Personalized functional gynecology: a new direction?

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http://dx.doi.org/10.1590/1806-9282.66.5.560

In recent decades, technological evolution has allowed for a monumental leap in the quality of disease diagnosis and treatment. The medical care in acute diseases is almost always successful thanks to the technological adequacy of hospitals and the therapeutic options currently available. However, when it comes to chronic non-communicable diseases (CNCD) we are still finding our way regarding the correction of molecular, metabolic, and immuno-inflammatory dysfunctions that constitute the background of the physiopathology of these nosological entities[1,2].

CNCDs are cutting our existence short, destroying our quality of life, burdening the government budget, and threatening the health of future generations. Unfortunately, conventional medicine has failed in responding to this challenge, and, as a result, the prevalence of chronic diseases continues to rise.

CNCDs are difficult to manage, costly to treat, require a multidisciplinary team, and, typically, are present throughout the second half of life. The forecast is that within the next few years, with the increase in longevity, 75% of the ´population will be affected, with a loss of autonomy and causing family and social dependence. The current therapeutic intervention is not enough to prevent or revert the evolution of morbidity. Recent reports suggest that over 85% of chronic diseases are caused by factors such as inappropriate diet, sedentary lifestyle, distorted behavior/lifestyle habits, and environmental toxins[1,3].

There is fear that the two types of therapeutic approaches are mutually exclusive. However, this fear is unfounded. The personalized functional intervention is based on the foundations of conventional medicine and adds other resources to the semiotics and treatment, with a focus on the individual behavior and environment, without ignoring the diagnosis of the disease, which can manifest in different ways depending on the individuality[4].

Six basic principles constitute the foundation upon which this modality of intervention was developed to correct functional disorders[4]:

1. Genomic and biochemical individuality of human beings.
2. Therapeutic intervention focused on the individual (anthropocentric).
3. Search for a dynamic balance between mind, body, and soul.
4. Familiarity with the interconnectivity of internal physiological factors.
5. Identification of health as 'positive vitality' and not merely as the absence of disease.
6. Promotion of organic reserves as a means of increasing the extent of health and not merely the extension of life.

Functional intervention is based on the integration of the information that comprises the biography of individuals, obtained through anamnesis, making it possible to identify antecedents, mediators, and "triggers" of physical, emotional, or environmental circumstances that trigger the body's interconnectivity system. These transgressive agents can cause metabolic and biochemical imbalances that, over time, trigger and perpetuate CNCD. Identifying the source of the imbalance, by obtaining the upstream flow of symptoms and signs, is extremely relevant in the therapeutic care because it enables to cut the roots of the problem, minimizing unfavorable outcomes to the patient or sequelae[5].

The Institute of Functional Medicine, in the United States of America*, believes that pathophysiological mechanisms originate from biomolecular changes and that they are related to the intricate relationship between gene expression, lifestyle, and ecosystem quality*[4]*. This paradigm shift is based on the concept that every human being has a genetic, biochemical, and metabolic identity*[4].

Fundamental physiological processes take place in the cell framework and the extracellular matrix integrated into an extensive network of intercommunication. A huge cascade of substances, organelles, receptors, hormones, growth factors, transcription factors, prostaglandins, cytokines, interleukins, and others, act at this stage executing a harmonious dance, in ideal conditions, or an anarchic and disastrous spectacle when in a state of adversity[5.6].

Aiming to broaden the quality of care for patients in the Climacteric Ambulatory of HC-FMUSP, we have recently started care and research activity that introduces this modality of intervention that operates primarily in the correction of lifestyle, environmental awareness, social adaptation of the patients. To accomplish this task, we have put together a multidisciplinary team of physicians, nutritionists, psychologists, physical educators, etc.

Gynecologists need to be prepared to explore more deeply the history of women's lives beyond what they learned in the basic curriculum. For a long time in their lives (from the fertile years to the menopausal transition) women are under the medical care of obstetrician-gynecologists[7]. The prevention of CNCD must occur in this stage of life through the correction of metabolic and biochemical imbalances. In the supplementary interview, it is necessary to observe adverse conditions in the everyday life of the individual (lifestyle and environment) that can act as a trigger for biochemical and metabolic instability. These include (a) the quality of the air, water, and soil; (b) exposure to microorganisms; c) physical activity and reduction of sedentary behavior; d) previous physical or emotional trauma; e) psychosocial factors, such as family, work, community, economic condition, and daily stress; (f) use of licit and/or illicit drugs; g) exposure to pollutants; h) contact with actinic radiation (solar).

Depending on the individuals' genetic susceptibility, exposure to these factors can generate oxidative stress and/or chronic inflammation, almost always preceded by biochemical and metabolic disorders that trigger and perpetuate the disease and are worsened with obesity[5].

At the turn of the millennium, there was a scientific achievement of the utmost importance for humanity: the completion of the Human Genomic Project, coordinated by the *National Institutes of Health and the US Department of Energy*[8] and with the participation of *Celera Genomics*[9]. It found that the human genome is composed of 50.000 genes, 3.2 billion base pairs, and 3 million SNPs (single nucleotide polymorphisms). That opened up the possibility of using specific genomic profiles that could assist in the prevention and treatment of diseases[10].

However, mutant genes are expressed only when activated by stressor agents, internal and/or external, upon protein transcription. It is clear that genetic modification is not pre-determined and that lifestyle and environmental conditions play a role in the outbreak and maintenance of the disease[5].

More recently, the concept of epigenetics emerged as the result of the molecular modification of nitrogenous bases without changing the gene sequence. Changes in methylation, acetylation, and non-coding DNA arising from the interaction with lifestyle and the environment cause functional disorders in individuals' phenotypes[11].

In 2009, the scientific community completed a further achievement that would contribute significantly to functional therapeutic interventions: The Human Microbiome Project. This is the genomic identification of the microbiota, by using 16 S DNA sequencing, that comprises a quadrillion microorganisms (10 times the number of cells) potentially able to interact with the intricate communication system of the organism[12.13].

These scientific achievements will require major adaptations in the teaching of biological sciences, demonstrating that pathophysiological disorders occur primarily in the intrinsic cellular function

and manifesting in different ways in the organs and systems that integrate our body[14]. Identifying the source of imbalance is perhaps more important than the very nosological diagnosis, which is manifested differently depending on the individuality of each human being.

The genomic era has enabled the identification of mutations and polymorphisms (SNPs) that affect the expression of CYPs involved in the metabolism of estrogens, presenting an opportunity to individualize the prescription of sexual hormones to prevent oncogenesis. Thus, it is possible to assess the significance of mutations in genes involved in the carcinogen metabolism, metabolic biosynthesis of estrogens, activation of steroid receptors, and response to DNA damage[15].

Environmental pollutants are a growing threat to our health. Heavy metals (lead, mercury, cadmium, aluminum, etc) as well as the persistent organic pollutants (POPs), molecules that have a similar configuration to estrogen, and motivate a state of relative hyperestrogenism[16]. We are experiencing an unprecedented degradation of the ecosystem, which generates detriments capable of inducing hormonal disruption, oxidative stress, and DNA damage[17].

Oxidative stress is the result of an accumulation of reactive oxygen species (ROSs) which surpass the body's antioxidative potential (AntiOx). several studies have shown that reactive oxygen species can harm the cell microenvironment, particularly the organelles and membranes, destabilizing the protein, lipid, and carbohydrate molecules, and nuclear and mitochondrial DNA[18].

The social changes associated with the degradation of the environment had consequences on the female reproductive life, inducing the emergence of dysfunctions that contributed to affect their health. In the field of gynecology, we will be able to advance in the treatment of various ailments, from the strictly dysfunctional (primary dysmenorrhoea, premenstrual syndrome, mastalgia, vaginosis, infertility with no apparent cause, and other illnesses) to expansive pelvic states (fibroma, endometriosis) and precursor lesions of genital neoplasms[19,20].

The goal is to correct the biological, psychological, endocrine, immune, and metabolic imbalances that originate the disease, thus anticipating unfavorable outcomes. In doing so, the disorders are corrected at the origin of the cascade of events that invariably contribute to the genesis and maintenance of gynecological affections and diseases[18-21].

The functional intervention model is inclusive by introducing the "focus on the individual" in a propedeutic assessment, thus increasing the scope of traditional medicine, which is focused predominantly on the disease. Identifying the dysfunctions that precede the disease provides the opportunity to act on its source, decreasing the possibility of recurrence of symptoms and signs. By identifying the origin of diseases characterized as "idiopathic", they can receive specific corrective treatment instead of 'off label' or empirical interventions, for which we do not have scientific evidence of efficacy and safety. Functional nutrition, tailored physical activity, stress management all in tune with the circadian rhythm, and with environmental awareness constitute the most important tools for achieving this goal[21-24]. CNCD patients can greatly benefit from the association of both interventions (conventional and functional) to restore their health and vitality. However, such integration between different areas of health and well-controlled long-term studies are still challenges we must face to offer personalized functional gynecology to the population.

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