spitting up blood
- Decision making difficulties
- Decline in learning ability
- Decreased eye sight
- Decreased sex drive
- Diarrhea (frequent)
- Difficulty completing familiar tasks
- Difficulty concentrating
- Difficulty getting warm
- Difficulty maintaining balance
- Difficulty solving problems
- Difficulty swallowing
- Difficulty walking
- Difficulty concentrating or finding words
- Dizziness
- Drained of energy
- Dreams that are bizarre and recurring
- Excessive mucous production
- Excessive thirst
- Eye discomfort or pain
- Eye redness
- Fatigue
- Feel depressed a lot
- Feel less alert or fuzzy headed
- Fever
- Food allergies
- Foot pain
- Foot swelling
- Fungal infection such as athlete's food that persists
- Frequent urination
- Graying of hair
- Hair loss (not due to chemotherapy)
- Have itchy scaly skin rashes
- Headaches frequently

- Hear voices inside you
- Hearing loss that comes on suddenly
- Heart palpitations (throbbing)

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- Heartburn
- Hip pain
- Hoarseness
- Increased susceptibility to infections
- Indigestion (frequent)
- Insomnia
- Irregular periods
- Itchy hands
- Itchy skin other than hands
- Jaw pain
- Leg swelling
- Learning new things more difficult
- Light headedness
- Long recovery time from infections
- Losing track of time
- Loss of coordination
- Loss of muscle tone
- Loss of taste
- Lower back pain
- Memory loss
- Mood swings from very high to very low and vice versa
- Mouth sores that don't go away quickly
- Muscle aches that last a long time
- Muscle cramps
- Muscle spasms
- Nasal congestion
- Nausea
- Neck pain
- Nervousness
- Nightmares regularly
- Nose bleeds
- Knee pain
- Numbness or tingling in hands or feet
- Pain in joints
- Heart palpitations
- Pelvic pain
- Perspire (sweat) profusely
- Post nasal drip that lingers
- Post traumatic stress disorder (PTSD)
- Problems finding the words you want
- Rapid hair loss
- Rapid heartbeat
- Scaly skin
- Seizures
- Shortness of breath
- Shoulder pain that lingers
- Sinus pain
- Skin mole growth
- Skin rashes

- Sleep less than 7 hours per night
- Sleep more than 9 hours a night
- Slow to heal from cuts, bruises or other injuries
- Slurred speech
- Smaller field of vision
- Sore throat that doesn't heal
- Stressed out most or all of the time
- Stuffy nose
- Swollen eye lids
- Tics (involuntary movements)
- Tingling in the hands or feet
- Tire easily
- Tired most of the time
- Tooth pain
- Tremors
- Twitching
- Unusual vaginal bleeding or discharge
- Urination difficulty
- Urination pain
- Varicose veins
- Vomiting
- Wake up more than 3 times per night
- Weakness
- Weight gain
- Weight loss (rapid)
- Wheezing
- Wrinkling or loss of tone in skin
- Yawning frequently

Total Symptoms Checks ___

Test Results

The following address results obtained from test doctors ordered done as part of annual examinations. Check all that apply to you.

- High or low blood sugar
- High or low BUN (blood urea nitrogen)
- High or low calcium
- High or low carbon dioxide (bicarbonate)
- High or low chloride
- High cholesterol
- High or low creatinine
- High glucose
- High or low potassium
- High PSA
- High or low sodium
- High triglycerides
- Low blood oxygen
- Low potassium

Total Test Results Checks ___

Prescription medicines regularly taken

Check each of the boxes that apply. If you regularly take five prescription drugs, for example, check all of the first 5 items, so that the total number of items checked equals the total number of prescriptions regularly taken.

- 1 prescription
- 2 prescriptions
- 3 prescriptions
- 4 prescriptions
- 5 prescriptions
- 6 prescriptions
- 7 prescriptions
- 8 prescriptions
- 9 prescriptions
- 10 or more prescriptions
- Have a heart pacemaker

Total Prescription Medicine Checks ___

Diet

Check each item that applies to the foods that are part of your regular eat.

- Alcoholic beverages (beer, wine, spirits) more than 1 drink per day
- Artificial sweeteners for coffee or tea
- Canned or frozen cooked foods regularly eaten (soups, pastas, meats)
- Bread and pasta made primarily from white processed flour
- Fast food frequently eaten
- Fewer than 3 fruits or vegetables a day
- Grilled, smoked or blackened meat, chicken or fish
- Food high in fat (whole milk, cheeses, foods cooked with butter and animal fat)
- Often eat processed foods (bacon, hot dogs, salami, sausages. deli meats
- Eat red meat more than 2 times a week
- Eat foods high in sugar (sweetened drinks and desserts)
- Salty food

Total Diet Checks ___

Life Style

These items refer to where you live, the type of work you do and chemicals you may be exposed to.

- Are a farmer that regularly uses pesticides
- Burn wood for heat or for cooking
- Constantly use a cell phone
- Drink chlorinated water
- Drink more than one alcoholic drink per day
- Exercise less than one half hour a week
- Have mold in your home
- Have new (less than 6 months old) carpet in your home
- Have pets in your home that you are allergic to
- Live down wind from a smoking industrial chimney
- Live in a city with air quality alerts
- Live or work close to a cell tower
- Live or work near high voltage electrical transmission lines

- Live near a heavily traveled highway or road
- Live near a landfill
- Live with a smoker
- Regularly experience allergic reactions in your home
- Regularly experience allergic reactions in your work place
- Regularly use room or furniture deodorants
- Regularly play contact sports
- Regularly sleep with lights or television on
- Regularly have outdoor lights shining into your bedroom while sleeping

Tobacco use. Check all of the items that apply. For example, if you smoke one pack of cigarettes a day, check both of the first 2 items. If you smoke two packs a day, check all of the first 4 items.

- Smoke 10 cigarettes or less daily (even just one)
- Smoke a pack a day (20 cigarettes)
- Smoke a pack and a half a day (30 cigarettes)
- Smoke two packs a day (40 cigarettes)
- Smoke more than two packs a day
- Smoke 1-5 cigars a day
- Smoke 6 or more cigars a day
- Use smokeless tobacco
- Work as a toll booth collector
- Work in very hot or very cold conditions regularly
- Work in an adhesives or coatings manufacturing plant
- Work in an agricultural chemical manufacturing plant
- Work as an automobile, diesel or aircraft mechanic
- Work with chemicals on the job regularly
- Work in a dusty environment regularly
- Work in a landfill
- Work in a hair or nail salon
- Work in metal refinery or mill
- Work as a miner
- Work in a noisy environment
- Work in a paint, lacquer, stain or varnish manufacturing plant
- Work as a painter
- Work as a pilot or flight attendant
- Work as a pesticide applicator
- Work in a petroleum refinery
- Work in a plastics manufacturing plant
- Work in a plywood or particle board manufacturing plant
- Work in a polluted environment (road paver, toll booth operator, for example)
- Work in a water or sewage treatment plant
- Work in wood treatment plant

Total Lifestyle Checks____

OSI, Total of All Checks____

Disease prediction

Elevated oxidative stress is well known to be a direct cause of non-communicable environmental diseases in all body systems as well as an indirect cause of infectious disease via undermining of the immune system [5] Total OS is increased in a dose response relationship no matter what the cause [1,6-9] and total OS can come from any one or multiples of the following parameters:

- **Genetics:** Many diseases are heritable. These include those carried by DNA, as well as epigenetic ones transmitted through the generations that are not carried by DNA.

- **Age:** OS increases naturally with age.

- **Weight:** Being overweight or obese is an OS elevating factor.

- **Current Illnesses:** All illnesses elevate OS.

- **Psychological stress:** Chronic emotional stress, anxiety and depression, continually elevate OS.

- **Current Symptoms:** All symptoms of environmental exposure, disease, inflammation due to injury and stress elevate OS.

- **Clinical test data:** All clinically determined parameter out of the "normal" range increase OS.

- **Medication taken:** All prescription and over-the-counter medications regularly taken chronically increase OS.

- **Diet:** High regular intake levels of sugar, salt, processed foods, saturated fats and chemical food additives increase OS.

- **Lifestyle:** Environmental exposures to chemicals and radiation at home and at work, regular alcohol, tobacco or recreational drug use chronically elevate OS.

Serum malondialdehyde, the biomarker most often used to measure OS, though a valuable indicator of OS which is stable in serum and easily analyzed for, can vary widely depending upon what a person ate, pollutants he or she may have been exposed to prior to serum being drawn, medications being use, state of emotional status and other OS elevating parameters. Serum MDA levels have been found to vary by as much as 19 percent over a six day period [6].

Determining steady state OS levels is valuable for both the patient and the clinician so that, if elevated, can be used to dictate disease prevention and treatment actions that can be taken to maintain health. The OSI offers the opportunity to accomplish this by producing a steady state profile of a person's OS status. The person, or surrogate, simply checks the items on a questionnaire that apply to her or him and the total number of checks equals the OSI. The following scale has been proposed as indicative of the likelihood of new disease onset:

OSI Level: Disease Likelihood

0-15: Low

16-30: Moderate

31-45: Probable

46 or higher: Likely

The OSI questionnaire is shown in table 1.

Though the OSI can predict the likelihood of disease onset, it cannot predict which disease will strike, as all disease is associated with elevated OS.

The items in the OSI questionnaire are listed alphabetically, rather than by connections to specific parameters, in the different sections so that the responder is challenged to consider each item alone, rather than as part of a series, to which he/she would just check all or eliminate all from consideration.

Identifying specific causes of individual diseases

Though the OSI cannot predict the onset of any specific disease, it can be used to identify those parameters more likely to cause an individual disease. Administered immediately after the onset of that disease, the OSI can identify which parameters are the primary contributors after a statistically significant number of individuals have been surveyed. This approach has been addressed for Alzheimer's disease (AD) [2] and hypothesized for other diseases.

Alzheimer's Disease

The following parameters have been associated with AD onset [5]. These are:

- Air pollution
- Pesticides
- Heavy metals
- Radiation
- Smoking
- Traumatic brain injury
- Chronic inflammation
- Infectious viral, fungal, bacterial and parasitic diseases
- Co-morbidity with other non-communicative diseases
- Diet
- Chronic Psychological stress
- Obesity
- Aging
- Genetics and epigenetics

All the parameters just listed raise OS. Clearly few individuals are subjected to all and numerous combinations of these are possible. Carrying out OSI surveys on statistically significant numbers of people upon first diagnosis of AD, however, has been projected to reveal which of these parameters are the most significant causative agents of AD [2].

Other diseases

The type of analysis just described for AD also lends itself to using the OSI to identify the primary causes of other diseases with multiple causes. These diseases include but are not limited to the following.

- Asthma
- Attention deficit hyperactivity disorder
- Autism
- Cardiovascular diseases
- Parkinson's disease and other neurodegenerative diseases
- Primary cancers
- Type 2 diabetes

Public health surveys

It is well known that chronic exposures to chemical pollutants are a cause of numerous environmental diseases. For example, living proximate to heavily traveled highways results in a greater likelihood of asthma onset and that the likelihood declines in a linear fashion with residence distance from such highways, where airborne concentrations of vehicle exhausts similarly decline linearly [11]. Accordin-

gly, the closer one resides to a heavily traveled highway, the greater the exposure to exhaust pollutants and the greater the oxidative stress impact on one's body. Thus, using the OSI, it becomes possible to numerically assign probabilities of disease onset related to such exposure as functions of distances from emission sources. Adding distancing questions to the OSI and surveying statistically significant numbers of individuals at increasing distances from pollutant emission sources up to where these emission provide zero impact, i.e., where levels of the pollutant equal ambient background levels, enables one to assess the pollution (and hence the oxidative stress) as a function of distance from the emission. This enables the establishment of safe residential distances from the particular emission sources [3]. Table 2 shows the OSI questionnaire addition that has been added for this purpose.

Table 2: *Additional questions to be addressed when completing the OSI questionnaire as part of a public health survey.*

Distance from home to nearest pollution emission source - petroleum of chemical storage tank, landfill or other chemical or radiation emitting source. Check only one.
• 0.1 mile or less
• 0.2 mile
• 0.3 mile
• 0.4 mile
• 0.5 mile
• 0.6 mile
• 0.7 mile
• 0.8 mile
• 0.9 mile
• 1.0 mile
• 1.0-1.5 miles
• 1.6-2.0 miles
• 2.0-2.5 miles
• 2.5-3.0 miles
• 3.0 miles or more
Years at current residence (enter number of years)

Health pre-screening

Patients can be given the OSI questionnaire prior to or at the time of routine health examinations. When indicated, clinicians can plot courses of action for disease prevention prior to the onset of symptoms.

Recently, the question of whether routine checkups for healthy people are necessary or a waste of time [10]. The OSI offers the opportunity to pre-screen such individuals to determine if their OS levels have increased and which parameters are contributory to the increases and need to be addressed.

Limited Medical Care Area Screening

The OSI lends itself to providing insight into incipient disease onset in areas where medical care and diagnostic capabilities are limited. Determining the OSI is not an invasive procedure that requires medically trained personnel. Accordingly, it can be administered in areas where medical care and diagnostic capabilities are limited and results communicated to clinicians for treatment recommendations where indicated.

Longitudinal studies of disease patterns and causes

Longitudinal studies based upon the OSI are projected to be valuable aids in the study of disease onset causes and patterns in several ways:

1. Once base line OSI values are established for an individual, the time to onset of new diseases can be monitored to reveal statistical patterns between OSI levels and disease onset times following first OSI determinations.

2. By measuring OSI values annually, relationships between changing OSI values and onset times for sequential disease manifestations can be studied.

3. Almost all late-onset diseases are co-morbid with each other [12]. Longitudinal studies can reveal if there are associations between OSI values and the onset of specific single diseases and co-morbidities, thus suggesting mechanistic relationships of the causes of different diseases.

4. Longitudinal studies can simultaneously shed light on which elements of the OSI are associated with multiple diseases so that multiple diseases can be studied at the same time.

5. A recently published study of dementia incidence associated with lifestyle and genetic risk in more than 196,000 people who developed dementia serves to demonstrate the value of identifying the role of lifestyle in Alzheimer's disease onset [13]. Though this study included only four lifestyle parameters; smoking, diet, alcohol consumption and physical inactivity (all of which raise OS) as dementia causative agents and considered only the cumulative effects of these, it serves to demonstrate the effect of oxidative stress elevation as a cause of all dementias including AD, which accounts for about three quarters of all dementias. The results reported also demonstrates the value of the OSI, which can assess the AD-causing parameters individually as well as cumulatively.

Limitations

There are three limitations to the use of the OSI to study disease. Firstly, the reliance of the data on patient or surrogate completion of the questionnaires, with its inherent error potential. This, however, is overcome by including statistically significant numbers of subjects in the studies.

Secondly, large numbers of subjects are required in order for statistically valid results to be obtained. Questionnaires, however, are routinely used to obtain valid medical information [14,15]. Given the large potential pool of participants, however, this limitation should not be a barrier to obtaining valid results.

Thirdly, though each of the items in the OSI is given equal weight, all are clearly not equal in health impact. The presence of Parkinson's disease, for example, clearly has greater impact than being 20 pounds overweight. That said, however, this effect is compensated for by the general increase in the number of symptoms and the number of medications taken, all of which increase with the severity of prevalent disease.

Conclusions

Multiple applications of the OSI include health pre-screening, disease onset prediction, identification of the causes of specific diseases, surveying public health impacts and providing insights into the mechanisms of disease onset.

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