Approaches to Aging Control

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Panel Antiaging

Estudiar nuestro organismo, nuestros genes y nuestros hábitos permite establecer pautas para mejorar nuestra calidad de vida

PERFIL A MEDIDA, TOTALMENTE PERSONALIZABLE

- [ ] Hematología básica
- [x] Perfil oxidativo
- [ ] Glicosilación
- [ ] Marcadores inflamación
- [x] Daño / Reparación ADN
- [ ] Perfil hormonal
- [ ] Ácidos Grasos / Membrana eritrocitaria
- [x] Perfil coagulación
- [ ] Perfil digestivo
- [ ] Elementos minerales en sangre
- [x] Elementos minerales en orina
- [ ] Elementos minerales en orina basal y trasquelación
- [ ] Perfil hepato-renal
- [x] Metabolismo óseo
- [ ] Perfil cardiovascular
- [ ] Perfil metabólico
- [ ] Perfil neurodegenerativo
- [ ] Perfil tumoral
- [x] Perfil infeccioso
- [ ] Perfil inmunitario
- [ ] Perfil bioquímico
- [ ] Pruebas genéticas

REPRESENTACIÓN GRÁFICA DE RESULTADOS

El informe de resultados recoge de forma gráfica su estado de salud para facilitar una rápida interterpretación de los diferentes parámetros analizados.

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SUMARY

Nº 18 - SEPTEMBER 2014

Editorial

Our health or risk of disease depends on our biologic responses to what we eat, drink, and breathe. Our environment is full of synthetic chemicals that contaminate every ecosystem in the world. Virtually, all people are regularly exposed to a complex mixture of industrial chemicals that did not previously exist in human history. Rapid industrialization and nearly ubiquitous contamination of air, soil, and water with hazardous waste, by products of resource extraction, fossil fuel combustion, and synthetic chemicals continued during the 20th century.

Chemicals include lead and other heavy metals, PCBs and other persistent organic pollutants, pesticides, endocrine disruptors, Bisphenol A, food additives. etc, some of them persistent and bioaccumulative. Also, a number of prescription and non-prescription drugs or their metabolic byproducts, including antibiotics, anti-inflammatories, antidepressants, cholesterol-lowering agents, and hormones are present in surface waters and drinking water sources around the country.

Indoor environment is also important. Many people now spend more than 90 percent of their time in buildings. In many buildings, indoor air is contaminated with a complex mixture of chemicals from many sources. Disease risks related to the indoor environment vary with levels of specific contaminants but can include asthma, bronchitis, cancer, and reproductive, developmental, and neurological disorders.

An important issue is that health in the later years of life strongly depends on health in earlier years. Several studies have shown that the umbilical cord blood of newborn babies contain more than 200 toxic compounds, which are reported to cause cancer in humans or animals, brain and nervous system toxicity and developmental and reproductive problems. These results indicate that most of the time we are exposed to many toxic substances without knowing it.

Many pollutants known to affect human health are gradually coming under regulatory control. However, there are emerging issues for which environmental pathways and effects on health are as yet poorly understood. Examples are electromagnetic fields. While some progress has been made in the regulation of toxic substances, there remain thousands of chemicals that haven't been reviewed. The number of chemicals in commerce is around 150.000. However, only 200 of them have been reviewed for their impact on human health and the environment. Maybe this is the reason why breast, testes, thyroid, prostate and ovaries cancer rise continuously even at early ages.

Nowadays, more is known about the molecular mechanisms that are activated by the human-environmental interactions. These processes include gene mutation, enzyme induction, oxidative stress, inflammation, changes in membrane permeability and hormone disruption. All these changes contribute to the risk of neuroinflammation, neurodegeneration and cardiovascular disease.

In summary, a clean environment is essential for human health and well-being. Key elements to minimize the impact of environmental factors are eating healthy, staying active physically and mentally, avoiding harmful toxicants and pollutants. Healthy nutrition is essential, beginning with fetal development. Lifelong nutrition is strongly connected with health in later years. Inventory your home for hazardous materials you may be using for home cleaning and maintenance, garden care and personal care and replace with less-toxic alternative products or processes. Be aware of the specific contaminants in drinking water and filter if necessary. Eliminate or reduce pesticide use in the home and on lawns and gardens, etc.

However, individual actions are not enough and policy interventions at many levels are necessary: For example: encouraging more localized, diversified and sustainable food production rather than factory farming would enhance nutrition, would reduce reliance on pesticides and minimize the use of fossil fuels for long distance transport. Transitioning to clean, renewable energy and reducing fossil fuel consumption in general would drastically reduce air pollution. It is also important favoring the development of energy-efficient mass transit and the construction of bike paths.

Sevilla is the fourth best city in Europe in terms of number of km of bike lanes. The council, the university and many other institutions have been working to encourage cycling. The goal is to save energy while minimizing air pollution and combating obesity (by the way, our pre-congress courses focus on these two important issues -Environmental Medicine and obesity). These policies are examples of interventions that would help to address the oncoming wave of age-related chronic disease.

Obesity is a "Communicable" Mind Disease.

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Keywords. Body, Mind, Cognition, Obesity.

Abbreviations

E: Extroversion; I: Introversion; BMI: Body Mass or Mind Index; CD: communicable diseases; NCD: non-communicable diseases; GIT: Gastro-Intestinal Tract; Ω: Omega; %en: Percentage of Energy Intake; bIT: biological Information Technology.Abstract

It is remarkable that animals including man in the wild do not suffer overweight. Even modern husbandry animals don't. In contrast, companion pets may and societal man does. The human part – the mind – appears responsible for the disease. It is important to analyze facts as primary and secondary risk factors. Food is here secondary. It contributes, yet not causes the problem. Just as cholesterol contributes, but not causes heart disease. (www.columbus-concept.com). Once understood & accepted, such basic principle allows one to take the right decision: to consult a psychologist prior to a nutritionist in any potentially successful attempt of addressing the problem of overweight. Overweight expresses mind strain. Reducing that strain through tracing back the environmental stressor causing & fuelling it will go a long way in reducing the burden of obesity in mankind. (www.tsimtsoum.net)Introduction

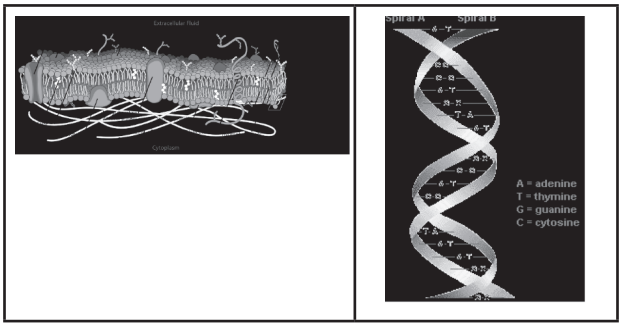
To be "lean & fit" at the image of animals in the wild logically appears as an optimum in terms of body health. Variants in the gradient all the way from "fat & fit" to "lean & lazy" are other respectable body health standards among animals – including humans – roaming in tamed environments. The "fat & lazy" comes as least encouraged phenotype, body health-wise. Of course, animals adapt to their environments and body shape and condition are fairly well predicted on environmental / cultural grounds. Memes appear central. Yet, biases to the rule are no exception within humans; the "lean & fit" evolutionary standard is found here and there, now and then, but then perhaps more as – or perceived as – rebel to one's own environment / culture. Cognition appears critical to weight management in tamed environments and as corollary humans have therefore the potential to succeed where theoretically animals could not. Obesity is a communicable mind disease (CD), not a non-communicable body disease (NCD). Adjusting sight on the epidemic – a cognitive process on its own – would help a long way addressing and tackling it, efficiently.

Facts

Barn chickens fed mesh feeds ad libitum do not take on weight, no exception. Home pets spoiled with human varied foods all become obese, no exception. Laboratory rats fed either standardized rat ration or more sophisticated human ration don't or do become obese, as a rule. From those basic inter-convertible observations repeatable at length, one must conclude that food variety – not quantity – is the primary issue. Humans in general appear to behave very similarly to their un-conscious animal counterparts, at a difference of size though: there appears to be no rule per se within humans; some will take on weight and/or become obese under certain conditions, some others not. It is like there would be some potential – not necessarily activated – resistance

mechanisms in place within humans to eventually counteract the nature-derived tendency of wolfing on attractive foods, variety being just one aspect of it. Such mechanisms are obviously cognitive and depend on the capabilities of analyzing and scoring facts, balancing choices and taking Cartesian decisions.

The non-cognitive mind is of course a biological characteristic of all animals, from barn chickens to home pets to laboratory rats to humans. We have reported earlier on the hypothesis that cell membranes are in fact the substrate of the mind and on how fatty acids in cell membrane phospholipids can absorb, process and transfer information (memes) (figure 1) [1].



The mind therefore captures information related to the ever broadening variety of attractive foods and attractive ways of marketing them. In fact, as marketing become a science on its own, one should probably state this the other way round, ie foods are made attractive through ever more refined communication and marketing tools, and ever more broadening and appealing variety. A scoop of ice cream can be presented and perceived as a banal desert to a routine meal or a unique orgasm to experience at a unique point in time or anything in between depending on the targeted audiences and the tools selected to reach out with them. Such example is illustrative of the mind-wash humans are submitted to in tamed environments, name them modern societies. Information is being propagated in all more sophisticated ways one from the other – from appearance to experience to perspective – in order to reach target, ie short term memory and, in fine, provoking the immediate action, ie purchasing act & use (ingestion). So far so good, this is the basis of modern economy, not an excuse for becoming obese; there is per se no obligation to purchase and consume.

The disease – obesity – requires that short transforms into long term memory, ie mindset, from where if not an obligation purchasing / consuming may turn into an (unconscious) automatism. Such transformation requires passing over a barrier, ie cognition. Humans are equipped with a cognitive brain which at all times would logically restrict them from taking on weight, if only for the price to pay post weight gain – but do not use it for whatever reasons may be and leave the non-analytical mind diffuse into and eventually imprint as meme the long term memory, with the expected outcome, ie the body takes on weight. In Hippocrates words, "the body falls sick", but really the mind is diseased. In that respect, the BMI would benefit from being re-coined body-mind index, in substitution for the current misleading reference to the consequence, ie the body-mass index, rather than the cause.

As many other degenerative chronic diseases – whereby information in one way or another appears to have taken over the ability of humans to analyze and think – obesity is a mind disease. Human being a social animal, obesity becomes – in turn – a communicable disease. But, clearly, the cognitive brain is faulty and from that perspective, overweight and obese humans behave as chickens, pets, and laboratory rats, ie un-conscious mindset digitized robots, save their respect.

Socrates stated it in his way as human commander ahead of his time (or perhaps not, depending on where we consider ourselves being today next to our long gone civilized ancestors): "don't be taught, learn". It says it all here along our analysis on causality between food and body fat, which could be ending as "don't leave your mind (environmental memes) decide, use your brain (cognition)".

Information is in need, ever more, but at the same time, data analysis and processing becomes essential, ever more. Listening, looking, reading, feeling, smelling, touching are fine to the extent that the short term acquired information can be

analyzed down to its relevant meaning (ie an orgasm-type ice cream is most probably worth trying! – and, if true, then worth enjoying scarcely enough (in order to ensure orgasm at each time, forever) prior to being transferred as information / meme to the long term memory, and transform into mindset.

Within that framework of understanding, AP Simopoulos [3] once outlined the following two basic dietary principles of the Paleolithic, Homo sapiens, body regimen:

1. Energy Balance

- Expenditure = Intake, ie constant body composition.
- Slow Digestion, ie slow & constant uptake from GIT.

Layman term meaning: Do not take on body fat. Be active.

2. Essential Nutrient Balance

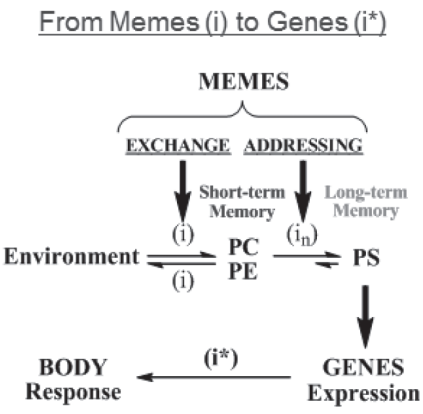
- ± 10% of total energy intake (%en) = essential nutrients.
- Optimized biomarkers for competing essential nutrients, ie Ω6/3 ≈ 1:1.

Layman term meaning: Don't be addicted. Have a complex diet.

Those are fairly easy to understand and to apply principles, yet their understanding and application appear a challenge for many, and reasons to circumvent them as many as there are overweight and obese humans around. With regards to their understanding, first, body fat is not synonymous with body weight, yet most people still rely on a body scale to try complying with the first principle and, as a result, sacrifice muscle for fat with age, thereby promoting degenerative diseases at constant weight; second, non-essential nutrients such as cholesterol, saturated fats, sugar and the like are not relevant in terms of health because simply they do transform into one another, metabolically; essential amino/fatty acids, vitamins and minerals – accounting for some 10% of the daily energy intake (%en), are what counts when it comes to health. This is for the second principle.

Missing target on these two basic evolutionary principles (memes) leads to the inception of so far referred to as degenerative chronic non-communicable diseases – referring to the body as per Western Medicine standards. Tissue inflammation appears central in the deregulation of metabolic pathways that set into place as a result of the long term dietary insults. In that respect, the deviation of the essential omega-6/3 fatty acids make-up of modern diets from its duly established evolutionary standard has most probably precipitated the outcome, ie explosive rates world wide of morbidities and mortalities related to NCD's of all sorts.

A change of mindset is needed. The brain still can help, though probably far more laboriously than if we had educated Socrates' School of Thought earlier on, pro-actively (figure 2) [2].



Within that second framework of understanding, RB Singh [3] once outlined the following two basic information principles of the Contemporary, Homo modestis, mind regimen:

1. Information Balance

- Given = Taken, ie constant mind composition.
- Slow Imprint, ie slow & constant uptake to long term memory (MINDSET).

Layman term meaning: Don't be brain-washed. Learn.

2. Essential Information Balance

- ± 10% of total information intake = essential information.
- Optimized biomarkers for competing socio-psychological influences, ie pE/I ≈ 1:1.

Layman term meaning: Don't lie to yourself. Be true to yourself.

Conclusion

In short, it appears that the mind must be managed in a very similarly wise manner as the body. Investing into understanding how cell membrane fatty acids may work as biological grids for recording / processing environmental information (bIT: biological information technology) will help Human Medicine keep climbing the ladder. And in that respect, MA Crawford confirms that the 600 million old docosahexanoic acid (DHA) may very well play a pivotal role [4].

In the meantime, and as we progress on the understanding of the origin, presence and perspective of Humans on Earth and in the Universe, a re-balancing of omega-6/3 fatty acids at tissue level might be a quick safe fix for increasing body resistance to chronic degenerative diseases, be they mind- or/and body-derived.

Acknowledgements

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Figure Legends

Figure 1. Memes and genes shown here as their evolved repeatable and rhythmical basic elements, ie cell membranes and deoxyribonucleic acid.

An illustration of the memes/genes interaction is provided by the visible light-sensitive retino-hypothalamic tract to the suprachiasmatic nuclei, allowing for synchronization of circadian rhythms in cells of complex organisms. Cell membrane (http://cellbiology.med.unsw.edu.au/units/images/Cell_membrane.png). Deoxyribonucleic acid (http://library.thinkquest.org/C004535/cell_membranes.html).

Figure 2. Obesity is a mind CD (communicable disease). The diagram shows how environmental information (i) access the short term memory (RAM: cell membranes phosphatidyl-choline PC & -ethanolamine PE) and eventually got addressed as more complex information (in) into the long term memory (ROM: cell membranes phosphatidylserine PS), to then influence genes expression and body response. The addressing step is (or should be) a cognitive process, thereby distinguishing animals from humans.

Burnout: A modern epidemy

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Burnout is a global problem, which is triggered both by personal circumstances through increasingly complex individual demands, as well as multifactorily in the global world of profession (11). Stress-related diseases, which includes burnout, are increasing fastly and concern today 27.4% (mental illness) to 45% (burnout) of the population within the European Union, with total costs of 74 billion € per year in Germany (27). For several years, the problem is dubbed in both the lay press and in specialized media and discussed intensively even as a "fashion-diagnosis" (11).

In fact, burnout is not described by conventional medicine as a distinct disease, but only as a "key factor" which affects health status and claims takeover of health care leads.

A core problem of inadequate characterization is certainly the fact that over a long period burnout has been characterized almost exclusively symptomatically by psychologists and psychotherapeuts, a deeper biological definition using biomarkers started only a few years ago.

The **key symptom of burnout is "exhaustion",** which occurs after excessive stress, during depression and Chronic Fatigue Syndrome (CFS), but also due to other organic diseases (eg chronic inflammation, blood disorders, heart failure, sleep disorders aso) (28)

Psychological burnout has been described as related to a personal crisis, as an emotional reactive process, associated with disability, personal suffering and considerable cost (2). Psychiatry considers burnout less related to chronic stress, but rather as a sign of increased psychopathological vulnerability. In fact, associations to depression and anxiety disorders are fluid and require a consistent and accurate differential diagnostic procedure (15). Numerous studies however show that burnout primarily represents a stress-related exhaustion with individually differentiated psychogenic and biological findings and exhaustion of the stress-response-systems within the central nervous system (CNS), adrenal cortex, and the vagus-controlled regeneration (14, 18, 29)

For a better understanding of the complex entity of burnout the following considerations related to the psycho-social and biological phenomena of burnout are developed.

1. Psychosocial background of burnout:

Freudenberger (5) firstly used the terminology "burnout" to describe the "wear and energy depletion due to overclaims arising from the inside or from the outside." Today the main factors of burnout are the continous mostly occupational "wear and tear" of the individuum due to the intense work processes, with high complexity and time pressure, ambiguous success criteria, hierarchical management style, limited space for own contributions, high effort, low reward, uncooperative working environment as well as routine and boredom (2, 12, 15, 19). Additional individual factors play an important role, like high personal requirements on everyday life, complex family structures, high-grade uncertainty, which act altogether with an significant ongoing stress

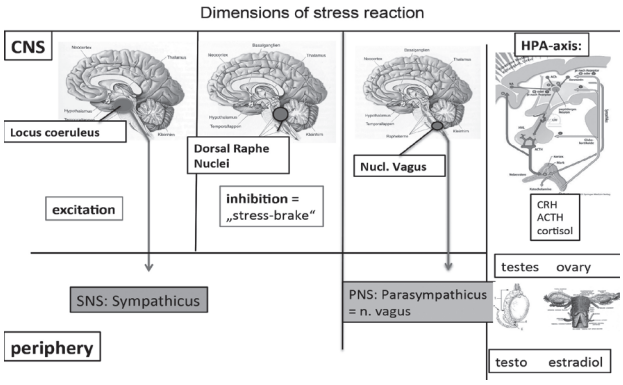


Fig 1: Description of five different dimensions of stress response: CNS, Limbic system and Locus coeruleus: Liberation of noradrenalin (less dopamin)
Dorsal Raphe Nuclei (DRN): secretion of serotonin as ¨stressbrake", for the limitation of the stress reaction
Nucl. Vagu: Parasympathicus fort he regulation oft he tonic regeneration after stress
Hypothalamus-pituitary-adrenal axis: CRF and ACTH stimulate the secretion of cortisol for the energy supply
Testes/ovary : Decrease of reproductive endocrine function of testosterone (male) and estradiol (female)

and pressure. In principle burnout may affect everybody, but preferably people in social services, free lancers, managers, but also the unemployed ("bore-out") (2). For the psychopathological development further additional individual dispositions such as personal stress reinforcement, inadequate stress management and unrealistic expectation describe the enhanced overall load.

Psychosocial science differentiates four major models of burnout-development which are partially confirmed by great studies:

Demand-control model , describing increasingly complex professional activities and low personal influence as a reason for occupational stress and exhaustion (10).

The professional **effort-reward imbalance (= gratification-crisis)** which is the most common and scientifically proven origin of burnout, with consequent psychosocial discomfort. An imbalance between a high level of personal overexpenditure and small gratuity are common triggers of burnout and depression (19, 20). The psychopathological context of effort-reward model by Siegrist was confirmed in many great studies (eg the Whitehall II study) with huge cohorts of professionals (22)

Less important theoretical models are:

Organization - justice, with organizational injustice causing emotional retreat (1) and

Trauma - embitterment, expressing trauma experience within the profession environment as the cause of chronic emotional numbness (15)

The development of burnout in terms of personal and emotional characteristics frequently starts with an initial enthusiasm, going over stagnation, frustration, apathy finally to burnout. These essential steps include an initial emotional exhaustion, tendency to fatigue, which can be caused by lack of gratification with low pay, low esteem, low job security, diminished professional carrier perspective etc (12, 20). This results in reduced engagement, emotional flattening, and development of emotional and existential despair symptoms.

The physical consequences are hypertension, cardiovascular diseases (especially myocardial infarction) and development of depression. It remains unclear whether burnout is a transition symptoms of psychopathology, or an intermediate step towars depression due to chronic stress.

2. Neurobiological causes for burnout: Chronic stress

The consequence of any permanent professional load is chronic stress. During stress exposition numerous central and peripheral neural, endocrine and immune functions are initiated, which have developed most effectively during the timecourse of evolution.

These particular stress reactions have different speed and importance:

• **Ultra-fast activation of the sympathetic nervous system** through massive reaction of the limbic system with stimulation especially of the locus coeruleus (LC) releasing its neurotransmitter norepinephrine. The entire sympathetic nerve

system (SNS)(is stimulated for „fight or flight“ (6, 26, 28)

Within the CNS, the amygdala contribute the type of emotional color in the direction of anxious or sovereign reaction. Stress-experience and its resulting learning process are simultaneously proceeded in the hippocampus.

• Parallel to the activation of the sympathetic system, the **serotonergic Dorsal Raphe Nuclei (DRN)** are co-stimulated for balancing and limiting the stress response. Its inhibitory neurotransmitter serotonin acts as a „stress brake“ within the central nervous stress-reaction (6, 26, 28)

• In the periphery an equally ultrafast and tonically mostly independent system is working: the regenerative and stress modulating function of the **Vagus Nerve (PNS = parasympathetic nerve system**). The main nuclei of the vagus nerve (nucleus ambiguus and vagal motor nucleus) can be blocked only by sympathetic input and develop their own tonic function and dynamics. So the diagnosis of low vagal activity by means of heart rate variability (HRV) is an independent significant parameter of stress (evaluation of stress exposure time and degree of regeneration) (24) .

• Parallel to the stimulation of the excitatory adrenergic system the paraventricular nucleus (PVN) secretes **cortisol-releasing hormone (CRH),** which stimulates via pituitarian ACTH the release of **Cortisol** from the adrenal cortex, a substrate essential for the maintenance of energy supply of the CNS.

• **The endocrine functions** of testes (testosterone production) in men and ovaries (production of estradiol) in women are reduced by chronic stress in delay (28)

The biological stress sequence is organized very complex with numerous links between the various stress associated organs, which are responsible for the individual features of the stress-response (29)

Generally the stress-reaction can be differentiated in

• **Reactive physical stress** (pain, osmotic or chemical signals, inflammation)

• **Anticipatory emotional stress,** mainly evoked by threat, novelty and uncertainty, frequently associated with emotional trauma, particularly in vulnerable life-phases, but also by long-term negative emotional influences with threatening character.

Biological stress substrates:

The main stress substrates in the CNS are **monoamines**, which are released ultrafastly and effectively. The main substances are the monoamines **serotonin, norepinephrine and dopamine**, which allow fast downstream reactions and are responsible for specific effects:

Norepinephrine and dopamine for fast generalized stress response („fight or flight“), optimization of perception, adrenergic cardiovascular and CNS response, risk assessment in the decision strategy (dopamine) (6, 26), whereas

serotonin limits the stress response as „stress-brake“ and the post stress-related anxiety response. Serotonin is generally responsible for the control of stress reactions. Interestingly the metabolism of the excitatory substrate norepinephrine has remained extremely compact and untouchable

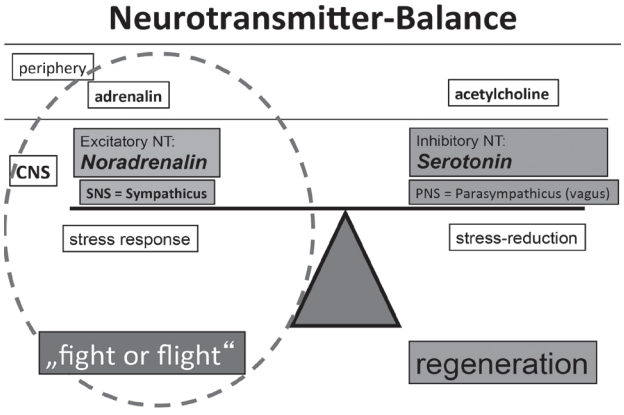


Fig 2: Schematic description oft he neurotransmitter balance between excitation (noradrenalin) versus inhibition (Serotonin) as well as SNS (= Sympathicus nerve system) and PNS (= Parasympathicus NS). While the stress response system is extremely stable during evolution, the serotonin system is very sensitive (hormone deficit, inflammation, nutrition).

during evolution, while serotonin metabolism has become extremely sensitive:

Hormone deficiencies (especially estradiol), chronic inflammation and permanent stress are reducing serotonin considerably, leading to a loss of CNS neurotransmitter-balance (28).

Among the **neuropeptides** the **CRH (cortisol-releasing hormone)** is of central importance. It is mainly released from from the Para Ventricular Nucleus (PVN) oft he hypothalamus and affects both the stress-memory and fear response, interacts with norepinephrine and stimulates the adrenal cortex (cortisol) via the pituitary gland (ACTH).

In a hyperexcitative state with increased release of CRH, hippocampus neurons and in particular dendritic spines are destroyed, triggering long-term regressive changes (6)

The release of **cortisol** from the adrenal cortex by CRH via ACTH is clearly subordinated and retarded. The diurnal, circadian rhythm shows highest cortisol values 30 min after awakening time, with linear decrease and lowest levels in the evening. After stress exposure cortisol increases with a peak after 30 minutes. Cortisol is transmitted through the blood-brain barrier into the CNS, where it is bound to high-affinity receptors (mineralocorticoid = MR and glucocorticoid receptors = GR). Cortisol also stimulates hepatic gluconeogenesis, so the CNS is continously supplied with continuous and adequate glucose levels (28)

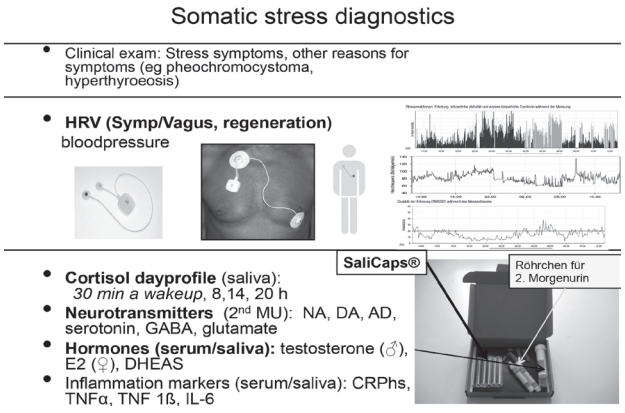


Fig 3: Sequence oft he somatic stress diagnostics, also needed in burnout patients

Nervus Vagus reaction:

Nucleus ambiguus and dorsal motor nucleus of the vagus nerve are separate, tonic active centers, which supply the vagus nerve with its myelin-rich and therefore fast fibers. The vagus nerve consists of **80% afferent sensitive fibers**, which give information about inflammatory changes in the supply area (stomach, oral cavity) to CNS-centers. From there, impulses are emitted from the **nucleus of the tractus solitarius (NTS)** for the two core groups of the vagus nerve, **causing a parasympathicotone independant function**. High activity of the stress system suppresses this tonic function, however during reduction of the stress load the regenerative function of the vagus nerve is enhanced (4, 23, 24) .The vagal system has great importance for the suppression of inflammation, since efferent vagussignals directly inhibit macrophage inflammatory function by binding of acetylcholine to the nicotinic acetylcholine receptors for the blockade of the proinflammatory transcription-factor NFKB and consequent impairment of the inflammatory functions of the innate immune system (4, 25). The vagal function can be diagnosed by measurement of the heart rate variability (HRV), a method based on the efferent vagal influences on the cardiac pulse frequency.

Clinical features of Burnout:

The leading symptom of burnout is „exhaustion".

Since exhaustion is also a common symptom of depression, it is advisable to initially identify or eliminate depression by means of simple questions or use of a depression tests like the Hamilton Scale for Depression or the Personal Health Questionnaire (PHQ).

Actual increased knowledge on stress biology recommend to use also biological markers for the qualification of burnout disease in addition to neuropsychological tests.

The basis of endophenotypes or biomarkers is the **Integral Stress Test (IST),** focusing on both, neuropsychological tests and somatic markers for the characterization of the stress (28).

A similar examination is the **"Neuropattern"** (7, 8) consisting of subjective symptom scale (phenotypes) and associated biomarkers (endophenotypes).

1. Neuropsychological tests for burnout:

These tests include the assessment of different, typical stress-symptoms, its severity and subjective perception, the daily stressors and the individual stress amplifiers (eg overwork, lack of differentiation, fear or anxiety, high self-expectations, perfectionism, and effort-reward imbalance) (9, 28).

The evaluation of these tests reveal a practical overview not only of the subjective stress symptoms, but also on possible behavioral treatment options for the reduction of exogenous stressors and alleviation of personal stress amplifier. Especially these amplifiers may be modified by means of a coaching process.

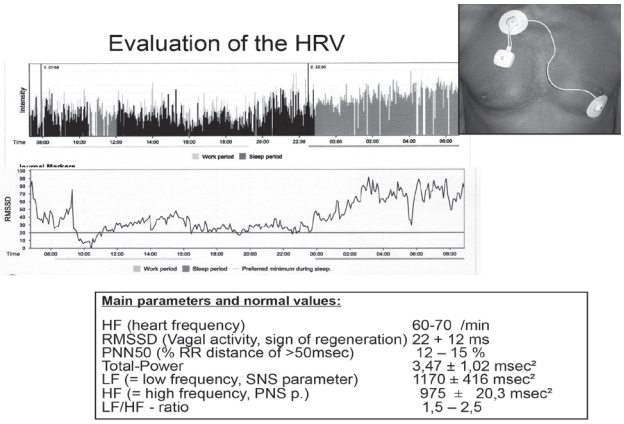
For the differentiation diagnosis of possible psychopathologies such as a major depression several depression-scales or the Personal Health Questionnaire (PHQ) are validated methods (21).

For the description and quantification of burnout the Burnout Inventory (Maslach) or the tripartite Copenhagen Burnout Inventory (CBI) are advisable and useful (13).

2. Somatic stress diagnosis:

Heart rate variability (HRV)

is a modern biophysical procedure which has been enabled by revolutionary microprocessor technique. The afferent vagal fibers are continously modulating the heart rate , which is analyzed by an ultraslim data processing systems. Different providers offer advanced micro devices today, which tap the R-signals of the ECG over two electrodes, enabling precise detection of heart rate variability in milliseconds for up to 4-5 days. The data are transmitted to a central server, where they are graphically and numerically processed, computed, thus delivering a complex data sheet. Several qualitative and quantitative equations have been developed for the description of Sympathetic



Main parameters and normal values:	
HF (heart frequency)	60-70 /min
RMSSD (Vagal activity, sign of regeneration)	22 + 12 ms
PNN50 (% RR distance of >50msec)	12 – 15 %
Total-Power	3,47 ± 1,02 msec²
LF (= low frequency, SNS parameter)	1170 ± 416 msec²
HF (= high frequency, PNS p.)	975 ± 20,3 msec²
LF/HF - ratio	1,5 – 2,5

Fig 4: Evaluation oft he heart rate variability (HRV) here with the device Bodyguard® (Firstbeat Technologies, Oy-Finland), a graphical description of HRV (upper part) and RMSSD (parameter of regeneration, lower part). Sleeping time is m,arked with a blue line , displaying optimum regeneration, as RMSSD is constantly high above the threshold value of 20 (red line). The main calculable and their normal values are described below: Sympathicus (LF = low frequency) and Parasympathicus (HF, RMSSD, pNN 50).

(LF = low frequency), and Parasympathetic (= vagal) (HF = high frequency) activity:

pNN50 = in % of heart beats, which differ more than 50 msec from neighbour heartbeats, RMSSD = root-square of median standard-deviation of heart beats, which is the most indicative parameter of regeneration

The aim of the method is the detection and quantification of stress phases, as well as regeneration with vagal activity during especially during the night, with consecutive documentation (16, 23)

Biochemical examinations:

Cortisol-day profile:

Determination of salivary cortisol 30 minutes after awakening, at 8:00, 14 :00 and 20:00 o clock are main parameters of adrenal function. It expresses the entire cortisol production rate (AUC = the area under the curve), the diurnal, biorhythmical variation and the linear decrease of values over the day. Typical for burnout are markedly reduced cortisol levels throughout the day (13, 16), mostly associated with loss of biochronicity (6, 28).

• **Neurotransmitter in the 2nd Morning urine:**

The typical stress-related neurotransmitters such as the excitatory noradrenalin (NA), dopamine (DA) and ihibitory serotonin (SE) , as well as other consecutive neurotransmitters like GABA (gamma amino butyric acid) and glutamate (GT) are determined by HPLC and fluorescence chemical detection. The main and essential information is the quantification of the major stress substrates (NA, DA) , and the neurotransmitter-balances of noradrenalin/serotonin and glutamate/GABA. These informations lead to an appropriate treatment, with enhancement of the stress-brake serotonin and GABA in most cases (6, 28)

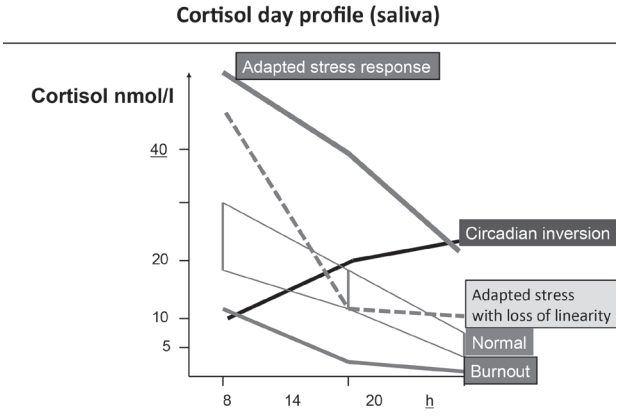


Fig 5: Different cortisol day profiles (here 8:00, 14:00, 20:00 o clock) according to various diagnose

• **Hormone measurements (blood)**

Are not obligatory. To measure the stress effects on gonadal function LH and total testosterone in men, FSH and estradiol in women may be determined. Furthermore the estimation of DHEAS as a marker for the prolonged adrenal stress load is reasonable.

Inflammation parameters

Chronic catecholamine excess stimulates the inflammatory responses of macrophages, while the anti-inflammatory effect of the vagus nerve is reduced, so that inflammation markers such as **CRPhs, TNFalpha, IL6** as well as IL-1ß should be determined.

Brain Derived Neurotrophic Factor (BDNF)

is a newer amerker of chronic stress exposition with obligatory decrease of BDNF with consecutive decreased production of spines and sprouting, as well as replacement of degenerated cells by stemcell for regeneration.

The determination of biological markers has revealed considerable progress for an exact diagnosis of stress associated diseases, as there is no or only a weak correlation between symptoms (phenotypes) and biomarkers (endo-phenotypes) (6)

Own investigations also stress on gender-specific differences within the stress response: while women feel much more subjectively emotionally affected, men complain fewer subjective stress-symptoms, but significantly more biological consequences.

In a simple study of 75 men and women diagnosed with burnout, after exclsuion of depression and CFS, both gender exerted different courses of stress biomarkers: In men burnout is characterized by loss of the cortisol (= energy) and DHEAS production in 1/3, and reduction of serotonin and norepinephrine in 1/3 , as well as development of hypogonadism (in almost 60%) , while women had less biological , however more subjective complaints (28)

Therapeutic procedures for Burnout:

Complex diseases also require complex integral measures, consisting of communication, coaching and/or psychotherapeutic treatments, naturopathic, scientifically and even pharmacological oriented interventions, according to the data obtained from neuro-biological diagnostics.

These include:

• Concrete **stress reduction** with cognitive behavioral tratment (CBT) for focused stress reduction strategies, accomanied by coaching, and in case of deep-seated problems also psycho-

therapeutic treatment. The concise results from the stresstest enables physician or counselor for the development of an individual of a focused stress-avoidance.

Any focus of treatment is directed on „self-development" according to Corssen (3)

• **Relaxation techniques**: individual optimal relaxation is mostly often achieved through trial and tentative application needs. Such techniques include **Mindfulness Based Stress Reduction (MBSR)** a mediatation procedure developed by Kabat-Zinn, yoga and yoga- meditation, progressive muscle relaxation according to Jacobsen, Autogenic Training, or any biofeedback methods.

• **Order therapy** (acc to Sebastian Kneipp) in modification:

In case of disordered endogenous biorhythms a re-rhythmisation must be achieved, by having the main activities during the „Sun-day", coupled with drastic reduction of activity in the late afternoon and evening.

• **Aerobic endurance sports** on the most days of the week, preferably guided by health personal or a personal trainer and accompanied by nutritional counseling, especially in presence of obvious malnutrition, micronutrient deficiency and/or obesity, or underweight.

• **Sleep Support,** particularly in men and women with significantly reduced regeneration, with non-regenerative sleep and / or significant sleep disturbances. The sleep-support includes on the one hand further diagnostic, such as melatonin secretion-rate in the morning and/or melatonin nightprofile in saliva, as well as an intense sleep-counseling, and prescription of somniferous sleep-substrates such as tryptophan, melatonin, GABA or GABAergic somnifera (zopiclon, zolpidem)

• **Bio-identical restitution of deficient neurotransmitter systems:**

According to the data from neurotransmitter-tests in the 2nd morning urine, the deficient neurotransmitter systems may be restituted by application of specific precursors and specific micronutrients:

Serotonin: serotonin precursors (L-tryptophan, 5-hydroxytryptophan in the relation 5:1), and the micronutrients vitamin B3, B6 and folic acid.

Noradrenalin: Administration of L-tyrosine and Mucuna pruriens (contains L-Dopa) in adequate dosages. Impairment of the corresponding enzymes should be stimulated (eg dopamin-ß-hydroxylase by vitamin C ester, iron and copper). Markedly elevated catecholamines could be caused by genetically impaired COMT (= catechol-o-methyl-transferase) due to heterocygotic (Val158Met) or homocygotic (Met158Met) polymorphisms. Therefore genetic exam may elucidate the underlying cause (17)

GABA: Prescription of GABA (sublingual tablets) or of GABAergic substrates theanine and taurine.

Glutamate: Elevated glutamate or alteration of the glutamate/GABA-ratio should be treated by reduction of glutamate by magnesium (eg magnesium citrate 300-600 mg daily), enhancement of ATP (adenosine-tri-phosphate9 or in excess situations even by pharmacological blockade of its receptorsites.

In case of excitatory neurotransmitter excess (catecholamines or glutamate) central inhibitory

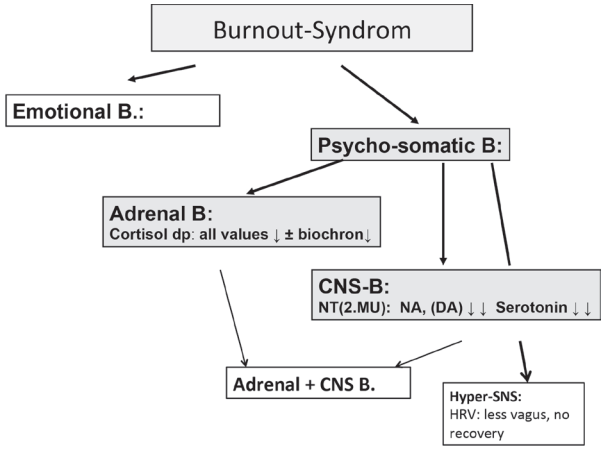


Fig 7: Schematic description of the 5 different types of burnout, according to biochemical (Cortsiol dayprofile, neurotransmitters 2nd morning urine and HRV data. The exact differentiation enables for a precise diagnosis and treatment option.

Biochemical characterisation of Burnout

	female (% / nr)	male (% / nr)	
Cortisol normal	**24,4** (10)	**17,6** (6)	*
Cortisol AU	**7,3** (3)	**32,4** (11)	*
Neurotransmitters 2nd MU:			
Serotonin ↓	**19,5** (8)	**35,2** (12)	*
NT-balance disturb	19,5 (8)	29,4 (10)	*
Noradrenalin ↓	**7,3** (3)	**35,2** (12)	*
Cortisol + NT normal	**7,3 (3)**	**2,9 (1)**	
Serum: DHEAS	**36,6** (15)	**88,2** (30)	*
testosterone <4,2 ng/ml		**58,8 (20)**	
<3,5 ng/ml		**38,2** (13)	
estradiol	variable	----	

* Statistically signif.

Fig. 6: Different endophenotypes of burnout according to biochemical and biophysical examination. 75 male and female with the diagnosis „burnout" after exclusion of a major depression and fatigue (CFS) were examined with the examinations cortisol day profile, neurotransmitters 2nd morning urine, serum exam of DHEAS, estradiol and total testosterone.

substrates such as Rhodiola rosea, magnesium citrate in conjunction with behavioral and relaxation promoting measures are indicated.

Cortisol deficits are treated with substitution of hydrocortisone (corresponding to the cortisol levels within the saliva cortisol dayprofile) in degressive dosages (eg hydrocortisone 5/2,5/0 mg daily).

After the primary intervention the recurrence of burnout must be prevented by a complex strategy of individual applications, such as daily practice of relaxation techniques to improve stress balance, and not only in stressful events. Furthermore concrete weekly exercise program (on the most days of the week), personal mindfulness in dealing with food and beverages, promotion of social contacts, employment, competence in relationship, development of new taregets and profit creation, respectful behavior in the workplace, improvement of teamwork and time sovereignty with more self-determination and tolerance in different situations(2, 3)

Conventional medical professionals do not regard burnout as an own disease entity. Translation of science , however, allows to categorize burnout phenotypically with psychosocial items and thus initiate specific psychotherapeutic or care measures. Organic and somatic deficits within the central nervous (CNS) and of adrenal adaptation can be detected, corrected or substituted. This individualized strategy reveals significantly better long-term results with avoidance of psychopathological development, such as depression, anxiety and panic disorders, addiction, drug problems and somatoformic disorders.

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Lifting effect with polydioxanone absorbable threads without anchors on face and neck

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Abstract

Polydioxanone is a synthetic, absorbable and monofilamental suture. The working hypothesis is to demonstrate that polydioxanone threads used in this study, without cones or spikes have indication of non-surgical facelift and necklift, with good results and safety. The objective of this study is to establish the indications, contraindications, side effects, duration and satisfaction degree of the patient after the completion of the treatment. We have made an evolutionary study during a year. The study was conducted on a sample of 100 cases in different clinics in Spain, France, Italy, Czech Republic and Ukraine. First identify areas of tension, sagging and bridge. Polydioxanone threads inserted with needle guide (G-25, G-27, G-29 or G-31) strategically in these areas, establishing a network. The insertion layer is the dermis and the biological mechanism of action is primarily by stimulating fibroblasts to stimulate neocollagenesis type I and type III. We observed no adverse effects, the most frequent side effects oedema, erythema and hematoma. The duration of the results observed between 12 to 18 months and can insert polydioxanone threads any time.

Keywords: non-surgical facelift, sagging, polydioxanone.

Introduction

New concept

We understand as new concept, a result based on the resources of the skin. The result is not obtained as a direct "cause and effect" of inserting polydioxanone threads. The effect is indirect, because the threads generates a biological stimulus on the skin and it can increase the production of collagen type I and type III by fibroblasts and collagen, autoinduction thereabout that conditions the results.

Collagenesis rejuvenation synthesis and components of the extracelular matéria (collagen, elastin, fibronectin, glycosaminoglycans and proteoglycans) are reduced with age (1-6). A mature activated fibroblast is capable of producing up to 3.5 million per day of procollagen macromolecules (7). Hence, the mature collagen represents about 30% of the total protein in the human body and to 70% of the protein content of the skin. The type I and III collagen up to 90% of the skin are organized into large bundles of fibers forming a network structure in 3D. (7,8). The structural fragment 'Gly -Pro- hidroxiprolyn is called collagen sequence (9). From 80 years, the synthesis of collagen is reduced by 75 % compared to those 18 to 29 years (3,4). As a result, there is a general reduction of collagen types I and III in the dermis correlated with age (10).

Polydioxanone

It is a synthetic, absorbable suture, monofilament, violet/ blue color, sterilized with ethylene oxide. Use in surgery on internal tissues, in which a long-term suture is indicated, is accepted by the scientific community. Also as material synthetic causes less reactivity than natural sutures. It also has reference recognized in the approximation of all types of tissue, ophthalmic surgery, gastrointestinal, plastic,

reconstructive, gynecologic, urologic, cuticular and pediatric cardiovascular tissue where it is expected that this growth.

Bibliographic review

Studies of Janik et al. in colorectal surgery showed great resistance (11). In prolaxes urinals Madhuvrata studies et al. concluded that after two years followed with a good quality of life among patients (12). Ruim et al. in his comparative study of sutures in abdominoplasty concluded that polydioxanone sutures were more useful than permanent sutures (13). In 2008, James and Kelly published their results in rhinoplasty using as polydioxanone suture with good results (14). Becker et al. published in 2010 no complications with the use of such sutures in periorbital fractures (15).

Parara et al. compared in a study erythema and irritation with 5 different types of sutures (polydioxanone, blue polypropylene, polyamide 6, metallic chips and polyglactin) with digital images processed by software method observe this conclusion, "polydioxanone was the suture with better results and fewer signs of irritation / erythema" (16) .

Ogawa on japanese studies in thoracic surgery conclude that the use of polydioxanone for its strength, reabsorption at 6 months and few side effects is preferible (17).

The sutures used in this study were of monofilament polydioxanone. We know that there are in market polifilamental polydioxanone sutures, but no monofilamental/ polifilamental comparative studies regarding the safety and effectiveness of non-surgical facelift.

However, studies Hennessev et al. about polydioxanone sutures monofilamental compared with polifilamental in abdominal surgery as well as with other types of sutures, they concluded that the twist of the sutures, particularly polifilamental, increased risk of fracture (18).

Extrapolating these data, and considering the lack of comparative studies between mono and polifilamental suture indications in non-surgical facelift, we conclude that the sutures of monofilament polydioxanone are extensively documented in literature references and it is prudent to opt for the more informed choice without being decisive. Goodrich's study concluded that in craniofacial surgery had no complications with the use of polydioxanone. (19). And in this respect, other studies such as De Toledo on using polydioxanone in dental surgery found no complications and satisfactory results (20). Thus, since sutures are less resistant cross tissue makes them suitable, for example, for vascular surgery. Its absorption is complete at 180 days and keeps 75% of the tensile strength at 2 weeks and 25% at 6 weeks (21).

During the time in which it is able to maintain tension of 2 to 6 weeks, self-induced collagen threads are generated around the threads mainly implemented by stimulating fibroblasts and activation neocollagenesis.

Justification

We know that through the years a gravitational sagging of tissues, especially in the face and neck occurs. In young people's face has a geometric shape in the form of "V", but due to gravitational ptosis, with over time, an inversion "A" is produced.

No purpose of this article is a review of the different types of lifting, but briefly say that basically the options are not reabsorbibles and resorbable threads. Regarding the technique and mechanism of action, non absorbable suture require incisions

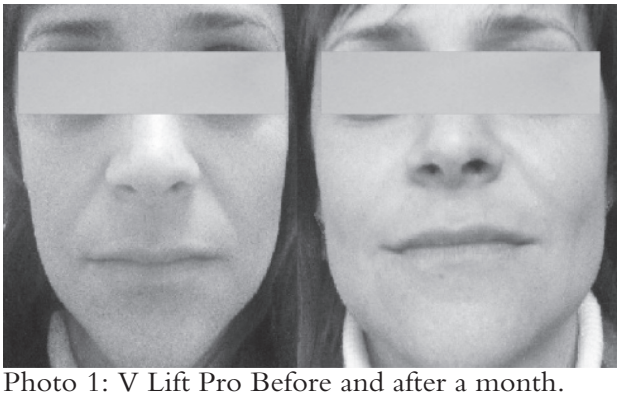


Photo 1: V Lift Pro Before and after a month.

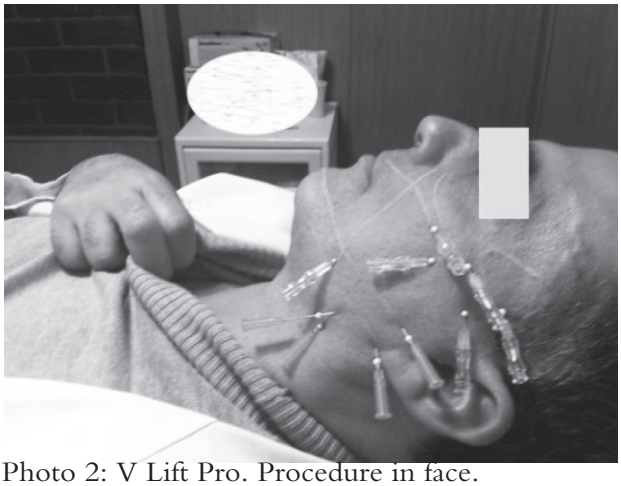


Photo 2: V Lift Pro. Procedure in face.

and anchors. The procedure is more aggressive, recovery time and complications are greater. The mechanism of action is essentially mechanical.

In a second generation absorbable threads have spicules, cones acting on mechanical anchoring mechanism and also stimulate collagen by biological mechanism.

V Lift Pro are absorbable sutures (polydioxanone) in monofilament, which act as an induced biological autolifting. No spikes, cones, anchors, incisions. V Lift Pro is not a trademark, it is a technique of applying threads of polydioxanone (PDO) with V-1682/12registration (intellectual property from author of this article).

Its mechanism of action is biological, neocollagenesis stimulating and producing a mechanical effect of the response of the skin itself. It is a new alternative to produce a lifting effect on the face and neck, body areas.

Material and Methods

JBP V Lift, polydioxanone threads provided by Japan Bio Products for the exclusive use of this study. Types: G-25, G-27, G-29 and G-31:

Sample: 100 randomly selected patients in different clinics in Spain, France, Italy, Czech Republic and Ukraine. Ages 35 to 75 years.

Sample description:

AGE/GENDER	FEMALE	MALE	TOTAL
36-45	23	1	24
46-55	26	2	28
56-65	24	5	29
66-75	17	2	19
TOTAL	90	10	100

Table I Distribution of the sample by age and gender

Inclusion criteria:

Sagging face and / or neck.

Agreement in compliance with the study.

Informed consent.

No general contraindications.

It was explained to each participant what constituted the study, risks and expectations.

It requested permission to use their images for scientific purposes.

Protocol

1. Study of physiognomy: taking three photos in three planes, frontal, lateral and oblique. Dynamic study with video asking the patient to gesticulate. Identifying areas of stress, sagging and bridge. Touch checking and marking with pencil. This phase is very important because we have to design a strategy for each patient. The tension zone is always in the superolateral area, the sagging area belongs to middle third of the face or neck, lower zone. Near the bridge linking the two areas described. Identify limits and insert needles in network

2. Apply anesthetic cream 30 minutes before the procedure, we can occluded. And cryoanesthesia, application before and after procedure, avoid browsing

3. Mesotherapy just before inserting the threads. We can use any type of product that stimulates collagen.

4. Insert the needle/ threads on dermis. With the bevel up.

5. First, the longest needles are inserted. The direction should follow this rule: in the vertical direction is always from the bottom upwards, as in the bevel, the thread is double, because one third of the thread is within the needle, and the rest parallel to the needle.

6. Second, the shorter needles are inserted. Basic scheme: long threads in mandibular arch, zygomatic and crosses to join them. Threads short in suborbital ridge and middle third.

7. Insertion procedure: layer dermis, continue checking until the end. Press in the entry and end and slowly remove the needle. Press and hold.

8. Correction manoeuvre: If at any time during the needle insertion noticed that we changed up, we can remove the needle, up one centimeter, never more, because we may lose the right direction of the thread, and restore the appropriate layer. If it not in dermis, it must be removed through the skin with the needle.

9. Apply cold after the procedure and press for a few minutes.

10. Apply mask antiinflammatory.

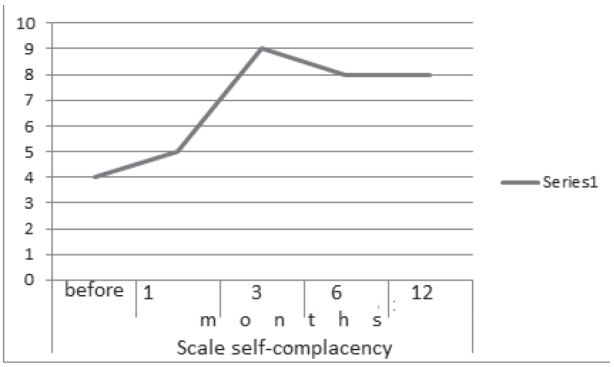
NOTE: Methodology for taking photos and videos

The pictures and video before treatment were conducted by the author of this article at all clinics and countries listed, as it is always done as training workshop at participating clinics. We use an Iphone camera for both photos and videos.

Successive photos and videos were made by doctors participating clinics (one clinic by country), and sent to the author. In the case of Spain by the same author.

Evaluation

The assessment following 2 criteria: Objective (iconographic) a month, 6 months and 12 months. Subjective Scale (complacency).



Graph. 1. Subjective Scale

There are a number of scales to measure a patient's self-satisfaction, the best known are self-administered questionnaires fixed format, the most common variables are taken from the patient satisfaction questionnaire CASPE (CASPE Research 1991), which uses the answers very satisfied / satisfied / dissatisfied / very dissatisfied

We used this scale in this study, using a single item "degree of satisfation with the results obtained"

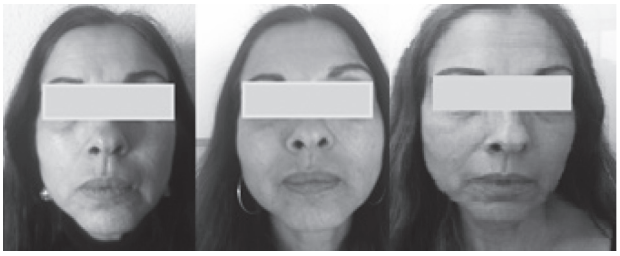


Photo 3. V Lift Pro. Before and after 6 and 12 months.

Discussion

The patients treated during this study did not show serious side effects or advers reactions. They were able to do their usual life and activities at once. Some minor side effects such as oedema, erithema and bruising were occured. The procedure was made with an anaesthetic cream. Each patient tolerated it properly. In some cases, when the guide needle brushed against a osseous ridge, they described an unpleasant sensation, which dissapeared in a few minutes.

SIDE EFFECTS		
description	absolut value	relative value
oedema	60	60 %
erithema	35	35%
pain	15	15%
haematoma	30	30%
others	2	2%

Table II. Side effects with the use of PDO threads in no surgical lifting

Oedema and erithema dissapeared within the 24-48 hours after the procedure.

Haematoma dissapeared around one week after procedure.

The pain described by some patients was related to the change layer to epidermis or when brushing against an osseous structure.

Other side effects occured in a percentage of 2%, when the needle crossed an filler of crosslinked hyaluronic acid in a recent filler (less than three months), appearing a big cold oedema associated to the water capture produced by the microparticles of hyaluronic acid extended by the needles "microtrauma", and in case of failing procedure, the thread is inserted in the epidermis, it can be seen and it can create an erithemal spot in the epidermis.

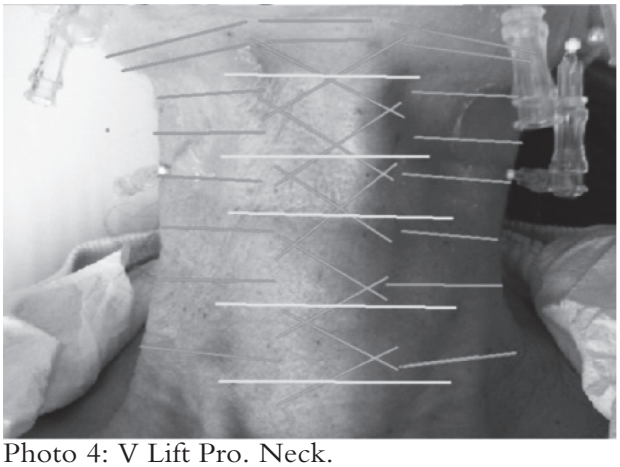


Photo 4: V Lift Pro. Neck.

No serious side effects were observed and neither the appearance of granuloma during the current year of the study.

It is very important **to know the right treatment, whenever side effects appear**.

Anticoagulant cream and ice in case of the oedema, erithema and haematoma.

Regarding the pain, there was not point in prescribing an "analgesic", because it dissapeared in very few time. But in some cases when it is necessary, it is advisable paracetamol or metamizol.

In case of a big oedema about a recent filler of hyaluronic acid, it dissapears spontaneously within a week. The suitable treatment is a corticosteroids in a declining ruled sheet of nine days.

It is essential for the success in results, to apply the technique properly, making crosslinked in the tension, sagging and bridge areas, as well as locating and marking suitably.

The procedure is easy and not little tiruues damage. An initial oedema is observed, but it will dissapear within a week. From the first month up an improvement will be occured. It will improve in the third month, and the results will during between 12 and 18 months depending on the age, the features of the patient and the individual answer.

Being objective, in photos, it was observed a reestructuration of the profiles and a lifting effect associated to the improvement in the skin's quality. In the subjective scale, each patient of this study showed a very high level of satisfaction.

It was observed in one case an inmediate inflammation. In this patient, the guide's needle crossed a recent fillers of hyaluronic acid. It was solved spontaneously within a week with the application of ice and anti-inflammatories. It is advisable to avoid crossing any type of crosslinked hyaluronic acid (< 6 months), as well as to know the suitable treatment if this reaction occurs (anti-inflammatories, ice and costicosteroid- therapy with in decreasing dose).

It is understood that the procedure stimulates the own resources of the dermis, giving advantage to the formation of collagen by fibroblastic reaction, generating an authentic biological autolifting.

Taking into account that this is the first study that it is made with Caucasian patients, it is necessary to count on more studies to be able to compare and to monitor more significants.

Conclusions

V LIFT PRO is a new alternative to obtain the effect of non-surgical lifting, that it is treated in face and neck, as well as in body areas and stretches marks.

Its mechanism of action has a double effect as solid filler and the fibrotic reaction generates the autoinduction of the own threads of collagen type I and type II.

The lifting effect is obtained, on the first place, by the solid filler (inserted threads), with an immediate mechanic effect.

The authentic effect and tensor mechanism is by its biological process and stimulation of the fibroblasts around the thread, with the rising of collagen and elastin.

Few side effects such as oedema, erithema and haematoma are occurred.

The one year follow-up, no granuloma formation or other side effects have been occurred in the context of the study.

To conclude, given the results obtained in this study we found that the smooth monofilament polydioxanone threads is an indication of non-surgical face and neck lift with good results and safety in the treatment.

For one hand, a bibliographic in security and effectivity of these threads in other tissues, clinically, have showed very good results with minor side effects with the preventive measures and although lack of studies, it can be affirmed that it is a safe and effective method.

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Marked reduction of breast, endometrial and ovarian cancer in users of bio-identical estradiol and testosterone subcutaneous pellets

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Abstract

The Women's Health Initiative[1] in the year 2002 shocked the world with its findings. The study demonstrated a combination of conjugated estrogen and a synthetic progestin increased the incidence of breast cancer after (5.2) years of usage. The study did not qualify this to only this regimen, but concluded that all estrogen and progesterone would do likewise.

In a review of 976 women treated between 1992 and 2002 with subcutaneous bio-identical estradiol and testosterone pellets, there were no cases of breast, endometrial, or ovarian cancer even in the individuals utilizing the therapy for over 20 years. There were 153 patients treated for 5-25 years, 471 for 3-5 years and 352 for less than two years. All women in the study (246) with an intact uterus were treated with micronized progesterone, not a synthetic progestin. Cyclic and continuous combined regimens of micronized progesterone were utilized in all women with an intact uterus. Conclusion: Subcutaneous bio-identical estradiol and testosterone, even with progesterone usage, imparts a protective physiologic environment that reduces the possibility of developing breast, endometrial, and ovarian cancer.

Introduction

The furor that arose after the results of the Women's Health Initiative (WHI) were published in July of 2002 led to the belief that all estrogen and progesterone combinations were likely to increase the development of breast cancer. This study, completed in January of 2002, proves that the conclusion derived from the WHI was erroneous in the following assumptions: 1) All estrogen and progestins are the same, therefore, carry the same risks for the development of breast cancer; 2) Oral estrogen and progesterone compounds are identical in their action and risks when compared to subcutaneous, transmucosal, or transdermal preparations of estrogen and testosterone; 3) The oral form of conjugated estrogen coupled with a synthetic progestin (medroxyprogesterone) is a good model upon which to base all studies and subsequent research[4]. Their outcomes could be considered universal for every form of estrogen and progesterone given to post-menopausal women.

The purpose of this study was to demonstrate that biologically identical 17-beta-estradiol, when coupled with biologically identical testosterone, and given in the form of subcutaneous pellets with oral micronized progesterone did not increase the incidence of breast1, endometrial, or ovarian cancer. Davelaar in his study demonstrated that estradiol in a pellet delivery system did not increase the incidence of breast cancer in women using it for extended periods as long as twenty years[2]. The results of the study will show that the WHI study results do not apply to subcutaneous pellet therapy with bio-identical 17-beta-estradiol and testosterone, and micronized progesterone.

Methods and materials

Nine hundred and seventy-six (976) women were followed over a ten year period (1992 to 2002). The patients were followed in a private setting,

and are still being seen as part of an ongoing study of the effects of subcutaneous pellet hormones on osteoporosis, cardiac disease, and the development of Alzheimer's disease. The patients were evaluated prior to initiating subcutaneous pellet therapy (SPT), with appropriate lab work, a complete gynecological examination, and a mammogram. No family history of breast cancer whether in first or second degree relatives excluded any patient from the study, therefore, eliminating any chance of placing any bias in the study. In fact, five breast cancer survivors were a part of the study as well. The patients were followed with repeat lab work at one, six and twelve months after insertion, and received annual gynecologic examinations and mammograms and annual lab studies thereafter. All patients were instructed to notify the principal author if any evidence of an abnormality in the breasts, abdomen, or uterus were perceived by the patient or found by any other physician.

The patients received varying dosages of biologically identical 17-beta-estradiol pellets (6mgm-25mgm) coupled with biologically identical testosterone pellets (50mgm-150mgm) compounded by Solutions Pharmacy of Chattanooga, TN. Patients with an intact uterus were given 200mgm micronized progesterone, in compounded oral capsules, sublingual tablets, cream, or in the proprietary form (Prometrium). The dosage of estradiol and testosterone varied according to the patient's symptoms, age, weight, and levels of serum follicle stimulating hormone (FSH). The pellets were inserted every four to six months according to the emergence of menopausal symptoms or evidence of a rising FSH level.

The hormone pellets were inserted primarily in the gluteal area in the upper outer quadrant of the buttocks. A few patients requested implantation in the abdominal wall, which was done in an area lateral to the superficial epigastric vessels.

FIG. I

Age Range	Number of Patients	Mean Age
25-40	46	38
41-45	109	43
46-50	127	48
>50	694	62
Total: 976		

The insertion process proceeded as follows: the area for insertion was prepped with alcohol, anesthetized with either one or two percent xylocaine with epinephrine buffered with sodium bicarbonate; a four millimeter stab wound was made with a number eleven (#11) blade; the hormone pellets were then placed in the subcutaneous fat using a pellet trochar; finally, the stab wound was simply bandaged. No wound infections occurred.

In our study, excessive bleeding from the insertion site was rare. When it was encountered, it was easily managed with one suture of 4-0 ethilon and a pressure dressing. In patients with a history of bleeding or adhesive allergy, a single stitch of ethilon suture was routinely used for closure. The suture was removed by the patient in four to five days.

Results

A total of 976 women were included in this study. Nearly ninety-six percent (936) were perimenopausal or postmenopausal (see Fig 1). Nearly seventy percent (683) had been on other forms of HRT for an average of four years prior to initiating subcutaneous pellet therapy. The majority had been on conjugated estrogen, with or without progestin (Premarin, Prempro, Premphase, Premarin and Provera). Over twenty-five percent (246) of the patients had an intact uterus and were given natural micronized progesterone, either in a combined continuous regimen, or in a cyclic fashion. The micronized progesterone regimen was determined by the age of the patient, presence or absence of a menstrual period, and the patient's desire for amenorrhea. The dose given was 200mgm daily in a single or divided dose in each regimen. Endometrial biopsy and transvaginal ultrasound were done if abnormal bleeding (<3%) occurred during the study.

In the study group, there was only one case of breast cancer during the study period. The patient developed a stage I noninvasive, node negative

cancer in the first year of therapy. Therefore, considering the time from the first cancer cell to diagnosis to be seven years, according to cell duplication studies, it can be assumed she had the disease prior to starting on pellet therapy. In this study group, there were no cases of ovarian cancer, and only one case of endometrial cancer. The endometrial cancer was found after the patient's first six months in therapy which would indicate preexisting disease. The patient had a Stage 3 Grade I, well differentiated tumor and has remained disease free after therapy.

There were only 6 hysterectomies performed on patients who did not respond to conservative management (Table 2). Uterine fibroids were the cause in five patients; endometrial cancer in one patient. In the study group, there were four breast biopsies done in the ten years that were studied.

The incidence of breast cancer was calculated at 0.01% (1 in 976) which is statistically significant P<0.01%. In fact, if breast cancer development is estimated to be an average of six years, then the corrected incidence of breast cancer for the study is 0.

Discussion

The use of hormone replacement therapy (HRT) by the perimenopausal and postmenopausal woman is now more controversial than before the WHI study. The confusion by physicians and patients that followed the publication of the Women's Health Initiative, prompted many women to abruptly stop their forms of HRT The study implied that all estrogen coupled with any progestin or progesterone increased the incidence of breast cancer after only 5.2 years of use. The study appears flawed and does not apply to all forms of HRT because:

1) Conjugated estrogen and synthetic progestin do not represent all other forms of estrogen and progesterone in chemical structure or biologic activity.

2) Oral HRT does not and cannot produce the normal, steady physiologic level of estrogen and testosterone that the human body produces normally, nor do oral estrogen products maintain the physiologic ratio of estradiol to Estrone of 2:1[3,4].

3) Biologically identical 17-beta-estradiol has never been shown to increase the incidence of breast cancer, in any form[2].

Our findings suggest that estradiol in subcutaneous pellet form is not just another form of HRT, but a superior therapy, in that the incidences of all of the more common female cancers were decreased through this treatment. Why has this therapy been over-looked in the United States? Pellet therapy has been utilized in the United States since 19395, but only a limited number of physicians know of or utilize this form of therapy. The primary reason is lack of education about this form of therapy in the United States, although subcutaneous pellet therapy (S.P.T.) is utilized routinely throughout the rest of the world. Most of our education about hormone replacement is delivered through the research sponsored by the pharmaceutical industry. The information delivered has an immediate bias to emphasize all estrogens, progesterone, and testosterone are identical in biological structure.

The discussion of this study will demonstrate a significant decrease in female cancers in the study subjects. What explains the significant absence of three of the more common forms of cancer in women in the study?

Endometrial cancer

The incidence of endometrial cancer is well known to be diminished if a patient receives progesterone to alter the effects of unopposed estrogen. The study adequately demonstrates that the incidence of endometrial cancer is not increased if an absorbable form of 17-beta-estradiol is utilized. More importantly, subcutaneous pellet therapy releases minute amounts of hormone steadily throughout a twenty-four hour period, and maintains the physiologic ratio of estradiol to Estrone at 2:1[4]. When minute amounts of testosterone are released in conjunction with minute amounts of 17-beta-estradiol the endometrium realizes an additional benefit6.

This positive effect of testosterone augments the effect of micronized progesterone in stabilizing the endometrium. It certainly would be correct to assume that the use of combined S.P.T. does not increase the incidence of endometrial cancer, and may in fact protect against the development of abnormal endometrial tissue. Within the study group the presence of dysfunctional uterine bleeding was less than 3%. In 5 of 7 patients fibroids were found. Only five hysterectomies were done solely because of fibroids (see Fig 2). Hysteroscopy with thermogenic balloon ablation eliminated the other cases of dysfunctional bleeding not corrected by hormonal suppression with progesterone or estradiol dosage adjustment or both. All endometrial specimens were sent to pathology and found to be benign at the time of ablation.

Ovarian cancer

Ovarian cancer has long been a frustrating disease to diagnose in enough time to successfully treat the patient. Yet, in the National Nurses study[7], women on oral contraceptives were found to show a marked reduction in the incidence of ovarian cancer after five years of usage. The explanation offered is that oral contraceptives rendered the ovary dormant. This is effected by a marked suppression of the serum FSH, thereby halting follicular development. In fact, because of the National Nurses Study, oral contraceptives have been used in high risk individuals to protect against ovarian cyst formation, and reduce the possibility of the development of ovarian cancer.

What then explains the absence of ovarian cancer in the present study? The answer lies in the marked suppression of the FSH levels induced in SPT patients. We specifically designed the dosage of estradiol pellets for each patient to effect a suppression of FSH levels below 20, the pre-menopausal range in our laboratories. The continuous release of hormone from pellets produces a steady suppression of FSH over a four to six month period which is identical to what is seen with oral contraceptives. This marked suppression of FSH induces a dormant state in the ovary as is seen with oral contraceptives the patients who entered our study on oral hormones replacement did not demonstrate such suppression in the FSH levels, except in high doses, i.e. estrogen 1.25-2.5mgm, estradiol 2mgm. Most patients on low to moderate dose i.e.: conjugated estrogen 0.3, 0.625 or estradiol 1mgm oral therapy had FSH levels of 40 or higher. It logically follows that lower levels of FSH give less ovarian stimulation from the pituitary to the ovary, and therefore a lower risk of ovarian cancer through the use of pellet therapy would be expected. This study demonstrates this protective effect elegantly. During the study period and even up to the present there have been no cases of ovarian cancer in our study subjects. The sustained suppression of FSH by the steady continuous release of estradiol induces a state of dormancy for the ovary thereby reducing the chance of ovarian cyst formation which predisposes the postmenopausal ovary to malignant degeneration.

Breast cancer

The Women's Health Initiative was stopped prematurely because the participants using the conjugated estrogen and synthetic progestin hormone (Prempro) were developing breast cancer at an increased rate above what had been postulated. The results of the study were released and chaos and pandemonium ensued. Patients and physicians were led to believe that all types of estrogen when coupled with a progestin (medroxyprogesterone) did increase the rate of breast cancer development after only three years of usage. The subsequent fallout produced widespread stoppage of all forms and types of HRT. Most physicians recommended that their patients stop HRT. This study had one very obvious flaw; the assumption that conjugated estrogen and medroxyprogesterone adequately represented all forms of estrogen and progesterone. The proper conclusion in this study, and all prior studies using conjugated estrogen, is the usage of conjugated estrogen (Premarin, etc.) coupled with medroxyprogesterone increases the incidence of breast cancer development. The implication of all other estrogens in either oral or absorptive forms should not have occurred. There have

FIG 2			
Number of Patients with Intact Uterus	Number of Patients with Bleeding Requiring Surgery	Endo-metrial Ablation	Hysterec-tomy
246	7	1	6

been no large studies of other forms of estrogen specifically looking at the incidence of breast cancer development over a prolonged period of time until now.

This present study was over a ten year period (1992 - 2002). Nine hundred and seventy six patients were followed. Only one case of breast cancer developed. This individual developed the disease in her first year of usage of subcutaneous estradiol pellets which certainly began prior to starting pellet therapy. With this case excluded, the incidence of breast cancer in the users of S.P.T. was zero. What accounts for this marked reduction, since the expected incidence of breast cancer is 1:9 for all females?

Lewis and Jordan 8 in the Journal of the National Cancer Institute have shown that 17-beta estradiol in small physiologic doses induces apoptosis in human breast cancer cells unresponsive to estrogen deprivation therapy (tamoxifen). This effect is a result of 17-beta estradiol causing a release of cytochrome c and other mitochondria/factors inducing apoptosis and cell death.

In addition the usage of testosterone in every patient most likely suppressed breast cell proliferation as seen in Hofling's study[17]. The combined effect of these two hormonal induced changes most likely reduces the possibility of developing dysplastic breast cells in the menopausal and post menopausal female.

Popular opinion is the risk of breast cancer can only increase with HRT use, but our study showed a decreased incidence well below what is seen with menopausal non-users of HRT considering Lewis and Jordan's study[8] one prime reason for the decrease is that subcutaneous 17-beta-estradiol pellets are composed only of biologically identical estradiol, not synthetic or equine estrogen and deliver continuous physiologic doses of estradiol. Furthermore in the study, the participants with an intact uterus were given micronized progesterone, not a synthetic progestin. The majority of these patients employed continuous combined therapy regimens. More importantly, S.P.T. releases hormone in a slow-steady manner with little chance of variation for four to six months. This more closely resembles the physiologic release of endogenous hormones. S.P.T. also releases only minute amounts of hormone into the blood stream in a continuous manner unlike oral agents[3]. This dosage of estradiol and how it is delivered closely resembles that of the pre-menopausal female.

Finally, decreased breast cell proliferation certainly occurs with the continuous secretion of biologically identical testosterone as delivered by subcutaneous pellets, consistent with Hofling's study[17].

Breast cancer incidence is known to rise as a woman ages. What accounts for this increase? It can certainly be assumed that a woman's own estrogen is breast-protective[8] until the levels of estrogen hormone begin to vacillate (perimenopause) or disappear (post menopause). Younger women (i.e. 40 years old or younger) have a much lower incidence of breast cancer. Does it not seem reasonable to then strive to recreate the physiologic environment seen in and women in her early forties. 1) FSH levels kept in premenopausal range; 2) Biologically identical 17-beta-estradiol and testosterone released into the blood stream through direct absorption in a steady physiologic manner; 3) Estradiol to Estrone ratio kept at 2:1.as indicated in Thom's study[4].

The only form of therapy that recreates this model is subcutaneous pellets. This study demonstrates that if a woman is given biologically identical 17-beta-estradiol in a physiologic dose, at a steady state, the incidence of breast cancer is markedly reduced. Furthermore, it demonstrates that 17-Beta-Estradiol with testosterone given in pellet form is probably breast protective[8,.17] .

Conclusion

The Women's Health Initiative incorrectly implied that all estrogen increases the development of breast cancer after three years. This inaccurate assumption prompted women to discontinue all forms of HRT and suffer the ravages of menopause, and possibly increase their risk of heart disease, osteoporosis, dementia and many other diseases. The present retrospective study was done to prove that the usage of bio-identical estradiol, testosterone, and micronized progesterone did not increase the incidence of breast, endometrial and ovarian cancer. The study affirmed that the recreation of the normal physiologic hormonal environment through the usage of subcutaneous estradiol and testosterone pellets imparts a protective effect against the development of breast, endometrial and ovarian cancer.

Furthermore, the usage of subcutaneous estradiol and testosterone pellets should be encouraged because of the positive effects seen on bone density 8.3% growth per year[3,10,11]; the lack of adverse impact on serum lipids[12]; the lack of adverse effect on cardiovascular health[11], and superior control of the symptoms associated with the menopause[13,14,15,16].

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Effects of arsenic on human health. importance of study method.

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Abstract

Arsenic (As), a natural element that behaves as a trace metal, it can be found in the soil, air and water and it is considered a carcinogen, carcinogen, mutagen and teratogen that it caused the public health problems. The human telomerase is composed of template RNA components (hTR) and two proteins, telomerase-associated protein-1 (TP1) and telomerase reverse transcriptase (hTERT). Arsenic trioxide (As2O3) treatment decreased down-regulation of hTERT expression, and down-regulation of hTERT mRNA expression, besides this, the telomerase activity is suppressed. It was demonstrated that As2O3 can be used as anticancer drug targeting telomerase. As speciation has aroused great interest since the toxicity of different species differs widely. It is considered that a daily oral intake of inorganic arsenic of 0.3 μg/kg will have no adverse effect on humans. Marine products represent the greatest source of As in humans. Studies of trace element availability in the soil are useful for inclusion in an analysis of the risks that such elements represents. Bioavailability refers to the extent that a contaminant is available to have an adverse effect on humans or other organisms. Knowledge of the different chemical species and their respective degree of bioaccessibility factor is essential for evaluating the potential risk to human health and the most suitable strategies that should be applied to eliminate wastes and to evaluate and manage the corresponding environmental and health risks.

Key Words: Arsenic, human telomerase, public health, cancer, study method.

Arsenic.

Arsenic (As), a natural element that behaves as a trace metal, can be found in the soil, air and water [1]. It exists in four oxidation states (-III, 0, + III and +V). The presence of organic species is normally insignificant [2].

Of the methods available for determining the different forms in which As may be found in a sample, speciation has aroused great interest since the toxicity of different species differs widely. In general, the toxicity diminishes as the degree of methylation increases and so increases in the following order: As (III) > As (V) > MA > DMA. The presence of As, therefore is not synonymous with toxicity since everything depends on the chemical species present [3].

In living organisms As (III) undergoes various processes of detoxification, including oxidation to As (V) and biomethlation to MA and DMA, among other substances. Figure 1 shows some of the chemical forms of arsenic that occur in nature [4].

The public health problems that As may cause and its classification as a carcinogenic has led to it receiving much attention.

In fresh water the concentration of As varies according to the its origin, the quantity available and the local geochemical environment. In subterranean waters, the concentration varies from <0.5 to 10 μgL-1 and represents an important problem for public health. In sea water and marine sediments the concentration

of total As may range from 1-2 μgL-1 or 3-15 mg/kg [5].

In 1975 the EPA (Environmental Protection Agency) established 50 μgL-1 as the maximum concentration of As in drinking water, which was reduced in 2001 to 5 μgL-1 in order to protect the consumers from long term exposure to its effects [6]. Indeed, in 2005 the USEPA concluded that the carcinogenic mechanisms of As were still far from clear and since then numerous studies have attemopted to evaluate any risks in this respect [7].

As regards the concentration of As in the atmosphere, human activity contributes 57% [8], while the maximum concentration permitted is 0.01 μg m-3 [6].

The natural level in soils depends on the rock type but the normal range is 1 to 40 mg/kg, not usually exceeding 10 mg/kg in non-contaminated conditions [5]. In the Sierra Minera de Cartagena La-Unión, and in zones where mining steriles are accumulated, such as the area known as Lo Poyo and Portman and el Gorguel bays, (Región de Murcia), concentrations higher than 3000 mg/kg have been measured [9].

The mobility and bioavailability of As in the soil is influenced by a variety of factors, including the chemical species in question, the pH, redox potential, the presence of manganese and iron oxides, soil texture and clay minerals, adsorption to carbonates and organic matter content [10].

Although As is found naturally in plant species, the concentration in their tissues rarely exceeds 1 mg/kg [10], while the limit established for fruit, vegetables and crops is 2.6 mg/kg of fresh weight [11]. However, when plants grow naturally in soils containing high As concentrations, for example in soils influenced by mining activities, high concentrations of As may be found in their tissues, where they may represent a risk to public health because the plants may form part of the diet of animals [9,12].

The concentration of As in marine environments has increased in recent years, mainly as a result of human activity [13]. This fact has gained much attention in recent studies because of the potential risk to humans due to the consumption of fish.

Marine organisms are capable of bioaccumulating arsenic in concentrations up to 1-100 mg/kg [14], the permitted maximum level for human consumption being 0.03 mg/kg for fish and 0.1 mg/kg for shellfish [15].

At present, the toxicity of As in fish is unknown, although it is known that it accumulates in fish in the retina, liver and kidneys, and provokes an increase in the hepatosomatic index and histopathological alterations in the liver [16].

Arsenic and human beings.

Given the metabolic pathway proposed for human beings, the methylation of arsenic will result in the reduction of As (V) to As (III), followed by the oxidative addition of a methyl group to the As, according to the scheme shown in Figure 2. It is believed that the glutathione acts as reductant and S-Adenosylmethionine (SAM) as donor [17]. The presence of concentrations of the metabolites Monomethylarsonate acid (MA) and Dimethylarsinic acid (DMA) in human urine is evidence of such a pathway [18]. It is accepted that the methylation of the inorganic forms of arsenic is a process of detoxification since, in general, toxicity diminishes as the organic character of the forms increases, as Table 1 shows. As can be seen, MA and DMA show an intermediate degree of toxicity, while trimethylated species such as TMAO, AC and AB are considered non-toxic.

It is considered that a daily oral intake of inorganic arsenic of 0.3 μg/kg will have no adverse effect on humans. This dose is calculated assuming the ingestion of 2 μg of As per day in foods and the consumption of 4.5 L of water per day [19]. Marine products represent the greatest source of As in humans, mainly fish, which provides 90% of the arsenic consumed. However, less than 3% of this As is in an inorganic form (Arsenate or Arsenite) [17].

In 2003 the EU established the maximum total arsenic content permitted in fish- and animals derived foods 6 μg/g. The directive recognised the differences in toxicity of the various forms of arsenic and called for the development of analytical methods that can distinguish between inorganic and organic

forms, since, on many occasions, the above level of total As may be exceeded while the main chemical forms involved may be non-toxic [20].

Effects of Arsenic in humans.

Arsenic is considered a carcinogen, mutagen and teratogen [2]. It inhibits the uptake of glucose into cells, gluconeogenesis, fatty acid oxidation, and the further production of acetyl CoA. Most importantly, arsenic inhibits the synthesis of GSH, one of the most powerful cellular antioxidants [21]. Both *in vivo* and *in vitro* studies have shown that arsenic is able to induce chromosome instability, aberration, telomere attrition [22] and the formation of reactive oxygen species (ROS) [23, 24].

Exposure to inorganic As may have several other effects, including irritation of the stomach and intestines, decreased red and white blood cells, alterations of the skin, and lung irritations. It has been suggested that the intake of significant amounts of inorganic As may increase the likelihood of developing skin, ling, liver and lymph cancer. It may lead to a loss of resistance to infections, brain damage and infertility and abortion in women [25].

Arsenic is distributed throughout the organism: liver, kidneys, spleen, skin, muscles, bone and nerve tissue, uterus, etc., although the toxicological characteristics closely depend on the As species in question.

Mineral As undergoes methylation after ingestion, and is transformed into monomethylarsonate and dimethylarsinic acid, which are excreted in the urine. This gradual methylation of As constitutes a form of detoxification since dimethylarsinic acid is 25 times less toxic than As (III). However, if large quantities of mineral As are ingested, the possibility of methylation is much reduced, and so the risk of toxicity is increased?. While arsenate is excreted rapidly in the urine, and is not apparently accumulated in the tissues, arsenite is accumulated and binds to the tissue proteins in the liver, muscles, hair, nails, skin and, especially, leukocytes, resulting in alterations in various enzymatic systems before being excreted through the bilis [26].

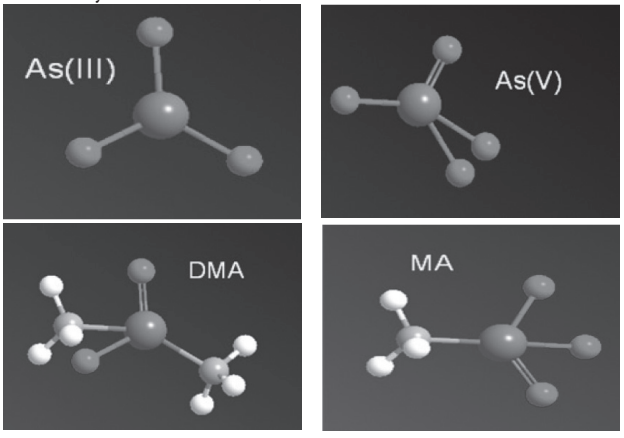

Figure 1.- Some chemical forms of arsenic that occur in nature.

Lastly, organoarsenic compounds as arsenobetaine are excreted as ingested and are not retained by the organism [26].

Relationship between Arsenic and the human telomerase.

A **chromosome** is a structure of DNA, protein, and RNA found in cells. In eukaryotes, nuclear chromosomes are packaged by proteins into a condensed structure called chromatin. This allows the very long DNA molecules to fit into the cell nucleus. Chromosomes may exist as either duplicated or unduplicated. Unduplicated chromosomes are single linear strands, whereas duplicated chromosomes contain two identical copies (called chromatids or sister chromatids) joined by a centromere.

Compaction of the duplicated chromosomes during mitosis and meiosis results in the classic four-arm structure (pictured to the right) if the centromere is located in the middle of the chromosome or a two-arm structure if the centromere is located near one of the ends. Chromosomal recombination plays a vital role in genetic diversity. If these structures are manipulated incorrectly, through processes known as chromosomal instability and translocation, the cell may undergomitotic catastrophe and die, or it may unexpectedly evade apoptosis leading to the progression of cancer.

Telomeres are the specialized nucleoprotein complexes at the physical ends of eukaryotic chromosomes [27]. Telomeres in most species consist of repeat units of a small number of nucleotides that together with secondary structures and associated

proteins stabilize the linear chromosomal DNA molecule, being essential for the maintenance of chromosomal integrity. Besides this, telomeres are important in regulating the replicative lifespan of somatic cells. It is a fact that telomere length decreases along with increasing cycles of cell divisions and, for this reason, telomere shortening was proposed to play a role in cellular senescence. Chromosomes lose a small amount of telomeric DNA after each cell replication. It has been proposed that when telomeres shorten below a critical length, a DNA damage response pathway is activated and induces cell cycle arrest [28]. More recently, it was a exciting discovery demonstrating that telomere shortening is associated with many health conditions (such as atherosclerosis, haematologic malignancies, cardiovascular disorders or cancer) and even that telomere lengths can be altered in response to social and environmental exposures.

Furthermore, telomere shortening leads to genomic instability which is hypothesized to play a role in cancer development and prognosis [29]. Telomerase is a protein-RNA enzyme complex that adds a six-base DNA sequence (TTAGGG) to the ends of chromosomes and prevents their shortening. This enzyme is specifically activated in most malignant tumors and it is usually inactive in normal somatic cells, suggesting that telomerase plays an important role in cellular immortalization and tumorigenesis [30]. In other words, most normal human somatic cells do not have detectable telomerase activity.

The human telomerase is composed of template RNA components (hTR) and two proteins, telomerase-associated protein-1 (TP1) and telomerase reverse transcriptase (hTERT). The hTERTis considered the limiting component for telomerase activity because is often up-regulated in cells expressing telomerase activity. On the contrary, repression of telomerase activity is associated with hTERT mRNA down-regulation, while the expression of hTR and TP1 remained unchanged. Most normal human somatic cells lack expression of hTERT express it.

Arsenic trioxide (As2O3) a poisonous material for living beings, is the main component of white arsenic of Chinese Traditional Medicine. This compound is

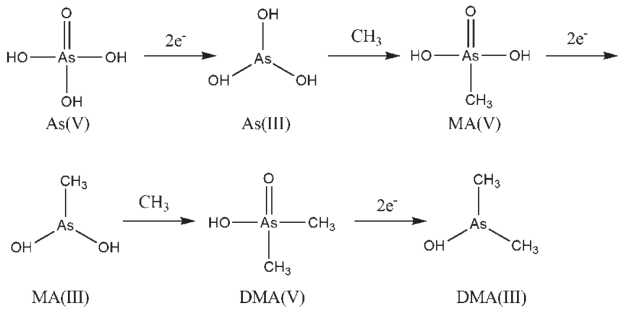

Figure 2.- Possible metabolic pathway of inorganic arsenic in the human body.

used externally to cure hemorroids, acute ulcerative gingivitis, astham, etc. Its anti-tumour activity was discovered by a group of Chinese doctors in the 70's [31]. As reported by Zhang [32], this compound was used to treat patients with acute promyelocytic leukemia (APL), resulting in a successful therapy. The pilot study demonstrated that the main mechanism for As2O3 to cure APL was to induce apoptosis and differentiation of the APL cells [33].

Arsenic trioxide (As2O3) might target mechanisms involved in the pathogenesis of other malignancies. The effect of in vitro As2O3 was studied on NB4 cells and it was dose-dependent. Relative high concentration induced apoptosis while it induced partial differentiation at low concentrations. Twenty years ago, it was demostrated in China that As2O3 is a very effective treatment for acute promyelocytic leukemia (APL). APL patients resistant to all-trans retinoic acid (ATRA) and conventional chemotherapy can still respond to As2O3. It was demonstrated that this compound triggers relatively specific NB4 cell apoptosis at micromolar concentration (as proved by morphology, histogramic related nuclear DNA contents, and DNA gel electrophoresis). These authors suggest that induction of cell apoptosis can be one of the mechanisms of the therapeutic effect of As2O3 [34].

Similarly, effects of As2O3 on HL-60 cells hTERT gene expression and telomerase activity during apoptosis induction has also been studied by flow cytometry [35]. Results demonstrated that incubation of HL-60 cells with 2 μmol/L of As2O3 for 24 to 72 h induced cell apoptosis in time-dependent way. Furthermore, the expression levels of hTERT mRNA

(determined by RT-PCR), the hTERT protein level (determined by immunofluorescence and flow cytometry) and telomerase activity (determined by PCR_ELISA) from HL-60 cells decreased with time after As2O3 treatment as compared to untreated cells (used as control). Concomitantly, there was no change of cell cycle in HL-60 cells after incubation of As2O3 for 24 h, as it was demonstrated by flow cytometry. In summary, this work corroborated that suppression of telomerase activity by As2O3 was mainly through down-regulation of hTERT expression, and down-regulation of hTERT mRNA expression preceded decrease of telomerase activity [35]. The findings should be helpful for investigating mechanisms of the antileukemic activity of As2O3 and developing novel anticancer drug targeting telomerase.

The inhibitory effect of As2O3 on growth and telomerase activity of BEL-7402 and SMMC-7721 (both hepatocarcinoma cells) has also been tested and they showed different sensitivity to the arsenic compound. Results demonstrated that each cell line requires an As2O3 concentration an incubation time to provoke significant alterations in the studied parameters [36]. While the growth and telomerase activity of BEL-7402 cells was significantly inhibited after 24h of incubation with 0.50 μmol/L of As203, being the detected inhibitory effect increased with both time and concentration of As2O3. On the other hand, at 24 h of incubation with higher concentrations of As2O3 (2.00 μmol/L, this concentration is considered safe and is used in clinical applications) was required to significantly inhibit the growth of the other tested cell line, SMMC-7721 cells, while 48 h of incubation were needed to detect significant decreases in the telomerase activity. Studies like this would suggest that it is necessary to determine if a carcinoma is sensitive or not to arsenic trioxide prior to its use for therapy.

Some considerations about the determination of Arsenic in soil.

Analyzing the total As concentration on a soil is not representative of the danger the contaminant presents. While it may point to the potential or future danger, it does not reflect the present threat, as long as previously accepted threshold values are not exceeded. It is therefore necessary to know in what physical and chemical forms the arsenic is, and the availability of fractions – which is a direct reflection of the danger [6].

Studies of trace element availability in the soil are useful for inclusion in an analysis of the risks that such elements represents [37].Chemically, the bioavailable fraction can be defined as a chemical species or the sum of various chemical species in the exposure medium [38].

Biologically, the bioavailable fraction can be defined as the portion of the total in the exposure medium that correlates with the total quantity of the element measured in the body (tissue) [38].

In the context that interests here, bioavailability refers to the extent that a contaminant is available to have an adverse effect on humans or other organisms [39, 40].

Once the element enters the gastrointestinal tract, the conditions it finds itself in will be very different to those existing in the soil [41], meaning that mechanisms need to be established for measuring its behaviour in this medium.

Before studying the absorption of contaminants in humans two aspects must be taken into account – the similarity between the material used in the assay and existing in the contaminated site, and, secondly, the degree to which the assay reflects the real physiological conditions of the human body.

Particle size is also an important factor when studying the bioavailability of a contaminant in the soil – the smaller the particle, the greater its bioavailability. Present day methods that evaluate the quantity of an element released from a soil during its passage through the stomach use the fraction lower than 250 microns, considering that it is the particles below this size that stick to the hands [42, 43].

Although *in vivo* methods involving animals offer good results in the evaluation of the bioavailability of trace elements in the soil, the time and expense involved mean that such methods cannot be applied on a routine basis. As a consequence, *in vitro*

assays using chemical extractions that simulate the gastrointestinal conditions of the human stomach have been developed. When appropriately applied, such experiments are a good measure of the bioaccessible fraction of the element, besides being cheaper and faster than *in vivo* methods [44].

Various factors must be taken into account in this type of extraction. For example, the extraction medium must simulate the fluids of the gastrointestinal tract, the temperature must remain at 37º C to maintain physiological conditions, the extraction times must be the same as the residence times in the different sections of the gastrointestinal tract, the mixing speed must be constant and reducing conditions must be maintained by bubbling argon. Without doubt, one of the most important factors is the pH, which, based on the bibliographic revision of the subject, should remain constant (1.5 ± 0.5) since the mobility of many elements depends on this parameter.

Basically, in such extractions, soils or plants containing trace elements in a solution of approximately pH 1.5 are incubated at 37ºC for a length of time that simulates the residence time in the stomach. After this time, the pH is raised to reach neutrality and the extraction is continued for a length of time that simulates the residence time in the small intestine, adding enzymes and organic acids that mimic the gastric and intestinal juices. The fraction of the element dissolved during the extraction process in the stomach and intestine represents the bioaccesible fraction, that is, the fraction that is soluble and available for absorption. The bioaccessible fraction is generally greater than the bioavailable fraction since not all the element solubilized in the stomach is subsequently absorbed by the small intestine. The solubility of an element in the conditions representing those of the stomach is used as an indicator of its potential bioavailability [45].

Compuestos de Arsénico	LD_{50}
Arsenite (As (III))	15-42
Arsenate (As (V))	20-800
Monomethylarsonate (MA)	700-1800
Dimethylarsinic (DMA)	1200-2600
Trimethylarsine Oxide (TMAO)	10600
Tetramethylarsonium Iodide (TETRA)	890
Arsenocholine (AS)	6500
Arsenobetaine (AB)	> 10000

Table 1.- LD50 (μg/g) of some forms of As in mice.

In vitro extraction methods are generally based on the gastrointestinal conditions of children of one to six years of age, since this is thought to represent the worst case scenario since at this age the pH in the stomach is at its lowest and so the element solubilized in the stomach will probably be greater [46]. The results are then compared with those obtained in animals in *in vivo* assays and extrapolated to humans to evaluate what exposure would have involved in reality [47].

Importance of oral bioaccessibility factor for characterizing the risk associated with the ingestion of soil.

In analyses of the risk associated with the accidental ingestion of soil, it is common to use the total concentration of a metal and assume that 100% of what has been ingested is bioavailable dose. In the study carried out by Martínez-Sánchez [48] it was demonstrated the importance of characterizing the risk involved in ingestion as a function of the arsenic contained in the < 2mm (M1) and < 250μm (M2) fractions and the bioavailable As in the < 250 μm (M3) fraction. The <250 μm fraction is the most dangerous since it easily sticks to the hands, from where it may be transferred to the mouth. To determine the bioavailable As, was used a modified version of the Solubility/Bioavailability Research Consortium method, in which the conditions that occur once As has entered the gastrointestinal tract are simulated. To characterize the carcinogenic risk the Chemical daily intake (CDI) was calculated according to the methods M1 and M2 (the most frequently used), and M3. The other parameters were those published by the USEPA (1989).

In this study, that can be used as a representative case, two scenarios were presented: the agricultural use to which the soils of Campo de Cartagena are put, and the use of soils close to the Mar Menor for residential purposes. Two receptors were simulated- adults and children. The results obtained show how the CDI is higher when bioaccessibility factor is not considered.

When M1 and M2 were used, some zones were considered unacceptable because of the risks (both carcinogenic and non-carcinogenic) they presented. However, the use of M3 showed the soils to have no risk. Therefore, it is very important to consider bioaccessibility factor as a factor when characterizing contaminated soils since by using the concentration of total As may cause unnecessary alarm and the erroneous diagnosis of any danger involved.

Conclusions

Although arsenic is a toxic element and potentially carcinogenic, it is important to distinguish between the different forms that may present themselves in a given medium.

Arsenic trioxide (As2O3) might target mechanisms involved in the pathogenesis of other malignancies. It is demonstrated that suppression of telomerase activity by As2O3 was mainly through down-regulation of hTERT expression, and down-regulation of hTERT mRNA expression preceded decrease of telomerase activity.

Knowledge of the different chemical species and their respective degree of bioaccessibility factor is essential for evaluating the potential risk to human health and the most suitable strategies that should be applied to eliminate wastes and to evaluate and manage the corresponding environmental and health risks.

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Healthy property of maqui berry extract

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Abstract

Introduction: Aristotelia chilensis belonging to the family of Eleocarpaceae, is a plant native to the Valdivian temperate rainforests of Chile. From its berries it is obtained a juice from the important medicinal properties, due to its extraordinary concentration of bio-active phytochemicals, mainly anthocyanins. *Materials and methods*: The present review is based on information collected from scientific journals, books, and electronic search. These sources include Scopus, Pubmed, SciFinder, Web of Science, and Google scholar as well as local books of this plant. *Results*: The reported data on traditional uses, phytochemical studies, and biological activity of Maqui, have been reviewed. Antocyanins and other bioactive molecules, and mineral elements identified so far have been summarized. A broad range of activities of plant extracts and fractions, such as antioxidant activity, anti-inflammatory effects, a-glucosidase inhibition, pancreatic lipase inhibition, anti-diabetic effects, analgesic effects and prevention of skin photo-aging, have been presented. *Conclusion:* Its many qualities make the maqui berry undisputed sovereign of the family of so-called "superfruits" as well as a valuable tool to combat oxidative stress and cellular inflammation, and by these to lower risk for age associated diseases.

Introduction

Ageing is a challenge for any living organism and human longevity is a complex phenotype. With increasing life expectancy, maintaining long-term health, functionality and well-being during ageing has become an essential goal. Healthy ageing involves the interaction between genes, the environment, and lifestyle factors, particularly diet. In recent years, there has been a growing interest, supported by a large number of experimental and epidemiological studies, for the beneficial effects of some food-contained compounds in preventing various age-related pathologic conditions, ranging from cancer to neurodegenerative diseases. Spices, herbs and fruits represent a rich nutritional source of active phenolic substances endowed with potent antioxidative and chemopreventive properties. Although the exact mechanisms by which polyphenols promote these effects remain to be elucidated, several reports have shown their ability to stimulate a general xenobiotic response in the target cells, activating multiple defense genes, activating a number of different molecular targets, impinging on several signaling pathways and showing pleiotropic activity on cells and tissues. A possible general mechanism of polyphenols healing activity, relate to their ability to overexpress highly protective inducible genes, involved in the cellular stress response and to inhibit inflammatory processes. In this context our research group has shown how some polyphenols are able to strongly activate heterodimers of NF-E2-related factors 2 (Nrf2) signaling, a critical transcriptional factor for the adaptive response to oxidative stress, and efficiently inhibit NFkB activation, the master regulator of cellular pro-inflammatory events. This double pathways interference by polyphenols, induce an over expression of endogenous antioxidants, and inhibit the production or expression of pro-inflammatory mediators including cytokines, chemokines, cell adhesion molecules, matrix

metalloproteinases, cyclooxygenase-2 and inducible nitric oxide synthase. Therefore, molecules such as anthocyanins, curcumin, catechins and other food polyphenols, should be considered as effective means for the prevention of oxidative and inflammation-mediated dysfunctions, associated to age related chronic diseases. In this review we have examined the nutritional value of the Maqui berries (Aristotelia chilensis), and its main biological activities, with a special focus on those that might offer protection against age-related diseases.

Maqui: from traditional use to phytochemical characteristics.

Maqui belongs to the family of Eleocarpaceae, with 10 genera and about 400 species, is a plant native to the Valdivian temperate rainforests of Chile. Maqui berries, very similar to blueberries, are rich in anthocyanins (delphinidins and cyanidins), antioxidants responsible for their purple coloration and, in all likelihood, for many of the medicinal properties attributed to it. Maqui's therapeutic qualities have been known for centuries to the Mapuche, indigenous people who have traditionally lived in the southern part of Chile. According to the conquistadors the Mapuche warriors ate very little solid food and drank both a fresh and a fermented beverage called "chicha" made from maqui berry which might have contributed to the strength and stamina that the warriors exhibited. The Mapuche Indians have used maqui's berry leaves, stems, fruits and wine medicinally for thousands of years. Traditionally, it is believed to heal wounds, relieve sore throats and as analgesic. Today, maqui berry is regarded as "super fruit" due to its superior antioxidant properties. Currently berries maqui are marketed in the form of juices and infusions, and supplements are also derived from the maqui.

Phytochemical screening of maqui extract (fruits or leaves) revealed the presence of antocyanins and other flavonoids, alkaloids, cinnamic and benzoic acid derivatives, other bioactive molecules, and mineral elements [18]. There are several reports concerning the anthocyanins chemical composition of *A. chilensis* indicating relatively high anthocyanin content (~135 mg for 100 g fresh weight). The total anthocyanin content in the maqui berry extracts (MBE) was ~35%, of which the anthocyanin proposition is ~80% of delphinidin, and malvidin, petunidin, cyanidin, peonidin derivatives being the rest. Recently Delphinol® (trademark owned by MNL Chile) an high polyphenols standardized extract of maqui berries, bearing ≥ 25% delphinidins, has been introduced in the European and Japanese supplement market.

Biological activities

Regarding biological activity, maqui show good responses in terms of antioxidant, anti-inflammatory anti-diabetic, anti-photo aging, etc. The broad range of activities of the fruits indicates that multiple mechanisms are responsible for its biological healing properties, linked to their characteristic phenolic content.

Antioxidant activity

In vitro antioxidant potential of maqui berries have been widely explored. Maqui fruits represent a rich source of antioxidant compounds, considering that they show high activity with respect to the DPPH. decoloration assay. This is due to their high anthocyanins content as demonstrated by the positive and direct correlation between DPPH. and total anthocyanins content (TAC). Maqui fruits show higher oxygen radical absorbance capacity (ORAC) values than over 100 different kinds of foods, including fruits, vegetables, nuts, dried fruits, spices and cereals (20 times stronger than lemon, 3.5 times stronger than blackcurrant, and 2.9 times stronger than wild blueberry).

The effect of anthocyanins on lipid peroxidation was examined *in vitro* (using artificial membrane lipid bilayer model). Results showed that anthocyanins strongly inhibited lipid peroxidation by Fe2+ ion, particularly, delphinidin demonstrates powerful inhibitory effect.

Hydrogen peroxide is the simplest peroxide with powerful oxidizing capacity, hence a highly reactive oxygen species. The effect of anthocyanins on hydrogen peroxide was examined on membrane lipids (using rat brain homogenate). Delphinidin

exhibits strongest inhibitory effect on hydrogen peroxidation of membrane lipids with lowest ID_{50}.

The antioxidant effects of *A. chilensis,* with its exceptionally high content of phenolics, have been studied in different cellular models. Maqui extract has been shown to protect both LDL from oxidation and endothelial cells from intracellular oxidative stress[1], suggesting that it could have anti-atherogenic properties[2], being atherosclerosis a possible consequences of oxidative stress on LDL cholesterol in the vascular wall. Oxidized LDL support foam cells formation and is a potent inducer of inflammatory molecules which leads to apoptosis of vascular endothelial cells thus progression of atherosclerosis.

The majority of in vitro and in vivo studies conducted so far have attributed the protective effect of bioactive polyphenols to their chemical reactivity toward free radicals and their capacity to prevent the oxidation of important intracellular components. However, observations from our and other laboratories, reveal a potential novel aspect in the mode of action of polyphenols that is, the activation of Nrf2 trascription factor, and by this, the upregulation of inducible genes characterized by antioxidant responsive element (ARE) in the promoter region. Unprecedent data from our laboratory have shown that maqui berries extract Delphinol®, strongly induce heme-oxygenase-1 (HO-1) expression and activity in endothelial cells via the activation of Nrf2/ pathway (unpublished data). Many studies clearly demonstrate that activation of Nrf2 target genes, and particularly HO-1, is strongly protective against inflammation, oxidative damage, and cell death.

Antioxidant activity has been also proposed as one of the possible mechanism of the strong neuroprotective activity of maqui anthocianions, in hippocampal cultured neurons exposed to soluble oligomers of beta-amyloid 1-40[3].

In vivo studies have also confirmed the ability of maqui berry to reduce oxidative stress in different tissues. Orally administered maqui berry extracts (MBE) suppress reactive oxygen species formation from lacrimal gland tissue, preserve and restore tear secretion capacity in dry eye. This effect is associated with the modulation of the lacrimal gland secretory system stimulated by MBE containing the anthocyanin delphinidin 3,5-*O*-diglucoside[4].

We have recently investigated the effects of oral administration of Maqui Berry anthocyanins, Delphinol®, on lipid peroxidation in healthy smokers subjects, aged 50-70 years by using a randomized double-blind study design[5]. A placebo-controlled, double-blind, crossover study (n=50) was conducted, during which anthocyanins from Maqui Berry (~ 300 mg/day) or placebos were orally administered to 50 healthy smokers subjects once daily for 4 weeks. Basic biochemical and hematological parameters were determined throughout the trial. Oxidative damage to lipids was assessed by measuring plasma-circulating oxidised LDL (immunoenzymatic assay) urine total F2-isoprostanes (HPLC with tandem MS), and plasma phosphatidylcholine hydroperoxides (PCOOH) (HPLC). Efficacy was defined as the change from baseline and after oral administration of berry anthocyanins, oxidative stress indicators in the supplemented group were better than in the placebo. Indeed, a statistically significant reduction in oxidised LDL, total F2-isoprostanes, and PCOOH was observed. Moreover, we found that anthocyanin treatment leads to a time-dependent decrease in lipid peroxidation.

Anti-inflammatory effect

The anti-inflammatory effect of anthocyanins was evaluated using mouse macrophage cells (RAW 264.7). Upon addition of LPS (lipopolysaccharides, inflammation inducer) to macrophage cells RAW264.7, the expression of cyclo-oxygenase-2 (COX-2) markedly up-regulated in response to activation of inflammatory cascades. However, in sample treated with delphinidin, up-regulation of COX-2 is inhibited. Meanwhile, the expression of COX-1 is not affected indicating that delphinidin is a COX-2 selective anti-inflammatory agent. COX-1 is important in the healthy maintenance of physiological functions. Upon UVB-irradiation on the skin, inflammatory cascade is activated with up-regulation of COX-2 and release of pro-inflammatory prostaglandins E2 (PGE2)[6 7]

Dichloromethane and methanol extracts, from both leaves and fruits, show similar effects against 12-deoxyphorbol-13-decanoate (TPA)-induced inflammation (63.9 and 66.0%, respectively). On the other hand, aqueous extract show an high effect (56.2%) against arachidonic acid induced inflammation, more than the reference drug nimesulide, reaching almost double the effect exhibit for hexane and dichloromethane extracts (30.0 and 31.5%, respectively). The topical anti-inflammatory effect of methanol extract (20%) is not significant. Tests carried out with a mixture of alkaloids extracted from the same plant allow to exclude the possibility that these are the cause of these effects[8 9].

The topical anti-inflammatory effect in the TPA and arachidonic acid assays and the analgesic activity of dichloromethane may be partly caused by the mixture of the pentacyclic triterpenoids, ursolic acid and friedelin, with quercetin 5,3′-*O*-dimethyl ether. This flavonoid has greater anti-inflammatory activity than the positive control mefenamic acid. Reports suggest that the topical anti-inflammatory activity of plant extracts is due to the presence of these compounds, mostly to the high content of ursolic acid. Quercetin 3-*O*-b-D-glucoside and kaempferol in methanol extract may be responsible for the inhibition of both topical TPA-induced inflammation and analgesic activity. *In vivo* assays show that kaempferol, in particular, has a significant dose-dependent anti-inflammatory and analgesic activity. *A. chilensis* extracts proved to be more efficient in relieving pain than inflammation in all the pharmacological models in mice, more potent than the maximum effect of the reference drug naproxen sodium (54%).

Other biological activitie

Anti-diabetic effects

Hydroalcoholic extract of maqui berry, after 3 weeks administration *in vivo*, has a significant effect in lowering glucose, improving endothelium-dependent relaxation and vascular contraction in alloxan-induced diabetes, possibly by the stimulation of the nitric oxide pathway. The results also reveal that chronic *in vivo* treatment of maqui extract prevents dyslipidemia in alloxan diabetic rats[10]

The effect of maqui berry extract on blood sugar level was examined using hereditary type II diabetes mouse model (C57BL/6J). First, high blood sugar level was stimulated in mouse by introducing high calorie/high fat diet, and successively maqui extract with rich content of anthocyanins was orally given to type II diabetes mouse. Blood sugar level was measured at 4-hour and 6-hour after oral administration of maqui. Blood sugar level decreased with increasing concentration of maqui. Delphinidin-3-*O*-b-D-sambubioside-5-*O*-b-D-glucoside, the main active component of maqui berry extract, is strongly suggested to contribute to the blood sugar lowering effect. In an experiment conducted using rat liver cells (H4IIE) found that Maqui inhibited the synthesis of sugar by enhancing insulin uptake to the liver cells (suppression of glucose-6-phosphatase). Further experiment conducted on L6 muscle cells confirmed that Maqui enhances the uptake of sugar into muscle cells and thus energy production. Maqui inhibit glucose synthesis in type II diabetic mouse by enhancing the uptake of sugar for energy production. The enzyme a-glucosidase catalyzes the final step in the digestion and breakdown of carbohydrates, so its inhibition can be effective for the regulation of Type II diabetes, by controlling glucose absorption. Maqui is exceptionally effective, with low IC_{50} values than the acarbose positive control (IC_{50} = 3.89 ± 0.79). Moreover, delphinidin and myricetin, present in maqui berries, have been reported as the best a-glucosidase inhibitors among the flavonoids[11]. For all these reasons Maqui Berry extract is recommended as a natural anti-diabetes agent[12 13].

Promotion of hair growth

With regards to hair growth, activation of dermal papilla cells of hair follicle is relatively important in promoting growth of hair matrix cells. Proliferation of dermal papilla cells strongly influences the process of hair growth. *In vitro* experiment was conducted to examined the effect of maqui in the proliferation of dermal papilla cells. Dermal papilla cells proliferation increase with increasing concentration of maqui. It is believed that promoting dermal papilla cells proliferation at hair follicles is important in the promotion of hair growth. In particular, 30% EtOH/water extract of maqui berry containing delphinidin

3,5-*O*-b-D-diglucoside and delphinidin-3-*O*-b-D-sambubioside-5-*O*-b-D-glucoside, significantly promoted proliferation of normal human hair papilla cells[14].

Anti-photo aging of the skin

The effect of maqui berry on photo-aging of skin was studied using fibroblasts cells and photo-aging is induced by UVB-irradiation. Results showed that maqui effectively inhibit UVB-induced cell damage of fibroblasts cells. Meanwhile, MMP-1 is the gene coded for interstitial collagenase, an enzyme that breaks down collagen. Upon UV-irradiation, expression of MMP-1 is up-regulated thus accelerating the degradation of collagen[15].

Inhibition of visible light-induced damage of photoreceptor cells

An experiment was conducted to evaluate the effect of Maqui Berry Extract on photoreceptor cells (isolated from mouse retina) upon irradiation of visible light. Results showed that Maqui at concentration as low as 1mg/mL significantly inhibited light-induced damage on photoreceptor cells of retina. Besides, light-induced apoptosis of photoreceptor cells was observed. The effect of delphinidin-3-sambubioside and delphinidin-3,5-glucoside on light-induced damage of photoreceptor cells of eye retina was studied. Both compounds significantly inhibit light-induced apoptosis of photoreceptor cells[16].

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SALA ESTÉTICA — SÁBADO 4 de Octubre de 2014

CIRUGÍA Y ANTIENVEJECIMIENTO

Moderador: Dr. Celso Bohórquez

9:00 "Últimas novedades en Cirugía genital femenina"
Dr. Jorge Gioscia

9:15 "Disfunción eréctil y cirugía peneana"
Dr. Mariano Roselló

9:30 "Cómo mejorar el aspecto físico desde dentro"
Dr. Alfredo Belzuzarri

9:45 **DEBATE**

10:00 **Simposio JanMarini Spain. Tratamiento domiciliario para el cuidado integral de la piel de venta en consulta.**
Jordi Alorda
Patrocinado por JANMARINI

11:00 PAUSA CAFÉ Y VISITA A LA EXPOSICIÓN COMERCIAL

LÁSER

Moderador: Dr. Manuel Asín

11:30 "Láseres térmicos y no térmicos en el tratamiento actual de las onicomicosis"
Dr. Justo Alcolea

11:45 "Peeling de Co_2 versus Smart Peel en el rejuvenecimento cutáneo"
Dra. Viviane Campos

12:00 "Rejuvenecimiento facial con múltiples frecuencias con láser 532/1064 y su combinación con carboxiterapia y LEDs"
Dr. Rubén Del Rio

12:15 "Efectos adversos de la depilación con láser. Revisión a los 20 años"
Dra. Paloma Tejero

12:30 **DEBATE**

13:00 **TALLER GMV**

"Blefaroplastia no ablativa (sistema Plasma PLEXR). Voluminización labial y rejuvenecimiento facial sin relleno, y otras técnicas novedosas"
Dra. Imma Adam Pous

14:00 PAUSA COMIDA

14:30 ASAMBLEA GENERAL DE MIEMBROS DE SEMAL 1ª Convocatoria. 15:00 2ª convocatoria.

DERMATOLOGÍA ESTÉTICA

Moderadores: Prof. Julián Conejo Mir

16:00 "Tratamiento de lesiones vasculares"
Dra. María Navarro

16:15 "Mi experiencia con Láser Fraccionado"
Prof. Julián Conejo Mir

16:30 "Dispositivos de uso domiciliario en estética, situación actual"
Dr. Jorge Soto de Delás

16:45 "Actualización en tratamiento de lesiones pigmentadas. Cuándo y cómo"
Dr. Daniel Brualla

17:00 "Plasma rico en plaquetas, mi experiencia"
Dr. Diego del ojo

17:15 **DEBATE**

17:30 PAUSA CAFÉ Y VISITA A LA EXPOSICIÓN COMERCIAL

CIRUGÍA ESTÉTICA ANTIENVEJECIMIENTO

Moderadores: Dr. Ramón Vila Rovira - Dr. Jorge Planas

18:00 "Nanofat en cirugía estética"
Dr. Jorge Planas

18:15 "Envejecimiento Corporal"
Dr. Ramón Vila Rovira

18:30 "Envejecimiento de surcos nasogenianos y cuello"
Dr. Cristino Suarez

18:45 "Envejecimiento palpebral. Tratamientos médicos y quirúrgicos"
Dra. Isabel Benito

19:00 "Tratamientos para rejuvenecer el pecho envejecido"
Dr. Antonio Porcuna

19:15 "Rejuvenecimiento facial con grasa autóloga"
Prof. Jose Mª Serra Renom

19:30 "Rejuvenecimiento de la mirada con técnicas combinadas"
Dr. Francisco Navarro Viana

19:45 "Cirugía Estética en el otoño de la vida"
Dra. Ángela García

20:00 **DEBATE**

*CIRCUNSTANCIAS IMPREVISTAS PUEDEN PRODUCIR ALGÚN CAMBIO EN EL PROGRAMA

SALA ESTÉTICA — VIERNES 3 de Octubre de 2014

MEDICINA Y DERMATOLOGÍA ESTÉTICA

Moderador: Prof. Joaquín Calap

9:30 "Tratamiento con retinoides del envejecimiento cutáneo"
Dra. Giovana Osorio

9:45 "Tricología Biodinámica: el cabello como marcador precoz de patologías crónicas biodegenerativas"
Dra. Elizete Nikoluk Kaffer

10:00 "Microscopia electrónica analítica en las alopecias"
Prof. Joaquín Calap

10:15 "Nuevo protocolo para el tratamiento de la alopecia androgenética"
Dra. Viviane Campos

10:30 "Toxina Botulínica y paralisis facial"
Dr. Celso Bohorquez

10:45 **DEBATE**

11:00 PAUSA CAFÉ Y VISITA A LA EXPOSICIÓN COMERCIAL

FLEBOLOGÍA ACTUAL

Moderador: Dr. Justo Alcolea

11:30 "Escleroterapia con microespuma de polidocanol"
Dra. Eugenia Pillado

11:45 "Tratamiento combinado de microespuma y láser en insuficiencia venosa crónica. Estudio comparativo"
Dr. Justo Miguel Alcolea

12:00 "Láser transcutáneo en el tratamiento de las venas de las piernas"
Dra. Virginia Benitez Roig

12:15 **DEBATE**

MEDICINA ESTÉTICA

Moderadores: Dra. Petra Vega

12:30 "Protocolo 10 en el tratamiento de la celulitis y la flacidez"
Dra. Mª José Freire

12:45 "Toxina botulínica, técnicas actuales de tratamiento"
Dr. Arthur Pimentel

13:00 "Abordaje holístico de la Menopausia desde la Medicina Estética"
Dra. Inmaculada González

13:15 "Correlación anatómica del uso racional de la toxina botulínica"
Dr. Celso Bohórquez

13:30 "Nuevas técnicas con toxina botulínica"
Dra. Elizete Nikoluk Kaffer

13:45 "Los balances musculares y la toxina botulica"
Dra. Samia Guerbaa

14:00 **DEBATE**

14:30 COCKTAIL BIENVENIDA. Lugar: Melia Sevilla

NUEVAS TECNOLOGÍAS

Moderador: Dr. Miguel Aragón

16:00 "Tecnología Plasma en el abordaje del envejecimiento facial"
Dra. Paloma Tejero

16:15 "Remodelación corporal con ultrasonidos y radiofrecuencia"
Dr. Miguel Aragón

16:30 "Biofotomodulación con LEDs. Protocolo de combinación de tratamientos en medicina estética"
Dr. Pablo Naranjo

16:45 "Celulas madre. Obtención y aplicación en dermatología y estetica"
Prof. Joaquín Calap

17:00 **DEBATE**

17:30 PAUSA CAFÉ Y VISITA A LA EXPOSICIÓN COMERCIAL

HILOS TENSORES

Moderador: Dra. Paloma Tejero

18:00 "Hilos subcutáneos en el tratamiento del envejecimiento facial"
Dr. Manuel Prieto

18:15 "Premium V-lift, un avance en hilos tensores"
Dra. Vicenta Llorca

18:30 "Hilos de sustentación en cara y cuello"
Dr. Arthur Pimentel

18:45 "Injection treatment with JBP Ultra-thin walled needles"
Dr. Shinichi Soyano

19:00 "Protocolos combinados para rejuvenecimiento facial global: microneedeling, peelings e hilos PDO"
Dr. Enrique Lorente

19:15 **DEBATE**

19:30 **CONFERENCIA MAGISTRAL**
"Autoestima y medicina estética"
Dr. Flórez Lozano JA.

***CIRCUNSTANCIAS IMPREVISTAS PUEDEN PRODUCIR ALGÚN CAMBIO EN EL PROGRAMA**

21:30 CENA: RESTAURANTE ABADES TRIANA. NECESARIA INSCRIPCIÓN, AFORO LIMITADO. COSTE 60€

JUEVES 2 de Octubre de 2014

TALLERES ESTÉTICA

8:30 **Entrega de documentación.**
TALLERES GRATUITOS SOLO PARA INSCRITOS AL CONGRESO
PLAZAS LIMITADAS
NECESARIO MANDAR BOLETÍN DE INSCRIPCIÓN A TALLERES

9:00 **CURSO PRE-CONGRESO HILOS. PRECIO: 100€ (Miembros Semal) 125€ (No Miembros). Plazas limitadas.**
Incluye Diploma acreditativo.
Dr. Jesús Chicón
PROGRAMA
Revisión histórica mini-hilos.
Clasificación mini-hilos.
Indicaciones de cada tipo de mini-hilo.
Presentación Air Disector.
Técnicas combinadas de mini-hilos con otros materiales

Taller facial con combinación de mini-hilos con pacientes reales.

Taller corporal con combinación de mini-hilos con pacientes reales.

12:00 **TALLER "El manejo de la obesidad a través de la resolución de la lipo inflamación. Nuevo Método PNK"**
Dr.Ignacio Sajoux
PATROCINADO POR PRONOKAL

13:00 **TALLER "Rejuvenecimiento Integral de la zona Peribucal con Hilos FTC y Erelle, Relleno de Carboximetilcelulosa"**
Dra. Mª José Freire
PATROCINADO POR REAL LASTING

14:30 **LUNCH & LEARN 2 Horas**
Se entregará bolsa de picnic a los asistentes. Necesaria inscripción. Aforo limitado
TALLER "RESTAURACIÓN DE LA PÉRDIDA DE VOLUMEN CON UN NUEVO INDUCTOR DE COLÁGENO"
Dra. Marta Serna
PATROCINADO POR SEBBIN

16:30 **TALLER "Mi experiencia en celulitis con Alidya"**
PATROCINADO POR REAL LASTING
Dra. Paula Rosso

17:30 **TALLER "Nuevos protocolos en Carboxiterapia"**
Dr. Juan López
PATROCINADO POR SKYMEDIC

18:30 **TALLER "Mesocarboxiterapia"**
Dr. Ignacio Ordíz
PATROCINADO POR MESOESTETIC

19:30 **TALLER "Japan Bio Products. Innovation Premium and Nanoneedles"**
Dr. Shinichi Soyano y Dra. Vicenta Llorca
PATROCINADO POR JAPAN BIOPRODUCTS

20:30 **TALLER "Rejuvenecimiento facial combinado con radiofrecuencia ablativa y minimamente ablativa"**
Dr. César Arroyo
PATROCINADO POR SYNERON CANDELA

***CIRCUNSTANCIAS IMPREVISTAS PUEDEN PRODUCIR ALGÚN CAMBIO EN EL PROGRAMA**

SALA ANTIAGING — SÁBADO 4 de Octubre de 2014

NUTRICIÓN Y SUPLEMENTACIÓN NUTRICIONAL

Moderador: Dr. Antonio Marco Chover. Vicepresidente European Council of Doctors for Plurality in Medicine.

9:00 "New orthomolecular approach in preventing and treating cardio-vascular diseases"
Dr. Jean Pierre Naim. Presidente de la Sociedad Suiza de Medicina Antienvejecimiento.

9:30 "The Role of Anti-Inflammatory Nutrition in the Treatment of Aging Skin"
Dr. Barry Sears PhD. Presidente, Inflammation Research Foundation. Marblehead, MA.

10:00 "Polyphenols and healthy ageing: nutritional effects of maqui berry"
Dr. Giovanny Scapagnini. Professor of neurological science.Italian National Research Council.

10:30 DEBATE

11:00 PAUSA CAFÉ Y VISITA A LA EXPOSICIÓN COMERCIAL

INVESTIGACIONES SOBRE ENVEJECIMIENTO

Moderador: Dra. Mercedes Eguiluz. Vicepresidenta Sociedad Española de Medicina Antienvejecimiento y Longevidad.

11:30 "6 fundamental drivers of aging"
Dr. Claude Dalle. Presidente de la Sociedad Francesa de Medicina Antienvejecimiento.

11:50 "Implicaciones de la sustancia P y el receptor NK-1 en la patología humana"
Dr. Miguel Muñoz. Hospital Universitario Virgen del Rocío.

12:10 "Burnout, depression and Fatigue: The differential diagnosis of exhaustion"
Prof. Alfred Wolf

12:30 DEBATE

13:00 CONFERENCIA MAGISTRAL
"Healthy ageing. The role of food we eat"
Dra. Natasha Campbell-McBride

14:00 PAUSA COMIDA

14:30 ASAMBLEA GENERAL DE MIEMBROS DE SEMAL 1ª Convocatoria. 15:00 2ª convocatoria.

TOXICIDAD AMBIENTAL

Moderador: Dr. Claude Dalle. Presidente de la Sociedad Francesa de Medicina Antienvejecimiento.

16:00 "Sensibilidades a químicos y alimentos. Diagnóstico y tratamiento"
Dr. Javier Hernández Covarrubias. Especialista en Medicina Ambiental. México DF.

16:30 "Toxic Metals and cell death. Chelation to support longevity"
Dra. Eleonore Blaurock-Busch. Co-chairman of the International Association of Trace Element.

17:00 DEBATE

17:30 PAUSA CAFÉ Y VISITA A LA EXPOSICIÓN COMERCIAL

OTROS TEMAS DE IMPORTANCIA EN MEDICINA ANTIENVEJECIMIENTO

Moderador: Dr. José Serres. Presidente de la Sociedad Española de Medicina Antienvejecimiento, SEMAL

18:00 "Reactivaciones virales en la edad adulta y Micro-inmunoterapia"
Dra. Josepa Rigau. Máster en Medicina Biológica y Antienvejecimiento.

18:15 "Aislamiento de células madre mesenquimales para el tratamiento de enfermedades degenerativas del aparato locomotor"
Dr. Jean Paul Osores.Especialista en Medicina Regenerativa. Lima. Perú

18:30 "Por la boca vive el pez: importancia de la salud bucodental y su influencia sobre la salud general"
Dra. Blanca Bermejo. Desarrollo área molecular.

18:45 "CoQ10 + NADH en tratamientos de fatiga crónica"
Dr. Mario Cordero. Instituto de investigación. Hospital de la Vall d'Hebron.

19:00 "El agua de mar como terapia antienvejecimiento"
Dr. Antonio Hernández. Máster en Medicina Antienvejecimiento.

19:15 "Oxi-termo-revitalización"
Dr. José Jesús Ruiz Joyanes.

19:30 DEBATE

20:00 CONFERENCIA FINAL
"Fármacos de la felicidad y longevidad"
Dr. Flórez Lozano. Catedrático. Dpto. Medicina Universidad de Oviedo.

*CIRCUNSTANCIAS IMPREVISTAS PUEDEN PRODUCIR ALGÚN CAMBIO EN EL PROGRAMA

SALA ANTIAGING — VIERNES 3 de Octubre de 2014

8:30 Entrega Documentación

9:00 Acto Inaugural

MEDICINA REGENERATIVA

Moderador: Antonio Ayala. Catedrático de Bioquímica y Biología Molecular. Universidad de Sevilla.

9:30 "Terapias Avanzadas, un modelo pionero en Europa"
Dr. Leopoldo Laricchia. Iniciativa Andaluza en Terapias Avanzadas. Coordinador científico.

9:50 "Uso de las células madre de tejido adiposo para el tratamiento de patologías asociadas a la edad"
Prof. Mario Muñoz. Departamento de Bioquímica y Biología Molecular. Universidad de Sevilla.

10:10 "Reprogramación celular in vivo: llevando la plasticidad al extremo"
Dra. María Abad. Tumour Suppression Group. Molecular Oncology. Spanish National Cancer Research Centre (CNIO)

10:30 **DEBATE**

11:00 PAUSA CAFÉ Y VISITA A LA EXPOSICIÓN COMERCIAL

MICROBIOTA

Moderador: Dr.Julián Bayón. Coordinador clínico. Sociedad Española de Medicina Antienvejecimiento y Longevidad.

11:30 "Microbiota intestinal, probióticos y prebióticos"
Dr. Francisco Guarner. Servicio de Aparato Digestivo del Hospital Vall d'Hebron, Barcelona.

12:00 "Utilización del sistema inmunitario para conocer la edad biológica y estrategias para modificarla"
Prof. Mónica de la Fuente. Catedrática de Fisiología. Universidad Complutense de Madrid.

12:30 **DEBATE**

USOS DE AGONISTAS HORMONALES

Moderador: Prof. Santiago Durán. Catedrático de Endocrinología.

13:00 "Cáncer de prostata y Agonistas hormonales: "Una relación consolidada en el tiempo""
Prof. Jesus Castiñeiras. Presidente de la Real Academia de medicina y cirugía de Sevilla.

13:30 "Hormonas y cáncer en la mujer"
Dr. Rafael Sánchez Borrego. Presidente de la Asociación Española para el Estudio de la Menopausia (AEEM)

14:00 **DEBATE**

14:30 COCKTAIL BIENVENIDA. Lugar: Melia Sevilla

EJERCICIO EN MEDICINA ANTI-ENVEJECIMIENTO:NUEVAS TECNOLOGÍAS

Moderador: Prof. Manuel Castillo. Catedrático de Fisiología. Universidad de Granada.

16:00 "Efectos de la electroestimulación integral mediante electrofitness- Biotraje MIHA Bodytec,sobre la condición física y la composición corporal"

Prof. Angel Gutierrez Sainz. Dpto. Fisiología. Universidad de Granada.

16:30 "Usos y aplicaciones de los nuevos sistemas de monitorización"
Lic. Juan Anelo. Director Técnico Health Center. Sotogrande. Cádiz.

17:00 **DEBATE**

17:30 PAUSA CAFÉ Y VISITA A LA EXPOSICIÓN COMERCIAL

EL SUEÑO COMO DETERMINANTE DE SALUD Y BIENESTAR

Moderador: Prof. Mónica de la Fuente. Catedrática de Fisiología. Universidad Complutense de Madrid.

18:00 "Sueño y su patología durante el envejecimiento"
Dr. Diego García Borreguero . Presidente de la Sociedad Española del Sueño.

18:30 "La presión arterial durante el sueño como objetivo terapéutico para reducir el riesgo cardiovascular"
Prof. Ramón C. Hermida. Director of Bioengineering and Chronobiology Laboratories. Universidad de Vigo.

19:00 **DEBATE**

19:30 CONFERENCIA MAGISTRAL
"Bioenergética del envejecimiento"
Prof. Plácido Navas. Catedrático de Biología Celular. Universidad Pablo de Olavide. Sevilla

21:30 CENA: RESTAURANTE ABADES TRIANA. NECESARIA INSCRIPCIÓN, AFORO LIMITADO. COSTE 60€

JUEVES, 2 DE OCTUBRE DE 2014

Los 10 cambios fisiopatológicos que explican la obesidad y sus posibilidades terapéuticas

DR. EFRAIN OLSZEWER (Brasil)

HORARIO: 10:00 - 14:00

LUGAR DE REALIZACIÓN: Real e ilustre Colegio de Médicos de Sevilla. Avda. de la Borbolla, 47.

Se entregará diploma acreditativo

Precio del curso: 150€ CON INSCRIPCIÓN AL CONGRESO. 200€ SIN INSCRIPCIÓN AL CONGRESO

PROGRAMA:

1. Fisiopatología de la obesidad
2. Conociendo las alteraciones fisiopatológicas que definen la obesidad
3. Actuación del eje hipotalámico-hipofisiario
4. Conociendo y modulando los neurotransmisores: serotonina, dopamina, noradrenalina, adrenalina, gaba
5. Actividad y modulación de los neuropeptidos: leptina, adiponectina, resistina, NPY, CART, cannabinoides, ghrelina, insulina y otros
6. Actividad hormonal y obesidad
7. Control del nivel de absorción de carbohidratos y grasas: modulación enzimática
8. Modular el gasto energético, estimular la actividad física
9. Activar la señalizacion de los adipocitos
10. Control de la inflamación por la modulación de la grasa visceral

Medicina Medioambiental, Envejecimiento y Enfermedades Crónicas

Dr. Javier Hernández Covarrubias (México)

HORARIO: 16:00 - 20:00

LUGAR DE REALIZACIÓN: Real e ilustre Colegio de Médicos de Sevilla. Avda. de la Borbolla, 47.

Se entregará diploma acreditativo

Precio del curso: 150€ CON INSCRIPCIÓN AL CONGRESO. 200€ SIN INSCRIPCIÓN AL CONGRESO

PROGRAMA:

1. Origen de la epidemia de enfermedades crónicas. Conceptos de Medicina Ambiental (carga total, individualidad bioquímica, diseminación, cambio...). Efecto de las ondas electromagnéticas, químicos, hongos y alimentos. Papel de la disbiosis (cándida, clostridium d.). Relación con genoma, nutrición y medio ambiente. Polimorfismos múltiples e individuales; epigenismo. Factores ambientales que afectan la salud. Deficiencias nutricionales.

2. Pruebas diagnósticas (clínica y laboratorio). La importancia de la história clínica ambiental, la exploración física (en especial de mucosas y piel), estudios de sensibilidades a alimentos, ácidos orgánicos, colesterol, vitamina D3, metales y minerales.

3. Tratamiento de enfermedades crónicas. Elaboración de un plan de salud personalizado y dinámico, a partir de información clínica y laboratorio.

*CIRCUNSTANCIAS IMPREVISTAS PUEDEN PRODUCIR ALGÚN CAMBIO EN EL PROGRAMA

XIII CONGRESO DE LA SOCIEDAD ESPAÑOLA DE MEDICINA ANTIENVEJECIMIENTO Y LONGEVIDAD, SEMAL

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Sede de los cursos pre-congreso y talleres prácticos: Real e ilustre Colegio de Médicos de Sevilla. Avda. de la Borbolla, 47.
Sede del Congreso: Hotel Meliá Sevilla. C/Dr. Pedro de Castro, 1. Sevilla.

Empresas Colaboradoras 2014

SEMAL

13TH INTERNATIONAL CONGRESS OF ANTI-AGING MEDICINE

XIII Congreso de la Sociedad Española de Medicina Antienvejecimiento y Longevidad

2, 3 y 4 de Octubre de 2014

SEVILLA

Reconocido de Interés Científico- Sanitario por la JUNTA DE ANDALUCIA

www.semal.org

Foto Plaza de España, Sevilla:
Alberto Beato García