

Hydrogen Peroxide Test Strip Use for Predicting Dysregulated Cell Death and Mitochondrial Mutation in Human Organ Systems

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Abstract

A review of the literature indicates that many research projects have confirmed that oxidative stress (OS) not only correlates with dysregulated cell death but may cause disease (0,1,2,4).

While many individuals that undergo oxidative stress may escape the dysregulated cellular damage or tissue death which leads to a disorder, it seems to be determined quite often by the activity of HIF (Hypoxia Inducible Factor). HIF can have not only an anti-inflammatory but also pro-inflammatory effect on cells (3). Mitochondria of the cells which can be affected include cells in the brain which can affect the Hypothalamus-Pituitary-Adrenal Axis (5,6). The oxidative stress created by mitochondrial dysfunction can affect gene expression, development of the immature brain and a deficit in human growth hormone and ghrelin, the hunger hormone(6). The brain inflammation and gastrointestinal inflammation that follows can linger for years causing the various symptoms of Autism, other childhood diseases and later for adults as they age, e.g. Dementia, Alzheimer's Disease, Cancer, Cardio-respiratory disease and other diseases (7,8,9,10). Oxidative stress causes are numerous, but prevention of chronic disease by safeguarding against dysregulated cell death is being investigated, internationally. Prospective parents and mature adults should become familiar with OS causes and make their best effort to reduce the risk of OS during pregnancy for the mother, in the child post birth, and adults as they age.

Testing for OS during illness or testing routinely is a reasonable screen to perform. Hydrogen Peroxide is a ROS (reactive oxygen species) (11) that may be especially easy and inexpensive to test for in the home. When Hydrogen Peroxide levels are abnormally elevated a physician needs to get involved immediately.

Introduction

The amount of research that is being done across the world into disease prevention and treatment is staggering. The brilliant minds available to study in-vitro and in-vivo response to insulting (injury or organisms) in humans and in animals continues unabated. The cost to society is overwhelming not only in dollars, but also in pain and suffering for the patient. Research into repurposing existing drugs and developing new drugs to help with symptom treatment seems to be of paramount importance. The overwhelming evidence available in many of these studies is in regard to how we acquire and reproduce energy in the form of Adenosine Triphosphate, also known as ATP. Our nutrition and activities have a great deal to do with acquiring ATP which is why experts recommend appropriate exercise and nutritional programs to assist in prevention of disease (12). When humans eat and work as experts tell us we should it's not a problem having enough energy to perform activity for up to 15 seconds before oxygen which we breathe and fat which we store begins to replenish the ATP. We do this constantly and the good news is we usually don't even have to think about it. When we play sports or occasionally get forced into longer term, vigorous activity, then we're going to rely on stored levels of carbohydrate because we will need it when our respiratory system won't allow us to breathe fast enough to reproduce the ATP we need. In review we eat and store small amounts of ATP, breathe and use fat to

replenish ATP and break down sugars and starches to replenish ATP when we cannot breathe fast enough during intense activity. Most humans have heard of the term antioxidants, and we get those from eating food as well (12). They are necessary to link up with any extra oxygen that is released during reproduction of ATP. Normally the whole process takes place efficiently, but there are OS triggers that can cause it to malfunction. The discussion section will briefly describe what can happen in our cells when we are exposed to these triggers which include poor nutrition and sedentary lifestyles.

Discussion

OS (oxidative stress) is part of life when it is caused by your body's reaction to inflammation-causing etiologies, many of which are the subjects of research. Inflammation is necessary and life sustaining when it progresses normally, but when ATP is not produced in the cell normally, inflammation can continue longer than it should, eventually causing dysregulated cell death. Mitochondrial function produces energy in the cell and should respond with a transition from stages which researchers call M1 to M0 followed by the M2 stage as healing occurs (13). In some research, these stages are also delineated by the following notations, M1, M0 and M2 human monocyte derived macrophages (hMDMs) during immune response. (14). M1 stage is pro-inflammation. M0 is proliferation (cell reproduction). M2 is anti-inflammation. Inside the cell M1 and M0 stage mitochondria can begin to produce an overabundance of adenosine triphosphate (ATP) energy preventing transition to M2, the anti-inflammatory stage. Instead of progressing from M0 to M2 the mitochondria in the cells revert to M1, so a cycle of pro-

inflammation is continued and inflammation can therefore become subacute or even chronic (13).

When this happens, reactive nitrogen species, (products), and reactive oxygen species can cause cell death to surrounding cells and even change gene expression and DNA (11,13,14,19,29).

Research is ongoing to identify substances which can end chronic inflammation and OS (15,16).

When hydrogen peroxide (H_2O_2) levels in human saliva, breath, plasma or urine are significantly higher than normal it is a biomarker of oxidative stress (17,18). Researchers have determined that normal concentration levels of hydrogen peroxide in human fluids are 1-6 micro moles/liter ($\mu\text{mol/L}$) (17,18). “The composition of saliva reflects dynamic changes in the organism, which makes it an excellent tool for determining clinically valuable biomarkers” (20). The operative hypothesis is that “neutrophil driven inflammation increases plasma exudation into the gingival sulcus and thus raises local fluid levels” (21) including the ROS hydrogen peroxide. “This intricate ecosystem (oral) plays a crucial role in both oral and systemic health” (22). Since the range of problematic H_2O_2 levels begins as low as 20-50 $\mu\text{mol/L}$ and the test strips used will measure between 1.47-117.6 $\mu\text{mol/L}$ it is reasonable to use the above hypothesis as a trial to predict abnormal levels of OS to determine dysregulated cell death.

Materials and Methods

12 subjects participated in this study, 7 males and 5 females. The age range was males, 75 y/o, 71y/o, 69 y/o, 39 y/o, 38 y/o, 5 y/o, 2 y/o and females 68 y/o, 39 y/o 32 y/o, 7 y/o, 3 y/o. All subjects were tested during illness with .05-4 ppm test strips from Industrial Test Systems (24). Converted this equals 1.47-117.6 $\mu\text{mol/L}$. The illness symptoms varied but all subjects except

one had malaise and body aches. Five of the subjects also had moderate fever from 102 to 103 degrees F. Two of the subjects were also tested after vigorous levels of exercise for 45 minutes but were negative for measurable H₂O₂ levels post exercise. Two subjects tested positive during illness and were tested repeatedly each time they were positive until H₂O₂ levels were not repeatedly measurable.

Results During Study

The study was conducted on 12 subjects who were tested when having various symptoms of illness. One of the subjects tested positive after reporting fatigue, body aches and distended stomach. After 12 hours of symptoms the sick individual provided 5 milliliters of saliva in a clean glass container, and the solution was immediately tested using a (.5 parts per million to 100 parts per million) test strip manufactured by Industrial Test Systems (ITS) (24). The test strip immediately changed color and was measured by the color metric chart at one part per million. When converted this equals 29.4 micro moles of hydrogen peroxide (almost 5 times normal). The subject had never tested positive for salivary hydrogen peroxide even with the use of the lowest range strips which begin at .05 parts per million (ITS). One of these lower range strips was immediately used to confirm the first test strip at a measure of one part per million. A second subject tested positive using the .05 level test strips after having symptoms of upper respiratory infection, including nasal drainage, body aches and malaise. These lowest level range peroxide strips were also used during the pilot study on two of the subjects, including both positive test subjects weeks prior to their illness. During 45 minutes of vigorous exercise the test strips failed to register any elevated hydrogen peroxide on either subject, indicating no OS. The other 10

subjects showed no change in salivary H₂O₂ during illness and were not tested post exercise. The first positive test subject continued to be positive for 48 hours and is now treated by a Pulmonologist for breathing difficulties, indicating that his ongoing respiratory illness correlated with a continuous (48 hour) bout of elevated H₂O₂ due to oxidative stress. This positive test subject had a second positive test 6 months after the first positive test. The second test was precipitated by similar symptoms of illness. A 3rd positive test was recorded six months after the 2nd test. This time the subject was tested due to upper respiratory symptoms of infection. This 3rd test was measured at approximately 50% less than the first two tests at 15 umol/L of H₂O₂. The 2nd positive test subject tested positive once at 15 umol/L of hydrogen peroxide 8 hours after the initial onset of symptoms. The patient then took a 7.5 milligram of Meloxicam tablet after testing positive. Meloxicam is a cyclooxygenase 2 inhibitor which is used to decrease inflammation. This patient was again tested at 2 hours, 10 hours and 18 hours after taking medication and was negative for each of those tests. In total the results of both positive tests subjects indicate that a positive test for H₂O₂ using low range test strips may be a rare and important symptom since only 2 of 12 subjects tested were positive during 18 months of testing, up to this date. The demonstration of this change in salivary hydrogen peroxide on these positive test subjects dictates that testing is continued, expanded and researched on others. Many researchers are hypothesizing and testing the repurposing of existing drugs to treat various metabolic diseases. (15,16,28,32,33). However, prevention of elevated, subacute or chronic levels of reported biomarkers like Hydrogen Peroxide or Nitric Oxide caused by the triggers of OS may be the ultimate answer to lowering the numbers of neurological diseases like Autism, Dementia or other systemic diseases.

Summary

When triggers of oxidative stress occur in the different systems of the body, three things may happen. Cell death induced by one of the scientifically described methods destroys affected cells and the cell destruction is localized to damaged cells (13,14). The second option is that anti-apoptosis, for example, can occur which encourages tumor growth and can fuel cancers (26). Therefore, halting the inflammatory process early is problematic. Finally, pro-apoptosis if unregulated produces a ROS as a bio marker, called hydrogen peroxide at abnormal levels (13,14,25). These processes are greatly regulated by hypoxia inducible factor (HIF) which is triggered during abnormal oxygen levels to the cells and can have either pro or anti-inflammatory effects regarding cellular death (3). Hydrogen peroxide, at abnormal levels is a sign that cells outside of the damaged localized cells are being affected and experiencing cell death and tissue death, as well (13,14). FAS receptors and caspases promote apoptosis (26,28). Members of the BCL-2 family inhibit apoptosis (26,28). Dysregulation of cell death can cause a chronic disease within hours of onset (28). Anti-apoptosis (failure to kill damaged cells) can cause cancer (26,28). Pro-apoptosis (continued cell death) can cause systemic diseases “e.g.”, neurological, cardio-respiratory, cancer and infectious diseases (19,23,26,28). Oxidative stress and inflammation taking place at normal levels is life sustaining, however, if it continues at abnormal levels, it can cause dysregulated cellular death and the body’s response can be changes in cellular replication (29). It is likely that inexpensive tests and medications already exist and can be used to help regulate cell death. Development of an in-home, inexpensive way to determine oxidative stress levels is not dissimilar from the development of the devices that measure human body temperature and correlate to a disease process (27). Measuring body

temperature did not become routine until the work of Carl Reinhold Wunderlich on over 25,000 cases was published in 1868 and titled: **Temperature in Diseases** bringing about the consensus that “a physician who carried on his profession without the thermometer was like a blind man endeavoring to distinguish colors by feeling”. Wunderlich’s observation that “A normal temperature does not necessarily indicate health, but all those whose temperature either exceeds or falls short of the normal range are unhealthy”, along with most of his other tenets are part of medicine today (27). Modern physicians and patients need a timely and accessible measure of oxidative stress so that after measurable onset of oxidative stress occurs it will not lead to dysregulated gene transcription precipitating a chronic disorder. This will support the time-honored logic that prevention is the best cure.

Conclusion

Normally, individuals will experience the trillions of mitochondrial deaths and replications that take place each day without any knowledge of that process. When mitochondria and cells are destroyed and rebuilt in some cells during processes with names like mitophagy, autophagy and apoptosis, it can take place flawlessly. However, when these processes fail us and become dysregulated as epidemiology would tell us will happen, sooner or later, you perhaps have the option to recognize this by an in-home, inexpensive screening process. Hydrogen peroxide test strips are very basic but can act like the proverbial Canary in the coal mine to warn us that action is immediately necessary. These strips can be even more precise if paired with a simple iPhone app or website called Photopea, which will be able to give you more specific information on the amount of this reactive oxygen species. The information correlates well with a research tool

by scientists and developed by National Institute of Health, it is called Image J (30).

Measurement of this reactive oxygen species early in symptoms of illness is necessary as Yasuhiro Ishihara and Norio Shimamoto discuss in their research “Therefore, a time point 9 h (hours) after exposure to oxidative stress is a point-of-no-return from apoptosis under these experimental conditions...” (31).

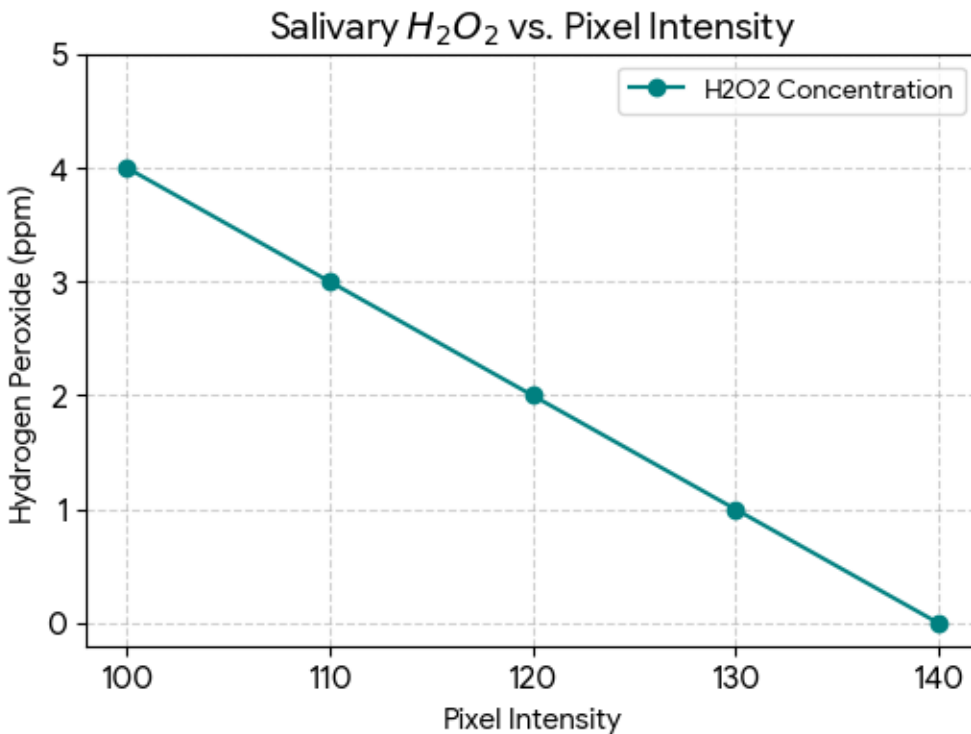
Declarations

Clinical trial number not applicable.

Human ethics and consent to participate declarations:

The study was conducted independently in the author’s personal laboratory without institutional affiliation or formal Ethics Committee review. All participants were fully informed about the aims and procedures and provided written informed consent prior to participation. Informed consent was obtained from all individual participants included in the study. Participants under age 18 consultants obtained from parent or legal guardian. All procedures were non-invasive, and participants voluntarily provided informed consent prior to sample collection. No identifying information was recorded, and all data were anonymized to protect participant privacy. The study adhered to the principles outlined in the Declaration of Helsinki and was conducted with a commitment to minimizing risk and ensuring ethical integrity. The researcher was certified by ACRP testing certification. The study involved minimal risk and did not require institutional review under local or federal guidelines. **Funding:** The author received no financial support for the research, authorship, or publication of this article.

Appendix



Equation: $(-.1X + 14) = Y$ allows you to find the PPM concentration for any photo evaluated for mean pixel intensity with a greater degree of accuracy in the 0 to 4 PPM range.

140+ is likely not abnormal

130+ requires immediate attention

120+ is 5 to 10 times normal

110+ is a likely dangerous infection/inflammation

100+ is a serious emergency and could cause long term disorders

This graph is the result of hundreds of test strip evaluations and refinement of the protocol in processing images of the test strips so they may enhance the specificity of the quantity of hydrogen peroxide being generated in the oral cavity during illness. While any color change in a test strip can be compared to the colormetric chart in the test strip packaging and calls for immediate communication with a physician, use of a cell phone may quantify the information for your physician to a greater extent.

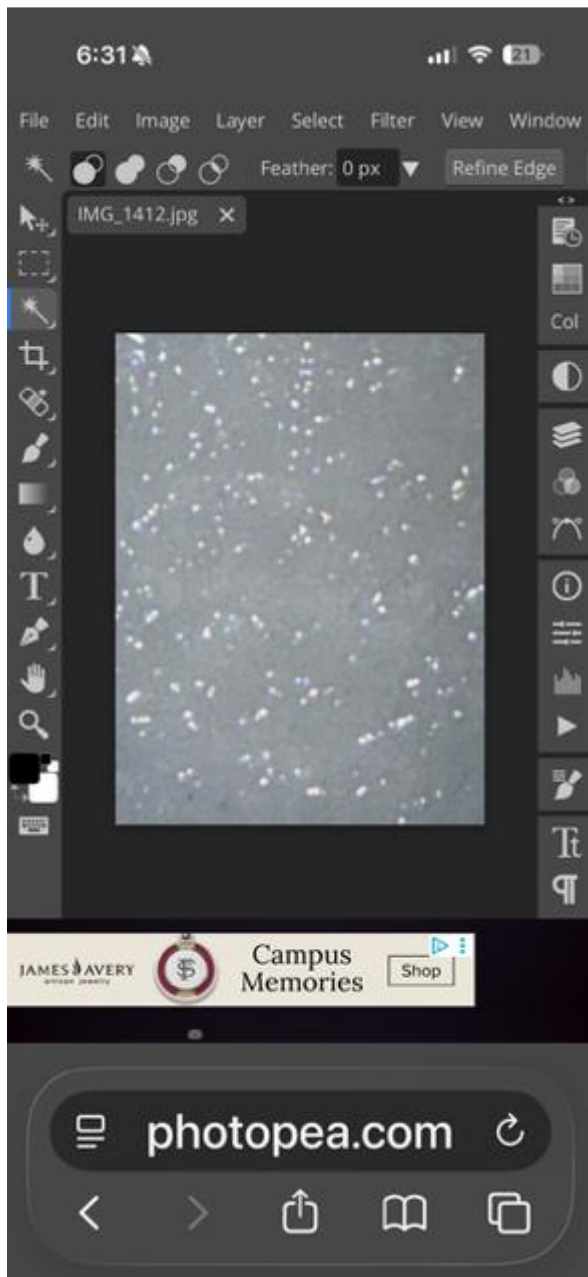
Protocol

1. Remove the .5 to 100 PPM test strip from its aluminum foil package and deposit saliva directly into a clean teaspoon. Immediately dip the test strip into the saliva and saturate it without touching the pad to the teaspoon.
2. Remove the test strip from the saliva and gently move it back-and-forth so that excess saliva is removed from the test pad. Place the test strip face up on a white surface, usually typing paper, and allowing it to sit for up to four minutes.
- 3 At the four-minute mark after strip saturation, begin to prepare your camera. Expand the screen to 10 X magnification and turn the flash on.
4. It's best to use a 6 cm block that will help stabilize your iPhone while you center the test strip so that the image will be filled with the test strip pad in this manner e.g.

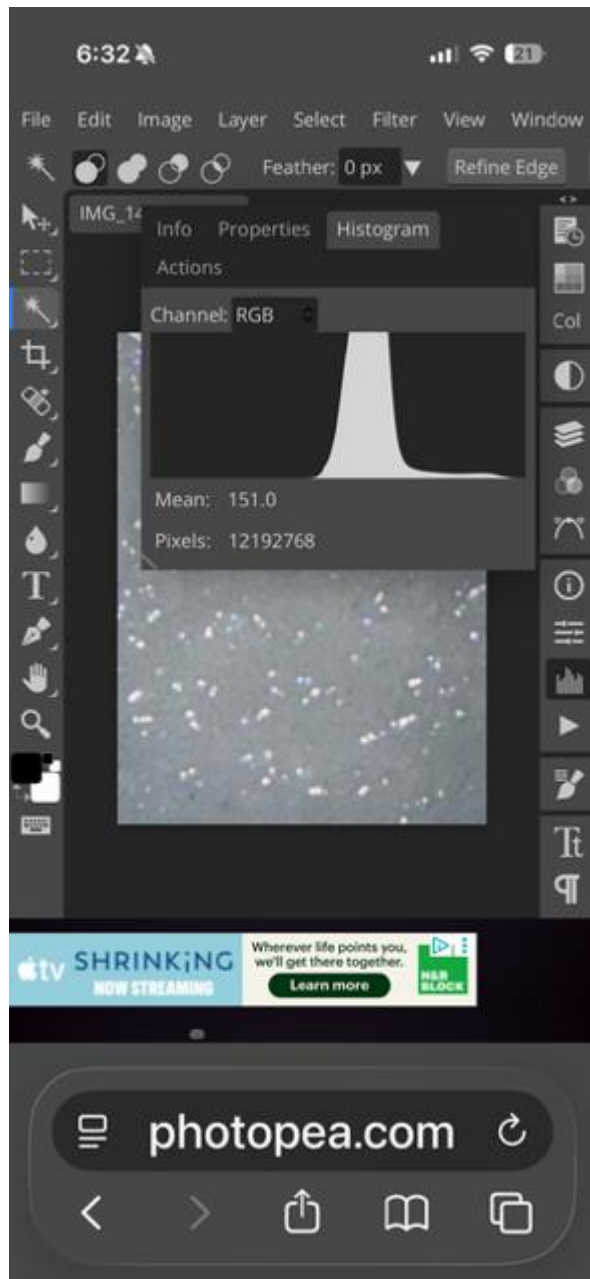


5. At the five-minute mark after saturation make sure all other lighting is at a very low level and take the picture of the image using the flash so that lighting is consistent. Relax!
6. Open The Photopea website and click on the prompt that says Open From Computer. The next prompt will be Photo Library, click on that. Click on the image you want to evaluate from the Photo Library and select for evaluation by clicking on the checkmark in the upper right corner of your screen.

7. Once the image appears on your screen, make sure there is no other demarcation on the image.



8. Go to the upper right-hand corner of the screen where it says Window. Click on Window then click on Color. Then click back on Window. Finally click on Histogram and this is the type of image you should see.



9. Note the two measurements in the image designated as Mean and Pixels. Pixels should always remain at 12192768 This ensures that the area was the same In any image evaluated. The Mean is what you will compare to the chart on the graph provided earlier.

10. This is obviously a histogram that shows no change in color and therefore it isn't measurable. The pixel intensity was 151.

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