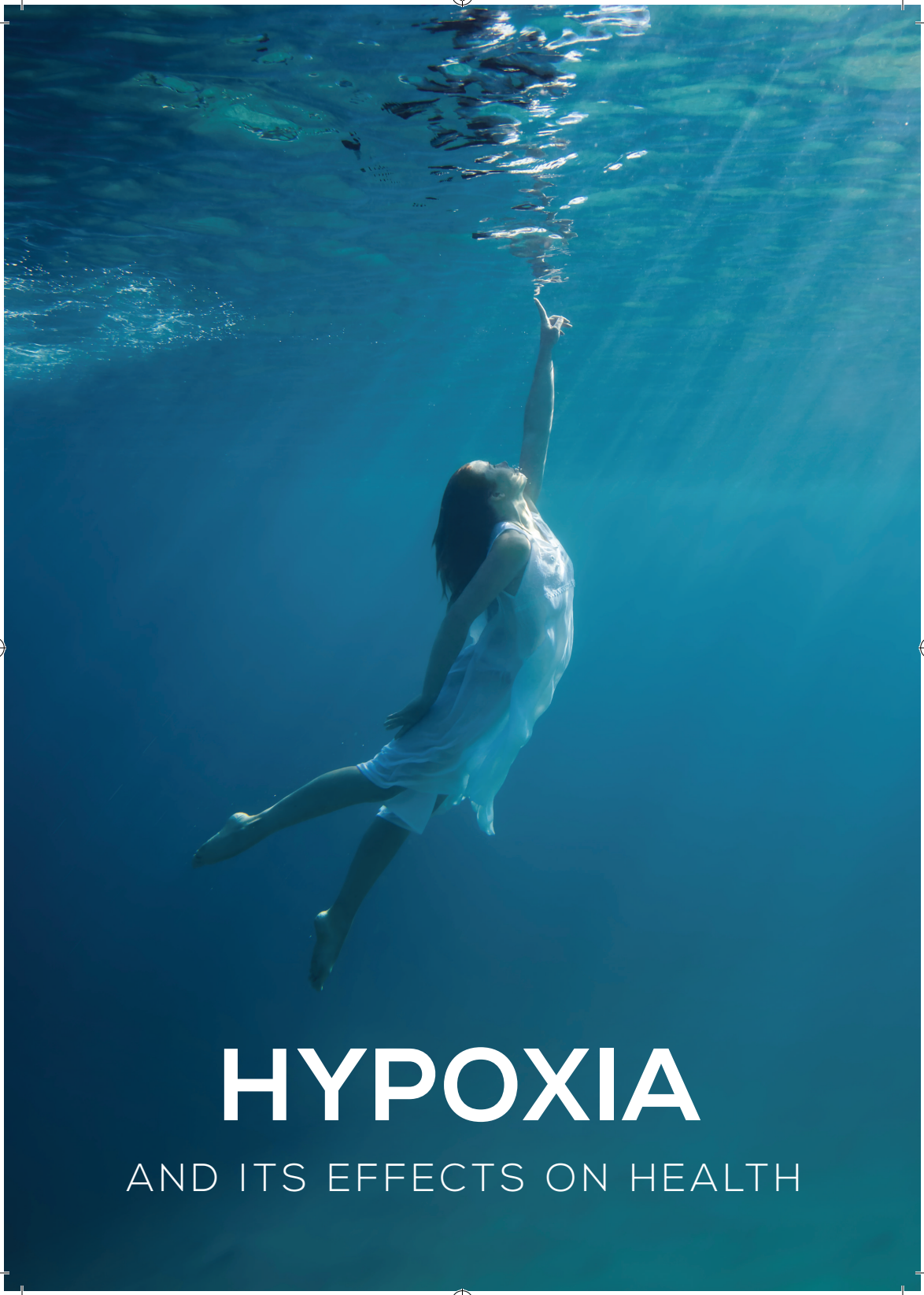


HYPOXIA

AND ITS EFFECTS ON HEALTH

CONTENTS

WHY IS OXYGEN IMPORTANT?

Oxygen is important to every cell in your body. Without it, your cells cannot make much energy and their metabolism is less effective.

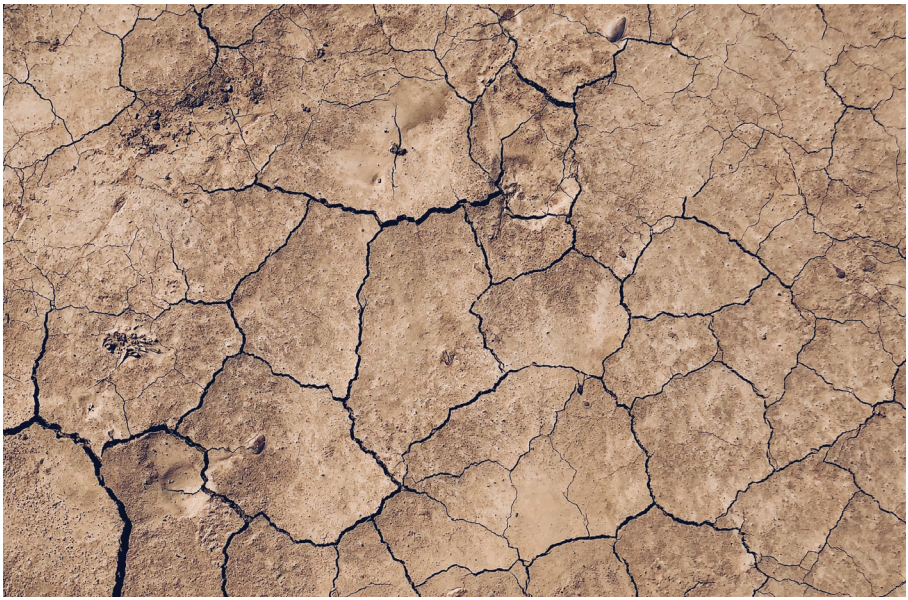
Oxygen and Energy

Within every cell there are thousands of little power-plants called mitochondria[a]. These are 'power plants' that generate energy in the form of ATP[b]. In order to fire up the power-plants to make the energy molecule ATP, in a process called oxidative phosphorylation (OXPHOS)[c], you will need a generous supply of oxygen to the cells[1].

Performance and Recovery

When you do not have enough oxygen, you switch from a highly efficient energy-making machine (OXPHOS) to being 16 times less efficient by using a non-oxygen energy process called anaerobic glycolysis[d] and in doing so, you generate a lot of lactic acid, the substance that makes your muscles feel sore and tired[2].

Athletes and sports enthusiasts are familiar with these processes that determine how well you perform and how well you recover from exercise. The more ATP you can create, the more energy your muscles get to use for exercise, translating into greater speed and strength of muscle contraction and longer endurance[3]. With more oxygen, you generate 16 times more energy using a process (OXPHOS) that does not produce lactic acid[1]. In other words, you create more energy to power your exercise and you will end up with better post recovery with less muscle soreness.



Cell Degeneration

Without sufficient oxygen, our cells have much less energy and perform their functions less efficiently[4]. This can be a problem because energy is needed to keep the cells healthy and optimally functioning. When cells are not functioning well, this is when the organs start to malfunction and brings on the start of diseases. Cells that are starved of oxygen can also start to break down and die prematurely, bringing on degeneration[5]. Degeneration of cells drives the ageing process in your body and leads to degenerative diseases such as dementia, retinal degeneration[4,6]. When a person ages, degenerative processes cause reduction in lung capacity, hardening and blockage of the arteries, resulting in a less effective delivery system to bring oxygen to the body cells[6]. This creates a vicious cycle of ageing and degeneration.

In conclusion, oxygen is an important universal nutrient that determines efficiency of energy supply to the living cells for powering energy intensive cell activities and maintaining overall wellbeing of cells.

Definitions:

[a]Mitochondria – these are tiny components inside a living cell responsible for generating energy using oxygen. They are like power generators for the living cell, making sure that the cell has a constant energy supply in order to stay alive and carry out its normal functions.

[b]ATP – Adenosine triphosphate, an energy-carrying molecule found in the cells of all living things. ATP captures chemical energy obtained from the breakdown of food molecules and releases it to fuel all cellular processes needed for life. It is the source of energy that keeps everything going.

[c]OXPHOS – Oxidative Phosphorylation is process whereby a cell uses oxygen to generate large amounts of energy in the form of ATP. This process, which takes place in mitochondria, is the major source of ATP in aerobic organisms.

[d]Anaerobic glycolysis – Anaerobic glycolysis is a method used by cells to produce ATP by transforming glucose into lactate when limited amounts of oxygen (O_2) are available. Compared to OXPHOS, anaerobic glycolysis creates 16 times less energy.

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WHAT IS HYPOXIA?

Hypoxia is a medical term used to describe a condition where bodily tissues are not receiving enough oxygen. In other words, hypoxia literally means low oxygen levels in your body.

Causes of Hypoxia

Hypoxia can be present in anyone because of a variety of reasons, and it is associated with many different medical conditions. It can be caused by decreased breathable oxygen in the air (like when you are travelling in an airplane or on a high mountain), decreased ability for the blood to carry oxygen to the organ tissues (such as in anemia, thalassemia[a], severe blood loss, or blocked arteries or capillaries), decreased ability of tissues to absorb oxygen (like lung disease) or decreased ability of cells to utilize oxygen (such as carbon monoxide[b] poisoning or abnormal mitochondria[c] function).

When a person becomes older, reduction in lung capacity, hardening and blockage of their arteries and small vessels may compromise the ability to fully oxygenate the body tissues. Environmental pollution, smoking and suboptimal breathing patterns can all contribute to poorer oxygen levels in the body.

Isolated Hypoxia

Often, hypoxia can exist in isolated organs or areas in the body affected by poor blood supply or abnormal behavior of the cells that have difficulty using oxygen. Many common diseases are associated with isolated hypoxia in affected organs. While generalized hypoxia can be measured by special oxygen measurement devices in the hospital, isolated hypoxia inside organs or within deep tissue can only be measured invasively and is therefore not commonly performed.

Definitions:

[a]Thalassemia – A hereditary, genetic blood disorder common in people of Mediterranean and Southeast Asian descent, where the oxygen-carrying red pigment inside red blood cells (hemoglobin) is structured abnormally and therefore unable to effectively carry oxygen.

[b]Carbon monoxide – A gas present in car exhaust fumes and cigarette smoke. This gas binds to red blood cells and prevents the red cells from carrying oxygen.

[c]Mitochondria – These are tiny components inside a living cell responsible for generating energy using oxygen. They are like power generators for the living cell, making sure that the cell has a constant energy supply in order to stay alive and carry out its normal functions.

THE CONNECTION BETWEEN HYPOXIA AND DIABETES

The lack of oxygen, or hypoxia, would appear very far removed from any connections with diabetes mellitus – a condition of abnormal glucose metabolism.

Indeed, in recent years, medical scientists are beginning to find out that hypoxia is closely associated with disease processes in diabetes, and is not only the result of abnormal blood circulation present in diabetes, but is also responsible for driving progression of some diabetic complications[1].

Fat Cell Hypoxia

Fat cell hypoxia is clearly a factor that contributes to the development of insulin resistance and eventually, diabetes. The role that hypoxia plays in the causation of a diabetic state was made clearer through the work of researchers at the University of California, San Diego School of Medicine. They discovered that eating fatty foods causes activation of a protein inside the fat cell membrane, called adenine nucleotide translocase 2 (ANT2), which consumes huge amounts of oxygen, leaving very little for the rest of the cell[2].

When a cell is oxygen starved (hypoxic), it becomes 'stressed' and will release nasty substances called 'chemokines'[a] that turn on the immune system's inflammatory response[a]. When this happens, the resulting low-grade tissue inflammation will impair the way cells interact with insulin, which leads to insulin resistance – a state where insulin gets less and less effective in lowering blood sugar. This precedes the development of type 2 diabetes[2].

Hypoxia in Diabetes Patients

Diabetes patients suffer poor blood flow through the narrowed small blood vessels (microangiopathy)[b] all over their body. This means that the oxygen carried in red blood cells have difficulty getting through these narrowed vessels to reach the body tissue.

In a clinical study conducted in the Netherlands, researchers found that people with diabetes, when compared to healthy subjects without diabetes, have consistently lower tissue oxygen values measured at various sites of the body[3]. They deduced that this could be due to the narrowed blood vessels supplying inadequate oxygen to the body cells, causing hypoxia[3]. The doctors at the Hyperbaric Unit, Royal Adelaide Hospital, The University of Adelaide, South Australia also discovered that increasing the patient's body oxygen levels using hyperbaric oxygen therapy[c] led to better response of the body to insulin with more effective blood sugar lowering, further drawing the link between diabetes and body oxygen levels[4].

Sleep Apnea

Obstructive sleep apnea (OSA) occurs when your throat muscles intermittently relax and block your airway during sleep, commonly observed as snoring. This causes breathing to repeatedly stop and start during sleep, leading to intermittent lack of oxygen to the brain. Severe obstructive sleep apnea (OSA) increases a person's risk of developing diabetes by 30% or more, according to a study of 11,000 patients published in the American Journal of Respiratory and Critical Care Medicine[5]. Intermittent hypoxia in people with obstructive sleep apnea is found to propagate insulin resistance and increase the risks of developing diabetes[6]. Now that that link has been confirmed in such a large trial with a long follow-up period[5], clinicians may be able to intervene and take diabetes prevention measures for patients with OSA who have not yet developed the disease.

Definitions:

[a]Inflammatory response of immune system – When the immune system is triggered, it will release armies of immune cells into the bloodstream to fight foreign invaders such as bacteria. This is a normal response to foreign invasion. However, long term (chronic) inflammatory response of the immune system can be triggered in the absence of invasion, by substances that the body cells produce during prolonged states of stress, substances called chemokines. This continual influx of immune cells will create a state of 'martial law' in the body, causing prolonged stress to normal cells, leading to chronic diseases such as heart disease, diabetes and arthritis.

[b]Microangiopathy – this is a complication of diabetes where the small vessels (capillaries) are damaged by high blood sugar and they become narrowed and blocked, preventing smooth flow of blood through them.

[c]Hyperbaric oxygen chamber – Hyperbaric Oxygen Therapy (HBOT) is a treatment that involves placing the patient inside a pressurized chamber with 100 percent oxygen. While the patient is inside the pressure chamber, it increases plasma oxygen concentration by 10 to 15 times and enables increased tissue oxygenation of the body. The oxygen concentration in plasma and the tissue oxygen levels returns rapidly to original levels within 10 minutes of the patient leaving the pressurized chamber. This is an established method of enhancing tissue oxygen for the duration that the patient is inside the pressurized chamber.

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A common feature of most cancers is a low level of oxygen, called hypoxia, the severity of which varies between tumor types[1]. Cancers are hypoxic (having low level of oxygen inside the cancer tissue), the cancer cells have adapted to thrive a low oxygen environment[2]. This relationship between cancer and hypoxia has been known since the 1930s when Dr Otto Warburg, a German Nobel Prize winner in Medicine, discovered that cancer proliferation occurs in the absence of oxygen[3].

Cancer and Oxygen Levels

Cancers that have lower levels of oxygen are more aggressive in behavior, with greater tendencies to invade and spread[4], resulting in poorer outcomes for patients. Several mechanisms have been proposed by cancer researchers on how hypoxia affects cancer aggression.

In environments with low oxygen, cancer cells undergoes frequent genetic distortions (genetic mutation)[a,5]; to become aggressive cells with a ferocious ability to spread[5]. Under hypoxic conditions, cancer cells take on very primitive shapes, literally sprouting limbs that allow them to move and invade into surrounding normal tissue[6]. At the same time, they also 'give birth' to numerous immature cancer stem cells that evade detection by the immune system and hide in various parts of the body to start new colonies of tumours[7]. Non-cancer stem cells are immature cells with the ability to multiply indefinitely to replenish tissues throughout the life of the person[8]. Cancer stem cells, unfortunately, also behave the same way to ensure the survival and recurrence of cancer in the patient's body[7].

Inhibiting Recovery

Professor Gregg Semenza, from Johns Hopkins Kimmel Cancer Centre puts it this way "There are still many questions left to answer but we now know that oxygen poor environments (hypoxia), like those often found in advanced human breast cancers serve as nurseries for the birth of cancer stem cells"[9].

According to Professor Semenza, "Chemotherapy may kill more than 99 percent of the cancer cells in a tumor but fail to kill a small population of cancer stem cells that are responsible for subsequent cancer relapse and metastasis[b]"[9].

Hypoxia and Cancer Treatment

Cancers use hypoxia as a protective shield against radiation therapy and chemotherapy[10]. The more hypoxic a cancer is, the more it is resistant to treatment[10]. Oxygen has a substantial impact on treatment response, and hypoxia presents a serious barrier to successful radiation therapy[11].

Radiation therapy is ineffective against hypoxic cancer because radiation interacts with oxygen inside the cancer cell to disrupt the cell's ability to multiply[11]. If the cancer cell is hypoxic, radiation is unable to effectively destroy it[11]. On the other hand, having sufficient oxygen can make a big difference to how successful radiotherapy is for treating the cancer; for conventional radiation therapy, regions of a tumour with high oxygen concentration are up to threefold more responsive to treatment than regions without oxygen[12].

Hypoxia Inhibiting Chemotherapy

Failure to respond to chemotherapy is also contributed by cancer hypoxia[13]. The effective delivery of cancer drugs into hypoxic areas of the cancer is hampered by low oxygen levels and acidic conditions in the body tissue due to anaerobic glycolysis[d,13]. Some chemotherapeutic drugs require oxygen to generate free radicals[c] that kill cancer cells and are ineffective when the cancer is very hypoxic[13].

Overall, hypoxia in the environment of a cancer is a critically important factor which promotes recurrence of malignancy and has a negative effect on response to most cancer treatments.

Definitions:

[a]Genetic mutation – Mutation is a change in the cell DNA that creates slightly different versions of the same genes.

[b]Metastasis – Metastasis is the medical term for cancer that spreads to a different part of the body from where it started.

[c]Free radicals – Free radicals are atoms or groups of atoms with an odd (unpaired) number of electrons. Once formed these highly reactive radicals can start a chain reaction that can damage cell membranes and cell DNA.

[d]Anaerobic glycolysis – the metabolic method used by cells to produce energy in the absence of oxygen. It produces lactic acid as a by-product.

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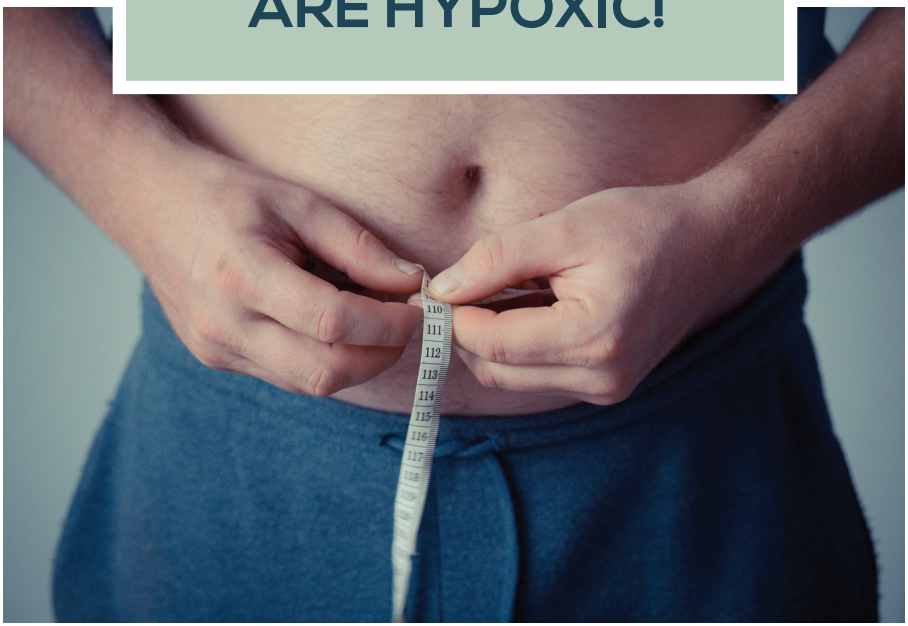
FATTY LIVERS ARE HYPOXIC!



Non-alcoholic fatty liver disease (NAFLD) is the most common long term liver disease in developed countries[1].

In this condition, the fatty changes in the liver are not due to alcohol and interestingly, a high fat diet actually reduces oxygen supply to the liver cells[2]. Oxygen, or rather the lack of it, is a central component of the disease process leading to formation of fatty liver[3]. Accumulating medical evidence from the past few decades provides strong support that interruptions in oxygen supply to the liver contributes to the start and progression of fatty change[3].

The Liver Needs Energy

The liver is a highly metabolic organ, requiring a high energy supply to fuel its metabolic activities[2]. As such, adequate oxygen supply to the liver is extremely critical for this tissue's function because without oxygen, cells produce 16 times less energy (ATP)[4]. Oxygen regulates metabolic activities in certain parts of the liver and when disease processes affect the liver, oxygen can make adjustments to how liver diseases progress[5].

Low supply of oxygen to these parts of the liver lead to hypoxic damage of the liver cells. How well oxygenated the liver cells are prior to suffering any stress or injury can dramatically affect the outcome with better oxygenated liver cells suffering less harm[6].

Oxygen and Fatty Liver

People with obstructive sleep apnea, the serious snorers, have been shown to develop fatty liver[7,8]. The intermittent 'strangulation' occurring throughout the night in severe snorers keeps disrupting oxygen supply to the body and creates sufficient overall hypoxia to reduce supply of oxygen–rich blood to the liver and cause liver hypoxia[9]. Hypoxia then stimulates fatty change within the liver cells.

Chronic hypoxia not only propagates fatty liver, it can induce formation of fibrous tissue within the liver, leading to development of liver cirrhosis[10].

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HOW IS HYPOXIA INVOLVED IN HEART ATTACK AND STROKE?

Hypoxia is the cellular weapon that kills the heart and brain during heart attacks[1] and strokes[2].

Heart muscle cells are very sensitive to lack of oxygen (hypoxia) because they require a constant large supply of energy to pump non-stop 24 hours a day, every day of your life. The brain is a very metabolically active organ yet it contains virtually no oxygen reserve[2]. Brain cells are critically sensitive to hypoxia[2] because they are constantly transmitting electrical signals that coordinate organ function, enable movement and orchestrate other bodily functions within a living person. These activities are highly energy intensive. As we have discovered in the preceding chapter explaining why oxygen is important, cells generate 16 times more energy when well oxygenated, compared to when they try to create energy in the absence of oxygen (anaerobic glycolysis)[a,3].

High functioning cells such as heart muscle cells and brain cells have high energy requirements all the time. That is why hypoxia is an undesirable state for heart and brain function.

The cardiovascular system, also known as the circulatory system, includes the heart, arteries, veins, capillaries and blood. The heart is literally the pump that moves blood through the network of blood vessels; tubes of

various sizes (arteries, veins and capillaries) to reach different regions of the body.

Supplying oxygen to the body is the most essential function of the cardiovascular system. All cells in the body require oxygen to generate energy (ATP)[b] in order to stay alive and perform their functions. The heart and its network of blood vessels is the transport system to ensure that oxygen is continually delivered to every cell. Although all cells require oxygen, brain cells are the most sensitive and begin to die in as little as few minutes if deprived of oxygen[2].

The heart pump itself uses 5 to 20 percent of the body's supply of oxygen[4] and has its own network of blood vessels called the coronary arteries that supply blood to the heart muscles. Heart muscle cells die within 20 minutes[4] if they do not receive enough oxygen. So hypoxia created by blocked arteries is especially lethal to heart and brain cells.

According to the WHO (World Health Organization), cardiovascular disease (CVD) is the number one cause of death in the world[5], with more people dying annually from CVDs than from any other cause. Cardiovascular disease generally refers to conditions that involve narrowed or blocked blood vessels, leading to chest pain (angina), heart attack or stroke.

What Happens During a Heart Attack or Stroke?

A heart attack is precipitated when a narrowed coronary artery suddenly becomes blocked with a blood clot and oxygen supply to the heart muscle is cut off. The heart muscle cells suffer immediate hypoxia[1]. Without oxygen, the heart muscle cells switch to anaerobic glycolysis to generate energy, making 16 times less energy (ATP) than before[3]. Heart muscle cells are very sensitive to low oxygen because they cannot afford to rest, they need to keep pumping blood for the rest of the body. Muscular pumping needs lots of energy (ATP). With this sudden energy crisis, the heart muscle cells become stressed and start dying. If a supply of oxygen-rich blood is not re-established within an hour, the heart muscle cells become dead and cannot be revived[6].

If large portions of the heart muscle are dead and non-functioning, the heart pump becomes disabled. Being the main pump that pushes blood around the body, a failing heart leads to poor oxygen supply to the entire body. This is a state called heart failure. If the heart pump stops because of extensive damage, the person will die.

A stroke is simply the same event described above, happening to an artery supplying blood to the brain. Hypoxia in brain cells is a very serious problem because brain cells die even faster than heart muscle cells when hypoxia sets in - dying within a few minutes from the time oxygen supply is cut off[2]. This leads to rapid cell death and permanent damage to the affected parts of the brain within minutes[2]. Depending on which region of the brain the affected artery supplies to, a stroke can result in a range of different neurological problems such as loss of ability to move a limb, loss of ability to speak, loss of sight or even loss of consciousness (coma). Damage in critical parts of the brain from a stroke can lead to death.

Definitions:

[a]Anaerobic glycolysis – Anaerobic glycolysis is a method used by cells to produce ATP by transforming glucose into lactate when limited amounts of oxygen (O_2) are available. Compared to OXPHOS, anaerobic glycolysis creates 16 times less energy.

[b]ATP – Adenosine triphosphate, an energy-carrying molecule found in the cells of all living things. ATP captures chemical energy obtained from the breakdown of food molecules and releases it to fuel all cellular processes needed for life. It is the source of energy that keeps everything going.

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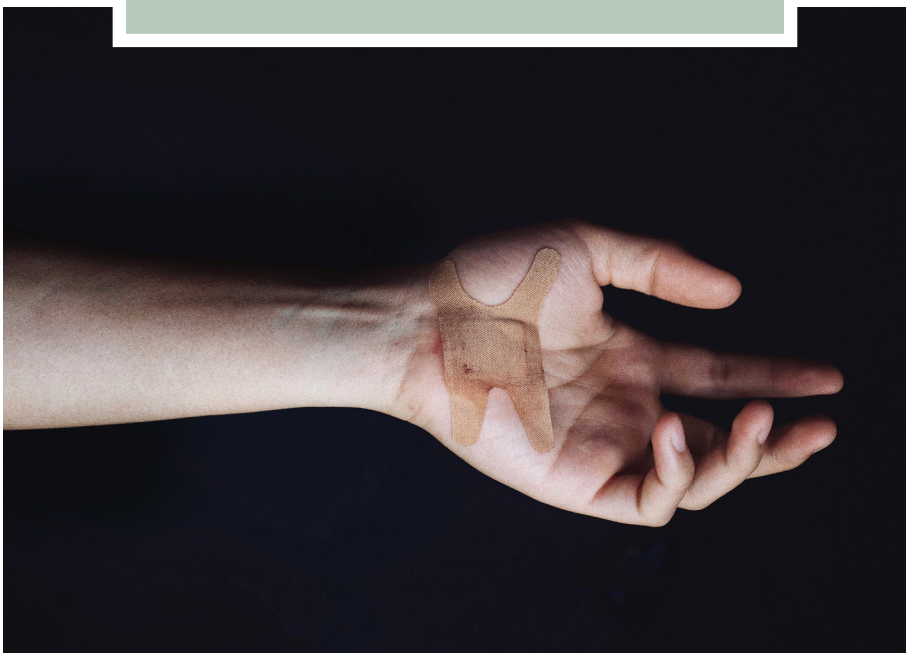
WOUND HEALING SUFFERS WHEN THERE IS HYPOXIA



Oxygen has a massive effect on the wound healing process, and one of the biggest factors that can inhibit the body's ability to heal a wound is low oxygen levels (hypoxia) in the affected area[1].

While the exact way oxygen works in the wound healing process is more complex than understood, it is widely recognized that oxygen is needed in nearly every stage of the wound healing pathway[2].

When the body acquires a wound, from surgery or trauma, the break in the body's integrity makes the wound vulnerable and it triggers a response to greater bacterial defense, cell proliferation, collagen synthesis and regeneration of blood vessels and nerves, among other reparative activities[3].

All these are high energy activities. As reported in the British Journal of Dermatology[3], oxygen's main function in wound healing lies in its capacity to effectively produce energy. In order for cells to fight infections, properly multiply and get organized into different skin cells to fill up the wound, they must have a sufficient amount of energy[1].

Like all functions involved in human biology, oxygen is essential for cells to generate energy (ATP)[a] effectively, using a process called oxidative phosphorylation[b].

When an area of the body does not receive an adequate amount of oxygen, a condition known as hypoxia, it can slow and even halt the healing process – resulting in chronic wounds[c].

The limitation of oxygen delivery to the wound is often due to many factors; however, the end result is always non-healing chronic wounds or ulcers. Chronic leg and foot ulcers occur in many adults with vascular disease or diabetes and are attributed to poor delivery of oxygen rich blood through blocked blood vessels, prolonged pressure, or abnormal nerve function[4].

These ulcers last on average 12 to 13 months, can relapse in up to 60% to 70% of patients, can lead to loss of function, amputation and decreased quality of life[4]. These wounds become infected because there is insufficient oxygen to mount an effective antibacterial effect and ultimately, the poor oxygenation of the skin over a prolonged period leads to gangrene (death of the tissue) of the affected area and amputation of the leg[5].

Doctors currently use hyperbaric oxygen therapy (HBOT)[d] , an oxygenation method to correct hypoxia in poorly healing wounds[6]. HBOT is usually effective to heal these chronic wounds but many patients are unable to tolerate the side effects such as pressure induced ear damage (middle ear barotrauma)[e,7], dental pains, difficulty with visual focus[8], risks of cataracts[9], and increased blood pressure[10]. Middle ear barotrauma is one of the most common side effects of HBOT. Patients experience problems with ear equalization, a feeling of pressure, ear pain, and discomfort during the time they ramp up the pressure in the chamber. As such, this current method of overcoming wound hypoxia is not suitable for every patient.

Definition:

[a]ATP – Adenosine triphosphate, an energy-carrying molecule found in the cells of all living things. ATP captures chemical energy obtained from the breakdown of food molecules and releases it to fuel all cellular processes needed for life. It is the source of energy that keeps everything going.

[b]OXPHOS – Oxidative Phosphorylation is process whereby a cell uses oxygen to generate large amounts of energy in the form of ATP. This process, which takes place in mitochondria, is the major source of ATP in aerobic organisms.

[c]Chronic wounds – Chronic ulcers are those that do not progress through the healing process in a timely manner and typically last 12 to 13 months.

[d]HBOT – Hyperbaric oxygen therapy (HBOT) an adjunct therapy to increase tissue oxygen with the use of 100% oxygen at air pressures greater than atmospheric pressure.

[e]Middle Ear Barotrauma – a common side effect of the high pressure–high oxygen environment during HBOT, leading to sensation of ear pain, ear canal swelling and rupture of eardrum with resulting deafness.

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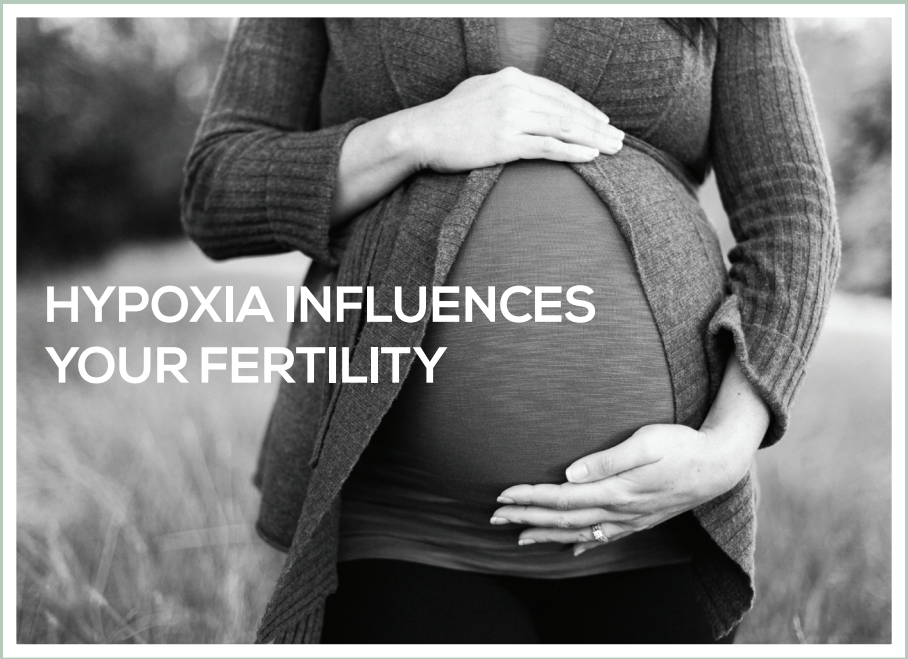

Hypoxia has been linked to disturbances in both male and female infertility. Researchers have recently investigated the relationship between obstructive sleep apnea (OSA) and male fertility[1]. They found that the intermittent disruptions to breathing (episodes of reduction in oxygen supply) that are the hallmark of sleep apnea is associated with decreased fertility among men[1]. It was found that hypoxia, or low oxygen supply, associated with airway obstruction in OSA patients, is an important factor causing diminished fertility[2].

Hypoxia and Male Fertility

Men and male animals produce large numbers of sperm every day, this highly prolific sperm production (spermatogenesis) in the testis consumes considerable amount of oxygen. Chronic hypoxia to the testis has been shown in rat studies to induce a state of low sperm count (oligospermia)[3]. In a human research study to define the effect of hypoxia on male fertility, researchers examined male mountaineers who travel to low oxygen regions at high altitudes. They documented that their sperm count became much lower than before the mountaineering trip and remains low for more than 6 months upon returning to sea level[5]. Fortunately for these men, this effect is reversible and their sperm count eventually recovered to their original

levels after 2 years[4,5]. The study concludes that hypoxia was responsible for lowering the sperm count of these men.

Females are not also spared the 'anti-fertility' effects of hypoxia on the ovaries. In humans and domestic animal species such as sheep introduced to low oxygen environments at high-altitude, the fertility of females is found to be reduced[6,7]. Exposure of sheep to high-altitude hypoxia affects the development and function of the 'corpus luteum'[7], a vital structure of the ovary that maintains hormones necessary for pregnancy. Without a normal functioning corpus luteum, pregnancy cannot be successful.

In a study by Yale School of Medicine researchers on age-related decrease in female fertility, the scientists reported that in women over the age of 40 years, hypoxia is necessary for egg damage to occur in the course of ageing of human eggs[8]. "More women are postponing childbearing, but with age, the cumulus cells that surround and nurture the eggs begin dying; we've found that this is caused by lack of oxygen," said Dr Pasquale Patrizio, director of the Yale Fertility Center and professor in the Department of Obstetrics, Gynecology & Reproductive Sciences[8].

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HYPOXIA AND ERECTILE DYSFUNCTION

Erectile dysfunction (ED) or 'male impotence' is medically defined as the persistent inability to attain and maintain an erection that is sufficient to permit satisfactory sexual performance[1]. The prevalence of ED in Asia varies between 9% and 73%[2]. Statistics derived from a population-based survey conducted in Singapore on men greater than 30 years of age showed a prevalence rate of 51.3%[3] while another study on the ageing population of Singapore showed an alarming rate of 73%[4]. In Korea, the ED prevalence rate was quoted to be 32.2%[5]. In Mainland China, the reported prevalence of ED is 38.3%[6]. In Taiwan, the figures range from 9% to 17.7%[7]. In a self-reported survey, the prevalence of ED in Malaysian men was 26.8%[8], but the prevalence numbers obtained from another Malaysian study was as high as 69%[9]. The overall prevalence of ED in Australia is estimated at 40%[10]. In any case, erectile dysfunction is a common problem faced by men all over the world. Ageing represents the main erectile dysfunction (ED) risk factor[11] and risk of erectile dysfunction increases in parallel with age. Medical conditions such as sleep apnea and diabetes are other significant risk factors[12]. Stress and other lifestyle practices such as smoking are also associated with higher rates of erectile dysfunction[13].

Low Oxygen Levels Cause Erectile Dysfunction

It is scientifically proven that oxygen is involved in the mechanism of penis erection through regulation of nitric oxide synthesis in the penile tissue together with chemicals produced by the body to increase blood flow[14,15]. In fact, recent clinical trials have shown that both the ability of penile tissue to produce nitric oxide (NO)[a] and the state of health of penile muscles depend on an adequate oxygen supply[16,17]. When oxygen levels are low in the penis, vasoconstrictor substances are produced that shrink the blood vessels supplying the penis[18,19]. When oxygen levels are high, nitric oxide and prostaglandins are produced, which increases blood flow into the penile tissue[18,19]. Research has shown that hypoxia causes a significant reduction of nitric oxide synthase[b] activity, suggesting that insufficient oxygen limits nitric oxide production in the penis[20], leading to poor ability to achieve penile erection. Thus, optimal oxygen supply plays an important role in healthy erectile function[19].

While there are disease factors such as ageing, heart disease, chronic lung disease and diabetes that cause male impotence, hypoxia is a known contributing factor in the development and progression of erectile dysfunction[19].

Definitions:

[a]Nitric oxide (NO) – Nitric oxide is a chemical produced naturally by our cells. Nitric oxide causes blood vessels to relax and increases blood flow.

[b]Nitric oxide synthase – an enzyme produced by cells to facilitate synthesis of nitric oxide.

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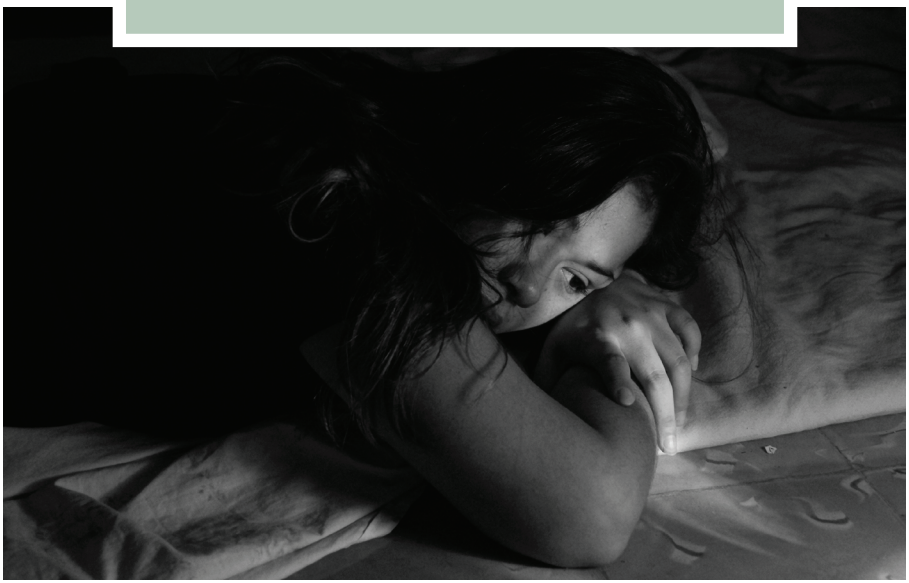
HYPOXIA AND PAINFUL MENSTRUAL DISORDERS



Women who suffer from heavy periods agree on how terrible it feels when that time of the month comes around. Heavy periods are often painful and can lead to excessive blood loss and iron deficiency anemia.

Menstrual cramps, also known as 'dysmenorrhea' or period pains, can happen both just before and during a menstrual period. The regular type of menstrual cramp affects healthy young women and is known as 'primary dysmenorrhea'. These cramps occur because contractions of the womb or uterine muscles strangle the uterine blood vessels, briefly cutting off oxygen supply to the uterus[3]. The resultant lack of oxygen, or hypoxia, within the womb muscles causes the sensation of painful menstrual cramps[3].

In women with heavy periods or severely painful menstrual cramps, there are usually underlying womb conditions that aggravate the pains, e.g. endometriosis and uterine fibroids. These are known as 'secondary dysmenorrhea'.

Hypoxia and Gynecological Disorders

Endometriosis is a common gynecological disorder, characterized by the

presence of womb lining tissue (endometrial tissue) in places outside of the womb[4,7]. Women with endometriosis suffer severe menstrual cramps[5], pelvic pain and infertility[6]. The common theory on how endometriosis starts is that of 'retrograde menstruation' where backward flow of menstrual blood through the fallopian tubes[a] brings womb lining tissue outside of the womb into places within the abdomen[7]. Recent research evidence points to hypoxia being responsible for supporting the steps necessary for the development of endometriosis[8]. Hypoxia switches on genetic codes to regulate the successful deposit, survival, and maintenance of womb lining cells outside the womb[8]. It appears that hypoxia orchestrates the production of signaling biomolecules (e.g. leptin, VEGF) in the body to stimulate growth of the endometrial tissue and formation of blood vessels to ensure continued survival of these endometrial deposits outside the womb[9].

Uterine fibroids, also known as uterine myomas, affect many women and is another common cause for heavy menstruation and menstrual pains[10]. The uterus (womb) is a muscular organ. A uterine fibroid is a benign muscle tumour formed in the wall of the womb[10]. Compared with normal uterine muscle, the oxygenation of fibroids is significantly poorer[11]. Fibroids thrive well with hypoxia. Some research even suggest that hypoxia drives the change of normal uterine muscles into fibroids[12].

Definition:

[a]Fallopian tubes – A woman's fallopian tubes are the two tubes in her body along which eggs pass from her ovaries to her womb.

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Acne is one of the most common skin problems, affecting about 90% of all people at one point or another during their life[1]. While acne usually starts in adolescence and young adulthood, it may be troublesome well into the adult years[2]. Lack of information about acne often prevents proper treatment. Genetics[3], hormones[4] and bacteria[5] have long been known to orchestrate acne formation. While you cannot really change your genetics or your hormonal status, you can certainly try to do something about the bacteria.

Hypoxia and Bacterial Growth

A major bacteria culprit in the formation of acne is the anaerobic bacterium called Propionibacterium acnes (P.acnes)[6]. This bacteria is a common resident on the skin of many people[6]. They are classified as anaerobic bacteria because they survive very well in low oxygen environments. In fact, researchers from the University of Leeds and the St James Hospital in the UK found out that this bug hates oxygen and its growth rate is markedly reduced in the presence of high oxygen[6].

Recent research on this spotty skin affliction has revealed the mechanism by which P.acnes causes acne. Ordinarily, P.acnes lives on the skin without giving much trouble. Only when it is caught in certain situations such as in a clogged pore, surrounded by oil and no oxygen, will it stir up the process of acne formation. A study led by Dr Robert Gallo and his researchers from the University of California, at San Diego, USA, discovered that the hypoxic (low oxygen) environment inside a clogged pore causes the bacterium to turn 'sebum' – the greasy substance produced by oil glands in the skin – into fatty acids that activate inflammation in nearby skin cells, causing acne to form[7]. This makes hypoxia an important triggering link between the bacteria and the sebum filled pore in the process of acne formation[8]. Hypoxia may therefore be an important factor to address when it comes to acne prevention.

Acne Formation and Scarring

Some acne sufferers know by experience that severe acne eruptions often lead to permanent scarring of the face. As acne often presents with wave upon wave of inflammation, over months and sometimes years, multiple skin wounds develop at sites of active acne. Acne wounds that try to heal in the midst of ongoing inflammation are more prone to scar formation[9]. Scarring of the skin occurs as a result of damage to the skin during the healing process of active acne[10]. There are two basic types of acne scar depending on whether there is a net loss or gain of collagen. Eighty to ninety percent of people with acne scars have scars associated with a loss of collagen – explaining why acne leaves behind pits and pock marks on the face[10]. Although less common, a small number of unfortunate people also suffer from lumpy scars left behind by increased collagen formation at acne sites.

Wound healing is one of the most complex biological processes and research has shown that oxygen is a critical ingredient in proper wound healing and restoration of normal skin appearance[11]. It has been shown that all the vital cell functions needed for healing of the skin all proceed at faster pace when there is more oxygen[12]. Oxygen also hastens removal of bacteria activity, which allows resolution of inflammation[13]. When inflammation is controlled, the skin is able to produce new cells and rebuild the skin tissue properly[9]. Hypoxia is a factor that works against proper wound healing and it is therefore important that healing wounds have a good oxygen supply.

In summary, the lack of oxygen (hypoxia) makes it conducive for overgrowth of acne-causing bacteria (P.acnes) on the skin. Hypoxia inside clogged oily pores triggers the bacteria to secrete fatty substances that cause inflammation of the pores and acne eruptions. Continued inflammation disturbs proper skin healing of active acne that could lead to permanent scar formation and hypoxia plays a role in poor wound healing.

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