

Myths and facts of anti-ageing medicine

Abstract

The anti-ageing industry treats the body like a glass with evaporating liquid that needs replacement. We inject hormones to counteract hormonal deficiency. We forget that hormones must be in the optimal range to be functional. More is not better. Then we inject stem cells to replenish the body's decline. We forget about immunorejection or tumorigenesis. We perform these treatments without longitudinal research that confirms the compatibility of specific individuals with the injected hormones or stem cells in their bodies. Marketing touts "virtually instant results" and "magically reversing aging," but more often than not, truth and marketing are incompatible. Inflammation is generally considered to be one of the main reasons for ageing, along with increased toxicity and oxidative damage. Energy devices, stem cells or hormone injections must provide us with 10-15 years of longitudinal research that investigates the long-term results of these procedures by examining several inflammatory variables and other health factors, before touting their safety and efficacy. Anti-ageing should focus on cellular repair without interfering with or traumatising the body. We should capitalize on effective health-enhancing interventions like caloric restriction, novel exercise methods, nutrition, lifestyle and other alternative medicine modalities that can reduce age-accumulated toxicity and inflammation to reinforce immunity and delay aging.

Keywords: anti-ageing, immunity, wellness, caloric restriction, effortless exercise, inflammation, toxicity, energy devices, RF, lasers, alternative medicine

Volume 11 Issue 2 - 2024

Xanya Sofra

New School for Social Research, City University, USA

Correspondence: Xanya Sofra, Ph D, New School for Social Research, City University, New York, USA, Tel +85293405069, Email science@iellios.com

Received: August 21, 2024 | **Published:** September 13, 2024

Introduction

Dissecting the Anti-ageing Myth

The anti-ageing industry makes simplistic assumptions that health is achieved by supplementing a biological deficiency caused by ageing. They believe that they can increase differentiated stem cells by injecting animal or plant non-differentiated stem cells into the body. They ignore the deleterious effects of immunorejection, or even worse, that the immune system may attack the stem cells' transplant damaging vital organs. They underestimate or underreport the dangers of injecting ESCs iPSCs or NTSCs in a healthy body which include triggering tumorigenesis and the formation of teratomas. There is no longitudinal research to certify the compatibility of specific individuals with hormones or stem cells extracted from animals or plants. Importantly, they are misunderstanding the difference between element and processes. The body generates the stem cells and all other elements that are necessary for youth and health. Generating is a process. It's not a matter of how many "elements" like stem cells, for example, are in the body's reserve. It is a question of whether or not the body has the capacity to produce and differentiate stem cells, whether these are already available or they are injected. It all depends on whether the body can initiate and complete the "process." It does not only depend on the number of available "elements" as anti-ageing professionals have assumed. The body is a Gestalt, an alive entity that is more than the sum of the cells that compose it. This Gestalt, this multidimensional alive entity is everchanging depending on the complex interacting functions that sustain life.

Laser and RF corporations claim that energy technologies are generally safe. However, this safety does not reach the statistical significance of below 0.5% ($p < 0.05$) as a thorough analysis of 34 laser and RF studies postulates by revealing an average of 9-12% serious side effects including melanoma and other forms of cancer. These results indicate that, on the whole and for most patients, laser and RF devices may be more or less clinically safe, however,

scientifically, the laser and RF devices safety does not reach statistical significance.¹⁻⁴ There are still two unanswered questions, unexplored by laser and RF research. The first is whether there is accumulated inflammation with time following laser and RF treatments which can be answered by measuring interleukins and the C-reactive protein after treatments with energy devices. The second is whether there is, indeed both a short and a long-term sustained rejuvenation effect after the improvement observed after laser and RF treatments that cannot be entirely explained in terms of inflammatory edema that masks sagginess and wrinkles.

There are underreported laser and RF side effects such as melanoma, hyperpigmentation, and hypopigmentation. Results usually rebound after laser and RF lipolysis treatments, or there is an unattractive transfer of adipose growth to other unwanted areas like the arms, chest and back, following the burning and elimination of the abdominal fat. Large corporations claim that laser and RF rejuvenation and lipolysis treatments reduce inflammation despite the trauma caused. However, there are no longitudinal studies to verify their claim that repeated trauma does not cause inflammation. Longitudinal laser and RF research is necessary because the literature on injuries demonstrates increased inflammation with repeated trauma.

A number of researchers have emphasized the close association of inflammaging with metabolic and other chronic diseases which surface as we get older.⁵⁻¹⁰ Frahsceschi et al have proposed new biomarkers like DNA methylation, glycomics, metabolomics and lipodomics to assess biological versus chronological age. Metabolic age is lower than chronological age in a healthy body and higher in individuals who have compromised themselves with repeated trauma. Overall, a healthy body looks younger than a sick one. Age delay is the result of wellness and strong immunity. Healthy lifestyle, nutrition and exercise are still centre stage of wellness.^{11,12} Impaired immune surveillance occurs when the focus of the immune system is concentrated on repairing repeated trauma which happens routinely during the so-called "minimally invasive" traumatic anti-

ageing procedures with lasers and RF. Impaired immune surveillance results in senescent cells, the accumulation of which speeds up the ageing process.^{13,14} Inflammation always follows trauma and repeated trauma will agglomerate inflammatory processes, the persistence of which will undermine immunity. In body lipolysis procedures, there is the phenomenon of paradoxical adipose hypertrophy seen after cryolipolysis that has been repeatedly documented.¹⁵⁻¹⁹

Research on the persistence of neuronal communications beyond barriers unveils a vast dynamic complexity of biological communication networks that may behave differently under unforeseeable circumstances.²⁰⁻²⁴ This precarious dynamic variability warrants the necessity of longitudinal studies before concluding the safety and efficacy of any technology.

In search of the fountain of youth

Ageing is traumatic. Our bodies deteriorate. We get fat no matter what we eat. Lines cross our faces in all directions like complex freeway interchanges. We go to the gym but cannot get rid of visceral fat. We think that we can cover the fat with clothes so we embark on a botox-and-fillers escapade to get rid of wrinkles. One of the underreported side effects of cosmetic injections is vascular occlusion.²⁵ This condition can be identified by the pain on the injection spot, as well as in areas distant from the injection site. Blanching, white, dusky or pale skin may also be signs of a reduction in blood supply as a result of cosmetic injection. Other side effects of fillers include allergic reactions, infections, chronic inflammation and granulomas. Some patients have experienced an incidence of hypertrophic scars as a result of fillers.

Side effects of botox include headaches, allergies, drooping eyelid, muscle weakness, shortness of breath, dysphagia, bruising fever, blurred vision, pain, xerostomia, etc. We euphemize the experience, repeating the cliché: “no pain no gain.” Trauma is so much in vogue that people frown at procedures that aren’t painful because: “if it doesn’t hurt it doesn’t work.” We forget that pain is the body’s alarm to signify harmful invasion leading to injury. Therefore the saying should be a warning stating: “The greater the pain, the more the damage caused to the body.” Importantly, with repeated botox and fillers, most patients do not actually, look younger. They look their age without their wrinkles and facial expressions. Young people have expression lines around their eyes and forehead but they exude a natural freshness that botox and fillers cannot reproduce or replace.

The collagen miracle and the invisible wound

All trauma increases collagen. Collagen is the scar developing over a healing wound. But open injuries are hideous. This is why the large laser and RF corporations invented the “invisible wound” under the surface of the skin so no one can observe and become averted by the grisliness of the trauma. And just like that, they contrived a method of forcing the body to increase its collagen in a certain area, which they announced triumphantly.

Collagen is a protein involved in scar formation. The more extensive the inflammation the greater the scar formation. This has been proven by comparing adult wounds characterized by high inflammation which are prone to forming scar tissue, to embryonic wounds that show no evidence of scarring as a result of the inflammatory processes being minimal.²⁶ Importantly, laser and RF research never investigated whether the collagen increase at the treatment site was accompanied by deficient amounts of collagen in neighbouring areas. That would disprove their entire marketing campaign so such research never happened. They never tested the null hypothesis as they should,

according to validity and reliability principles. They never examined if there is a systemic collagen deficiency in areas other than those receiving the laser or RF treatment. Their counterargument would probably be: “let’s laser and RF more areas!” Forgetting that collagen increase depends on the body’s supplies and capacity to produce the collagen. If the body reserves were vacant of collagen and the body is incapable of producing more collagen then lasers and RF would increase nothing!

The glorification of “collagen” has rendered it synonymous with youth maintenance, a big lie since there are 100,000 proteins involved in composing the freshness of youth and collagen is only one out of these 100,000 proteins.^{7,8,27,28} The bright light of multibillion-dollar marketing campaigns has blinded the public and mesmerized them to think that hurting themselves would bring them back in time. Putting trauma and youth in the same sentence is a contradiction in terms. And there it is: the definition of brainwashing; being hypnotized to believe the unreasonable.

As doctors, we need to open our eyes and see the obvious. A healthy person looks younger than a sick one. Health and strong immunity delay ageing. Anything that compromises immunity, like, for example, trauma, will speed up ageing. Most laser and RF companies pay scientists to do research and then pay well-known journals to publish their papers. Journals usually charge double if the device’s name is mentioned. Irrespective of how prestigious the scientists who compose this funded research are, funded research is advertising. What is important to remember is that advertising is brainwashing designed to sell, not offer factual evidence. Truth and marketing are incompatible.

The hidden “bad & ugly” aspects of stem cells

Stem cells offer tantalizing prospects for anti-ageing and regenerative medicine. They are used for skin repair, hair growth and the maintenance of various adult tissues and organs. They can modulate numerous incurable diseases such as heart conditions, diabetes, brain injuries etc.^{30,31}

The coin has two sides, and stem cells advocates focus on the positive one—the miracles of transplanting undifferentiated embryonic stem cells to cure a variety of diseases, without bona fide evidence from large well-controlled studies with proven validity and reliability. Even mesenchymal stem cells (MSCs) which are relatively safe from malignant transformations, and do not stir up ethical controversies, have limited clinical usefulness due to cellular senescence that impairs their differentiation potential leading to uncontrolled proliferation and tumour formation. Ageing is not the only process that diminishes the function of MSCs. Their phenotype is affected by the donors’ heterogeneity, the culture condition, and the cell passage in the body.³²⁻³⁴

The key factor that determines the usefulness of stem cells is differentiation. Cells must differentiate to become specialized cells, such as skin, bone, muscle, blood, immune cells, etc. Arrested differentiation leads to uncontrolled proliferations which results in the formation of possible malignancies.

Cellular differentiation depends on the increased ratio between:

- I. Mitochondrial differential that promotes activity, and
- II. Nuclear differentiation that prevents activity.

Embryonic stem cells have a low ratio and therefore a compromised differentiation potential, due to low mitochondrial content. Mutations in nuclear genes coding for mitochondrial proteins decrease the

differentiation rate leading to neoplastic growth, another word for tumours that may be benign, or malignant cancers.³⁵⁻³⁷

Embryonic stem cells (ESC) are established by using cells obtained from the inner cell mass of an early-stage human or animal embryo. Many protocols have been established for the differentiation of human or animal ESCs into numerous mature and functional cell types. Nevertheless, clinical application of ESCs, especially in the anti-ageing industry remains controversial due to concerns about teratoma formation and ethical issues raised from the embryonic source of the tissues.³⁸⁻⁴¹ There is normal and uncontrollable proliferation that aimlessly continues with deleterious effects on the body. Proliferation and differentiation are like a seesaw: when one goes up the other goes down.⁴² Cellular proliferation increases with age while differentiation decreases which is why cancers are more common in older individuals. Importantly, differentiation is blocked in cancer cells which have an unlimited proliferative capacity to form teratomas. Cellular proliferation without differentiation is dangerous. We don't need more cells. We need more **differentiated** cells.

One of the main difficulties with Embryonic Stem Cells is immunorejection. Promoting stem cells' graft acceptance is more difficult than host acceptance of a vascularized organ like a heart. Some researchers have used antibodies to block normal T-cell activation to reduce immunorejection and increase the EMC's systemic acceptance. However, such techniques win the battle over immunorejection and, by incapacitating the immune system, they lose the war over tumours growing unobstructed since the immune soldiers are temporarily paralyzed. Tumorigenesis is the main danger with EMC's and a worse problem than immunorejection.³⁰ Anti-ageing professionals should know that; yet, they focus on counteracting immunorejection in the pursuit of fast instant results, at the risk of exposing their patients to paralyzed immune soldiers and eventual cancers. This fast instant results' wish-fulfilment is the crux of social brainwashing that places beauty above health, and temporary symptom improvement over overall wellness.

The Nobel Prize in Physiology or Medicine 2012 was given to Sir John B Gurdon and Shinya⁴³ for their discovery of reprogramming mature cells to become "induced Pluripotent Stem Cells (iPSCs), Takahashi, et al.,⁴⁴ reprogrammed terminally differentiated fibroblasts by the transduction of four defined transcription factors Oct 3/4, Sox2, KLF-4, in addition to LIN-28 and Nanog, successfully producing iPSCs' differentiation into neurons, cardiomyocytes, retinal epithelial and pancreatic islet. iPSCs win the war over ethical issues attached to EMCs but being pluripotent, they also have the disadvantage of teratoma formation.

Bottom line, stem cells are useful and miraculous until they are not.

The myth of going back in time

As previously stated, refilling biological deficiencies is a simplistic approach to a complex problem. The body is a Gestalt that is more than the parts that compose it. A Gestalt is the "je ne sais quoi" a quality that cannot be described because it rises above and is not included in any biological process that we can identify individually, since it is a new entity synthesized by the interaction of different biological processes. The Gestalt (the je ne sais quoi) is what constitutes beauty, creativity, health, multi-intelligence and individual differences defining the uniqueness of an individual. The body is not an empty vessel that is filled at birth with supplies that eventually diminish until they completely run out. The body is an alive organism with multiple,

often unpredictable intercommunications, intracellularly, as well as in between the biological entity and the environment. The body is an interactional entity full of undiscovered or unknown processes with a wisdom that is beyond our understanding; therefore, there is no guarantee that our specific bodies will accept and/or utilize fillers, botox, stem cells, laser and RF procedures, etc without any adverse reactions or side effects. Basically, the anti-ageing industry focuses only on the "good" aspects of these procedures but not on the "bad and the ugly."

All the excitement about collagen increase underreports the fact that youth and health depend on the interaction of about 100,000 proteins in our body, and collagen alone is primarily involved in scar formation. There are no experimental laser and RF studies that investigate the possibility of a deficiency in another site of the body accompanying the collagen increase on the site where the laser or RF was applied.

Longitudinal studies examining inflammatory interleukins and C-reactive protein levels are necessary to confirm that trauma-based cosmetic procedures do not speed up ageing eventually, due to accumulated inflammation. Inflammation is generally considered to be one of the main reasons for ageing and disease, along with increased toxicity and oxidative damage. Importantly, immunity-enhancing interventions should be incorporated in an anti-ageing treatment plan. Some of them have been around for years and others are based on new scientific discoveries.⁴⁵⁻⁵⁷

Immunity enhancing interventions

Different types of exercise including effortless exercise have been recommended worldwide by health practitioners as a primary or secondary intervention for health problems that include glucose metabolism, liver function, inflammation, immune function and hormonal balance. Various exercise modalities have established a documented decrease in inflammation, cholesterol and visceral fat, and an optimal increase of Triiodothyronine (T3), testosterone and DHEA. Additionally, there is evidence of long-term optimal hepatic functioning, such as reaching optimal levels of albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT) and bilirubin.⁵⁸⁻⁶⁴ Sonography reports have confirmed a significant increase in liver health

Caloric restriction is one of the most effective nutritional methods. This includes intermittent fasting which has been proven to extend the life of mammals by upregulating the expression of the silencing complex of microRNAs (miRNAs). miRNAs are involved in cell growth, division and differentiation as well as the metabolism and development of an organism.^{65,66} There has been extensive research on herbal medicine, dietary supplements and their positive effects on wellness. Diet and lifestyle have also been recommended for years as health-enhancing methods. More scientifically advanced methods such as FRET and Resonance Signalling have been used for wound healing, and relief from neuropathic pain with permanent results offering a complex understanding of a technology that can repair cellular pathways and reinstate biocommunication.⁶⁷ There can only be one kind of anti-ageing, and that involves methods that promote wellness and longevity. The rest is like a temporary Band-Aid for short-lived beauty without the underlying health, and results that eventually rebound. In the absence of longitudinal studies to confirm long-term efficiency and safety and in the presence of occasional severe adverse reactions and side effects, several of today's technologies should be scrutinized with caution before being utilized for any purpose.

Conclusion

In conclusion, longitudinal studies examining inflammatory interleukins and C-reactive protein levels are necessary to confirm that trauma-based cosmetic procedures do not speed up ageing eventually, due to accumulated inflammation. Inflammation is generally considered to be one of the main reasons for ageing and disease, along with increased toxicity and oxidative damage.

As technology advances it actualizes new methodologies that were previously wishful theories. We have the means to use FRET and capitalize on the new scientific discoveries of resonant energy-transfer techniques to balance the body and enhance the potency and integrity of the immune system that should be center stage of regenerative and preventive medicine.

Statement of ethical approval

This study was performed in accordance with the ethical standards of medical research involving human participants as cited by:

- I. Ethical principles for medical research involving human subjects
- II. American Psychological Association (APA)
- III. Ellios Research Department for Development and Invention of Innovative Technology.

Conflict of interest

The author declares no conflict of interest. This study was conducted by independent operators who were not employed or contracted by the author.

Funding

No funding was received by a third-party or institution.

References

1. Jalian HR, Avram MM, Garibyan L, et al. Paradoxical adipose hyperplasia after cryolipolysis. *JAMA dermatol.* 2014;150(3):317–319.
2. Derrick CD, Shridharani SM, Broyles JM. The safety and efficacy of cryolipolysis: a systematic review of available literature. *Aesthet Surg J.* 2015;35(7):830–836.
3. Stroumza N, Gauthier N, Senet P, et al. Paradoxical adipose hypertrophy (PAH) after cryolipolysis. *Aesthet Surg J.* 2018;38(4):411–417.
4. Nikolis A, Enright KM. A multicenter evaluation of paradoxical adipose hyperplasia following cryolipolysis for fat reduction and body contouring: a review of 8658 cycles in 2114 patients. *Aesthet Surg J.* 2021;41(8):932–941.
5. Michaloglou C, Liesbeth CWV, Maria SS, et al. BRAFE600-associated senescence-like cell cycle arrest of human naevi. *Nature.* 2005;436(7051):720–724.
6. Chowdhury D, Lieberman J. Death by a thousand cuts: granzyme pathways of programmed cell death. *Annu Rev Immunol.* 2008;26:389–420.
7. Zhang Q, Raoof M, Chen Y, et al. Circulating mitochondrial DAMPs cause inflammatory responses to injury. *Nature.* 2010;464(7285):104–107.
8. Hopf TA, Colwell LJ, Sheridan R, et al. Three-dimensional structures of membrane proteins from genomic sequencing. *Cell.* 2012;149(7):1607–1621.
9. Ovadya Y, Landsberger T, Leins H, et al. Impaired immune surveillance accelerates accumulation of senescent cells and ageing. *Nat Commun.* 2018;9(1):5435.
10. Fülöp T, Larbi A, Witkowski JM. Human inflammaging. *Gerontology.* 2019;65(5):495–504.
11. Sofra, X. Gain without Pain: Beyond Sport Effortless Exercise Solutions. *Journal of Aesthetic Nursing.* 2020;9(5):202–210.
12. Sofra X. Liver Repair of NAFLD patients, Following Effortless Exercise and the Possible Involvement of Endogenous Stem Cells. *J Diab Metab Disorder.* 2022;9(1):36–47.
13. López Otín C, Blasco MA, Partridge L, et al. The hallmarks of aging. *Cell.* 2013;153(6):1194–1217.
14. Van Deursen JM. The role of senescent cells in ageing. *Nature.* 2014;509(7501):439–446.
15. Toumi H, Best TM. The inflammatory response: friend or enemy for muscle injury? *Br J Sports Med.* 2003;37(4):284–286.
16. De Heredia FP, Gómez Martínez S, Marcos A. Obesity, inflammation and the immune system. *Proc Nutr Soc.* 2012;71(2):332–338.
17. Yao X, Li H, Leng SX. Inflammation and immune system alterations in frailty. *Clin Geriatr Med.* 2011;27(1):79–87.
18. Chow MT, Möller A, Smyth MJ. Inflammation and immune surveillance in cancer. *Semin Cancer Biol.* 2012;22(1):23–32.
19. Legein B, Temmerman L, Biessen EA, et al. Inflammation and immune system interactions in atherosclerosis. *Cell Mol Life Sci.* 2013;70(20):3847–3869.
20. Saloman JL, Cohen JA, Kaplan DH. Intimate neuro-immune interactions: breaking barriers between systems to make meaningful progress. *Curr Opin Neurobiol.* 2020;62:60–67.
21. Kandel ER, Squire LR. Neuroscience: Breaking down scientific barriers to the study of brain and mind. *Science.* 2000;290(5494):1113–1120.
22. Wessler I, Kirkpatrick C. Acetylcholine beyond neurons: the non-neuronal cholinergic system in humans. *Br J Pharmacol.* 2008;154(8):1558–1571.
23. Chaban V, Cho T, Reid CB, et al. Physically disconnected non-diffusible cell-to-cell communication between neuroblastoma SH-SY5Y and DRG primary sensory neurons. *Am J Transl Res.* 2013;5(1):69–79.
24. Ma R, Chen L, Hu N, et al. Cilia and extracellular vesicles in brain development and disease. *Biol Psychiatry.* 2024;95(11):1020–1029.
25. King M, Walker L, Convery C, et al. Management of a vascular occlusion associated with cosmetic injections. *The Journal of clinical and aesthetic dermatology.* 2020;13(1):E53–E58.
26. Armstrong JR, Ferguson MW. Ontogeny of the skin and the transition from scar-free to scarring phenotype during wound healing in the pouch young of a marsupial, *Monodelphis domestica*. *Dev Biol.* 1995;169(1):242–260.
27. Zuckerkandl E, Pauling L. Evolutionary divergence and convergence in proteins. *Evolving genes and proteins.* 1965;97–166.
28. Graur D. Amino acid composition and the evolutionary rates of protein-coding genes. *J Mol Evol.* 1985;22(1):53–62.
29. Zhang Z, Harrison PM, Liu Y, et al. Millions of years of evolution preserved: a comprehensive catalog of the processed pseudogenes in the human genome. *Genome Res.* 2003;13(12):2541–2558.
30. Faiella W, Atoui R. Therapeutic use of stem cells for cardiovascular disease. *Clin Transl Med.* 2016;5(1):1–8.
31. Hsuan YCY, Lin CH, Chang CP, et al. Mesenchymal stem cell-based treatments for stroke, neural trauma, and heat stroke. *Brain Behav.* 2016;6(10):e00526.
32. Park JS, Kim HY, Kim HW, et al. Increased caveolin-1, a cause for the declined adipogenic potential of senescent human mesenchymal stem cells. *Mech Ageing Dev.* 2005;126(5):551–559.

33. Duscher D, Rennert RC, Januszyk M, et al. Aging disrupts cell subpopulation dynamics and diminishes the function of mesenchymal stem cells. *Sci Rep*. 2014;4(1):7144.
34. Turinetti V, Vitale E, Giachino C. Senescence in human mesenchymal stem cells: functional changes and implications in stem cell-based therapy. *Int J Mol Sci*. 2006;17(7):1164.
35. Mandal S, Lindgren AG, Srivastava AS, et al. Mitochondrial function controls the proliferation and early differentiation potential of embryonic stem cells. *Stem cells*. 2011;29(3):486–495.
36. Khacho M, Clark A, Svoboda DS, et al. Mitochondrial dynamics impacts stem cell identity and fate decisions by regulating a nuclear transcriptional program. *Cell stem cell*. 2016;19(2):232–247.
37. Seo BJ, Yoon SH, Do JT. Mitochondrial dynamics in stem cells and differentiation. *Int J Mol Sci*. 2018;19(12):3893.
38. Fujita J, Crane AM, Souza MK, et al. Caspase activity mediates the differentiation of embryonic stem cells. *Cell stem cell*. 2008;2(6):595–601.
39. Chen G, Hou Z, Gulbranson DR, et al. Actin-myosin contractility is responsible for the reduced viability of dissociated human embryonic stem cells. *Cell stem cell*. 2010;7(2):240–248.
40. Wang X, Li T, Cui T, et al. Human embryonic stem cells contribute to embryonic and extraembryonic lineages in mouse embryos upon inhibition of apoptosis. *Cell Res*. 2018;28(1):126–129.
41. Peng Y, Ma A, Xiao Z, et al. Technical specifications for ethics review of human stem cell research. *Cell Prolif*. 2023;57(3):e13556.
42. Zhu L, Skoultschi AI. Coordinating cell proliferation and differentiation. *Curr Opin Genet Dev*. 2001;11(1):91–97.
43. Gurdon J, Yamanaka S. *The Nobel Prize in Physiology or Medicine 2012*. Nobel Prize Outreach AB 2024. 2012.
44. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell*. 2006;126(4):663–676.
45. Franceschi C, Garagnani P, Vitale G, et al. Inflammaging and ‘Garb-aging’. *Trends Endocrinol Metab*. 2017;28(3):199–212.
46. Franceschi C, Garagnani P, Parini P, et al. Inflammaging: a new immune–metabolic viewpoint for age-related diseases. *Nat Rev Endocrinol*. 2018;14(10):576–590.
47. Haworth R, Sharpe M. Accept or reject: the role of immune tolerance in the development of stem cell therapies and possible future approaches. *Toxicol Pathol*. 2021;49(7):1308–1316.
48. Sofra X, Lampe N. Empowering the Woman: A Comprehensive Model of Sexual Anti-Ageing. *Journal of Aesthetic Nursing*. 2020;9(3):118–127.
49. Sofra X. How to get rid of visceral fat: a randomised double-blind clinical trial. *Journal of Aesthetic Nursing*. 2020;9(7):268–275.
50. Sofra X. Gain without pain: beyond sport effortless exercise solutions. *Journal of Aesthetic Nursing*. 2020;9(5):202–210.
51. Sofra X. The Importance of Systemic Balance in Safeguarding Health: A Randomized Double-Blind Clinical Trial on VLDL, Triglycerides, Free T3, Leptin, Ghrelin, Cortisol and Visceral Adipose Tissue. *Health*. 2020;12(8):1067–1084.
52. Sofra X, Badami S. Adverse Effects of Sedentary Lifestyles: Inflammation, and High-Glucose Induced Oxidative Stress-A Double Blind Randomized Clinical Trial on Diabetic and Prediabetic Patients. *Health*. 2020;12(8):1029–1048.
53. Sofra X, Lampe N. A Randomized Longitudinal Double-Blind Clinical Trial on Long-Term Neuropathic Symptomatology Relief & Pain Analgesia. *Health*. 2020;12(7):738–749.
54. Sofra X, Badami S. A Review of COVID-19 associated factors: CRP, Creatinine, Bilirubin, VLDL, HDL, Triglycerides, Cortisol and Thyroid Function. *J Endo Metabol Res*. 2020;1(2):1–17.
55. Sofra X. Dynamics of Female Sexuality; Hidden Emotional Issues. *Health*. 2020;12(6):694–708.
56. Sofra X. The Affinity between Obesity and COVID-19. *J Endo Metabol Res*. 2020;1(2):1–13.
57. Sofra X, Badami S. A Review of COVID19 associated factors: CRP, Creatinine, Bilirubin, VLDL, HDL, Triglycerides, Cortisol, and Thyroid Function. *J Endo Metabol Res*. 2020;1(2):1–17.
58. Hashida R, Kawaguchi T, Bekki M, et al. Aerobic vs. resistance exercise in non-alcoholic fatty liver disease: A systematic review. *J Hepatol*. 2017;66(1):142–152.
59. Aamann L, Dam G, Rinnov AR, et al. Physical exercise for people with cirrhosis. *Cochrane Database Syst Rev*. 2018;12(12):CD12678.
60. Romero Gómez M, Zelber Sagi S, Trenell M. Treatment of NAFLD with diet, physical activity and exercise. *J Hepatol*. 2017;67(4):829–846.
61. Sofra X, Badami S. Adverse effects of sedentary lifestyles: Inflammation, and high-glucose induced oxidative stress— A double-blind randomized clinical trial on diabetic and prediabetic patients. *Health*. 2020;12(8):1029–1048.
62. Sofra X. The Importance of Systemic Balance in Safeguarding Health: A Randomized Double-Blind Clinical Trial on VLDL, Triglycerides, Free T3, Leptin, Ghrelin, Cortisol and Visceral Adipose Tissue. *Health*. 2020;12(8):1067–1084.
63. Sofra X. How to get rid of visceral fat: a randomised double-blind clinical trial. *Journal of Aesthetic Nursing*. 2020;9(7):268–275.
64. Kogure A, Uno M, Ikeda T, et al. The microRNA machinery regulates fasting-induced changes in gene expression and longevity in *Caenorhabditis elegans*. *J Biol Chem*. 2017;292(27):11300–11309.
65. Connolly PH, Caiozzo VJ, Zaldivar F, et al. Effects of exercise on gene expression in human peripheral blood mononuclear cells. *J Appl Physiol (1985)*. 2004;97(4):1461–1469.
66. Sofra X, Lampe N. A Randomized Longitudinal Double-Blind Clinical Trial on Long-Term Neuropathic Symptomatology Relief & Pain Analgesia. *Health*. 2020;12(7):738–749.
67. Sofra X, Lampe N. Technological Advances in Accelerated Wound Repair and Regeneration. *Health*. 2020;12(7):717–737.