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Age-Related Cognitive and Functional Decline

As both the proportion of older people and the length of life increase, the key issues are performance and quality of life. Would aging be accompanied by a sustainable good health, good cognitive performance, sustained sense of well-being, and extended periods of social engagement and productivity, or would it be associated with reduced cognitive function, reduced energy, frailty, disability, and dependency.

Cognitive Aging

Decline in our cognitive functions are unfortunately considered by many as a “normal” part of the aging process. Along the human maturation, many cognitive abilities are being develops, the usually peak of our cognitive function is around the age of 30, from where it is subtly decline. These age-related declines most commonly include overall slowness in thinking and difficulties sustaining attention, problem solving, multitasking, holding information in mind and word-finding[1]. More than half of sixty years and older express concern about the decline in their cognitive abilities[2]. That decline may unfortunately culminate in dementia. Dementia occurs when the pathological processes (such as Alzheimer's) ends with significant brain cell death and tissue loss.

Aging and frailty

Normal aging is characterized by decrease in muscle mass, reduction in muscle power and increase in adipose (fat) tissue, leading to increased risk of frailty, falls, fractures, reduction of ability to perform activity of daily living, decline in quality of life and loss of independence. In addition, our lungs capacity and cardiac function decrease, our maximal oxygen consumption decreases and our ability to perform physical activities deteriorates. Most of the muscular activities become less efficient and less responsive with aging as a result of a decrease in nervous activity and nerve conduction.

Aging mechanisms

The past decade has seen fundamental advances in our understanding of the aging process and raised optimism that interventions to slow ageing may be on the horizon. The aging process is linked to several mechanisms/hallmarks:

- **Body tissues lack of energy/oxygen (hypoxia)** – Atherosclerosis (narrowing of the lumen of the blood vessels) is a chronic inflammatory response that occurs in all of our blood vessels. It begins in childhood and progresses throughout life, resulting in decreased blood supply and ensuing relative tissue lack of oxygen (hypoxia) [3,4].
- **Mitochondria dysfunction** - Mitochondria are the primary generator of energy, located in each of our body cells. Along age, the number of mitochondria decreases as well as the efficiency of each mitochondria function, leading to cellular function decline and degenerative changes. Moreover, mitochondrial dysfunction accelerates atherosclerosis and tissue hypoxia atherosclerosis [3,4] (see above).
- **Stem cells exhaustion** – Through life, we accumulate damages/injuries at the cellular, tissue and organ level. These need to be balanced with regeneration of new cells and tissues. The regeneration is possible by special cells called stem cells, which are able to multiply and differentiate (transform into) to the damaged tissue cells. The number of stem cells in young people is significantly higher than the number in older people and thus regeneration processes are much more efficient in the young. Moreover, in addition to decline in their numbers, stem cells function also decreases in older age as a result of mitochondrial dysfunction (see above), i.e the ability to differentiate and regenerate the damaged tissues is reduced. In other words, aging is not only a matter of the cumulative damage, but rather a failure to regenerate the damage due to a decreased in the number of stem cells.

A growing body of research suggests several methods for cognitive enhancement and for improving the quality of life in both healthy and pathological states. Non pharmacological lifestyle interventions including exercise, healthy diets, intermittent fasting and cognitive training have shown positive effects if intensively performed [5,6]. Unfortunately, so far, none of the pharmacological interventions had the ability to induce significant improvements on the age related functional decline [7].

HBOT mechanisms

Hyperbaric Oxygen Therapy (HBOT) is used for chronic and urgent medical conditions associated with tissue hypoxia (lack of oxygen supply). There are growing data on physiological effects of HBOT on different injured tissue, including the brain, using different models of pre-clinical as well as clinical studies.

- **Tissue oxygenation** – During HBOT, tissue oxygenation can be increased by 25-30 times[1–7]. Utilizing the simple law of diffusion, the high quantity of oxygen while breathing hyperbaric oxygen, transfers from the capillary to the mitochondria in all tissues, overpassing blockage/narrowing of blood vessels by the atherosclerosis process.
- **HIF and the hyperoxic -normoxic paradox** – The newly used HBOT protocol generates intermittent fluctuations between very high to normal oxygen levels. The mitochondria in our cells sense this relative change (from very high oxygen level back to normal level) as relative hypoxia those triggering many biological process that usually occur during hypoxia (low oxygen level), with the highest level of oxygen (hyperoxia)– the so called "Hyperoxic-Hypoxic paradox". One of the key molecular mediators that can be triggered by the hyperoxic-hypoxic paradox is called HIF (hypoxic induced factor 1alpha). This molecule is usually triggered when the body/cell senses low level of oxygen and stress, unleashing several processes to cope with the stress[8]. By the newly used HBOT protocol, HIF can be induced and preserved along the treatment period. Once HIF level is high, many of the regenerative processes and anti-inflammatory mechanisms are being initiated.
- **Regeneration of blood vessels (Angiogenesis) –** The release of HIF in high concentration (see above) initiates a cascade of events including triggering of another molecule - VEGF (vascular endothelial growth factor) - and stem cells recruitment, leading to the generation of new blood vessels (angiogenesis) [9] [10]. These new blood vessels are formed in the tissues where normal blood flow was decreased, thus decelerating the atherosclerosis process and restoring the supply of energy and nutrients to the aging tissues.
- **Mitochondria function restoration -** Both animal and human studies have shown HBOT can improve and restore the decreased mitochondrial function in different parts of our body including injured brain[11,12] [13].
- **Stem cells recruitment -** HBOT induces stem cells mobilization from their storage at the bone marrow to the blood stream and from there to entire body tissues. The number of circulating stem cells increases up to 3-8 times compared to pre HBOT level [14]. It is important to emphasize, that stem cells mobilized by HBOT home in on tissues that have suffered damage and signal a need for regeneration [14]**.** In addition to mobilization, HBOT induces the differentiation of stem cells to the different tissues such as heart, muscle, kidney and brain [15,16].

Aging functional decline and HBOT Research

Dr. Amir Hadanny and Dr. Shai Efrati have recently completed a prospective controlled trial was conducted in Shamir (Assaf Harfoeh) Medical Center, performed between 2016 to 2019, on 63 healthy volunteers, 65 years old and higher- the so-called "normal aging" population.

The volunteers were divided to 2 groups: the treatment group – was evaluated at baseline, and after 3 months of HBOT daily sessions. The control group was at baseline and after 3 months of follow up/control without HBOT. Comprehensive evaluations included cognitive assessments,

MRI scans, cardiopulmonary exercise test, blood samples, skin and muscle biopsies and quality of life questionnaires.

The HBOT protocol included 60 daily sessions, 5 days/week, 90 minutes of 100% oxygen at 2 ATA with 5 minutes air breaks every 20 minutes.

The exciting results with regards to the cognitive and functional improvement will be soon officially added for the general public following the publication in the scientific literature.

Treating Aging Functional Decline: Sagol Center Recommended HBOT Protocol

Phase I Medical Assessment

The process begins with a comprehensive medical, physiological, cognitive, and imaging evaluation assessment. The tests are conducted by trained medical staff including: Physicians, Neuropsychologists, Physiotherapists, Physiologists, Nurses, Dietitians and more.

The evaluation also includes metabolic/functional brain imaging: brain perfusion MRI+ brain microstructure (DTI) in addition to comprehensive blood tests with ***novel aging biomarkers (such as for example telomeres length)***, neurocognitive tests and physiological, nutritional and assessments.

Phase III HBOT Protocol

60 Daily consecutive sessions / 5 days per week / 2 ATA / 100% Oxygen for 90 min with 5 minutes air brakes every 20 minutes / total session time 120min.

Throughout the treatment period rehab training will be provided to patients by the professional cognitive and physiological professionals.

Phase III Post-HBOT Assessment

At the end of the treatment the evaluation and tests done at baseline will be **repeated** for an objective evaluation by the medical team.

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