Extracellular vesicles play a secondary role in the onset of Oncological and degenerative disorders, including T2DM, towards the Quantum -Biophysical-Semeiotic Constitution-Dependent, Inherited Real Risks. Spattini's Sign.

By Sergio Stagnaro

The highest goal achieved by the Quantum Biophysical Semeiotic is having brought to the clinical dimension molecular biological events.

This article aims to demonstrate that the extracellulare vesicles play a secondary role towards the quantum-biophysical-semeiotic (QBS) Constitution-dependent, Inherited Real Risks in the onset of degenerative diseases and cancer.

Extracellular Vesicles: Structure and Function.

Extracellular vesicles (EVs) are submicron-sized lipid envelopes that are produced and released from a parent cell and can be taken up by a recipient cell (1). EVs are capable of mediating cellular signalling by carrying nucleic acids, proteins, lipids and cellular metabolites between cells and organs.

Metabolic dysfunction is a collective term for the clustering of disease risk factors, including hyperglycaemia, dyslipidaemia, hypertension, obesity and insulin resistance. Metabolic dysfunction significantly increases disease risk for cardiovascular diseases such as acute myocardial infarction and stroke, but exclusively in presence of their Constitution-Dependent, Inherited Real Risks. The combined pathogenesis of metabolic dysfunction implicates numerous cell types, tissues, organs, inflammatory signalling cascades and humoral factors, now bedside assessed with clinical reliable tools

Blood-based biomarkers, such as glucose, insulin and HbA_{1c} are used in the diagnosis and management of type 2 diabetes and plasma lipoproteins in cardiovascular diseases, according to the traditional Medicine, Laboratory and Image Department Dependent. Other blood-borne factors, such as inflammatory cytokines (IL-6, TNF-α, IL-10), oxidised low-density lipoproteins, triacylglycerols, leptin, gherlin and adiponectin are imperfect markers of metabolic disease (2). Metabolic dysfunction is associated with changes in plasma concentrations of EVs as well as alterations in their EV cargo (3-5). Since EVs can act as messengers between parent and recipient cells, they could be involved in cell-to-cell and organ-to-organ communication in metabolic diseases. However, all such a events are secondary towards the events, molecular biological in nature, I have described as Inherited Real Risks (See later on).

Recent literature has shown that EVs are produced by cells within metabolic tissues, such as adipose tissue, pancreas, muscle and liver. A recent meta-analysis by Li et al. reported that levels of EVs of platelet, endothelial cell and monocyte origin were significantly raised in individuals with type 2 diabetes from 48 independent studies (6,7).

Constitution-Depedent, Inherited Real Risks.

Overlooking the primary role played by QBS Constitution-Dependent, Inherited Real Risks, these vesicles have therefore been proposed as a novel intercellular communication mode in systemic metabolic regulation. There is a large current literature that investigates the role of adipose-derived EVs in the regulation of obesity-associated metabolic disease. Unfortunately, no Author has understood the importance of the presence of Low Grade Chronic Inflammation in these pathological conditions, which divides Adipose Tissue in Type I and II (18, 19, 27, 48).

Interestingly, the focus on the EV-dependent communication between adipocytes, the vasculature and immune cells in type 2 diabetes supports my clinical quantum biophysical semeiotic point of view, according to which it playes a secondary role in T2DM onset, following the primary one, i.e. Diabetic and Dislipidemic Constitution-Dependent, Inherited Real Risk (8-42).

Starting from birth, Physicians can bedside recognize the numerous quantum biophysical-semeiotic constitutions and the dependent Inherited Real Risks employees with a common stethoscope and start Primary Prevention with Reconstructing Mitochondrial Quantum Therapy (44-48).

For instance, the adipose tissue that covers a healthy breast is of type I, physiological, in which inflammation is absent.

On the contrary, starting from the birth, in presence of breast cancer Inherited Real Risk, adipose tissue iis of type II pathological (48).

Spattini's Sign in both assessing quantitatively Extracellular Vesicles and differentiating them in oncological and aspecific variant.

The "pathological" EV, originated by cells showing an increased and impaired metabolism (e.g., Inherited Real Risks), parallel the seriousness of the underlying local inflammation, Low Grade Chronic Inflammation. Therefore, it can be evaluated at the bedside by means of Spattini's Sign:

In health, ungueal pressure on the specific trigger-points brings about the Gastric Aspecific Reflex after a Latency Time of 10 sec. and Duration < 3 sec. – 4 sec.<. A small Tonic Gastric Contraction follows the reflex, showing slow realization (Fig. 1).

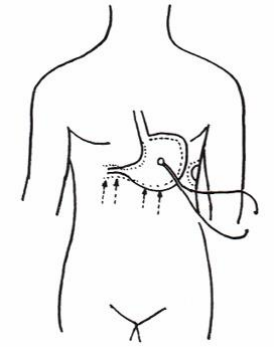

Fig 1

Aspecific Gastric Reflex: in the stomach, both fundus and body are dilates, while antral-pyloric region is contracted

On the contrary, in presence of local inflammation, the Latency Time can be normal in initial stage, or lowered, but the Duration is always pathologically increased. 4 sec. or more. Finally, an intense and rapid tonic Gastric Contraction appears.

Spattini' Sign (43), allowing the physician to bedside evaluate quantitatively any type of inflammation, including the low Grade Chronic Inflammation, is the reliable clinical tool used in my research, aimed at demonstrating that in the onset of oncological and degenerative disorders the Constitution-Dependent Inherited Real Risks play a central role (44-47).

The pathological action of extracellular vesicles, derived from adipocytes, parallel the inflammation level in the local tissue, as I have demonstrated in previous articles by means of Spattini's Sign (48-52).

Intrerestingly Spattin'i Sign shows a Latency Time of 6 sec. or more in case of aspecific inflammatory condition, while the Latency Time is characteristically 5 sec. or less in presence of overt oncologica disorders, allowing physician to make the differential diagnosis at the patient's bed.

The Glycocalix bedside Evaluation corroborates the secondary Role played by Extracellular Vesicles in the onset of chronic degenerative diseases and cancer, according to quantum-biophysical-semeiotic theory.

For the first time, Quantum Biophysical Semeiotics has made possible to evaluate clinically the functional anatomy of the glycocalyx, firstly in the Beta cell of the islets of Langerhans and those of the target organ of insulin, and subsequently in the cells of all biological systems, including the diencephalic neuronal centers of PNEI – Psycho - Neuro - Endocrine - Immune - system, at the base of Di Bella's Oncological Terrain (54).

As known, the glycocalyx (or cell coat) is a cloak that covers the cell membrane and shows a complex structure primarily composed of glycoproteins, glycolipids and glycosaminoglycans, whose main representative is hyaluronic acid, synthesized in the cell itself by three different complex enzymes. From a functional point of view, the glycocalyx is part of the cell, on the one hand, and the interstitial tissue, on the other.

Many cellular receptors, including the hormonal one, sway as antennas in the glycocalyx, whose diameter is generally double that of the cell membrane. These receptors are stimulated by their effectors, according to two different and successive phases in accordance with my discoveries. The first phase has a catalytic nature and is simultaneous to the opening of the relative segment of the n-DNA aimed to the necessary information for the synthesis of its hormone at the time of its initial release, caused by the physician in different ways (53, 54). The second phase, slower but prolonged, is represented by the binding of the hormone to its cellular receptor, with the activation of its post-receptor pathways, as taught by orthodox academic medicine.
The glycocalyx actively participates and facilitate or hinder this binding according with the current structure, the movement of many vital substances, including water and electrolytes, which move from the cell to the interstice and the microvessels and vice versa. The cell shape and continually renews its glycocalyx, whose structure and function obviously depends on the mode of being and functioning of the cell, revealed by the behavior of the respective Tissue Microvascular Unit, according to the theory of Angiobiopathy. In previous works it has been demonstrated that the

natural history of diabetes mellitus is characterized by five stages according to the QBS, following early direct genetic alteration of beta-cells and insulin target cells, i.e., the cell-muscle skeletal function. The function of the glycocalyx in these tissues appears altered starting from the first decade of life, on average around at the age of five, characterizing the second stage of T2DM, which affects subjects at Real Risk of Diabetic, depending on their QBS constitution (3-5), so that the clinical diagnosis of DM is facilitated (33). A refined method for assessing the glycocalyx of the neuronal cells of nerve nuclei of encephalics at the base of Oncological Terrain, OT., in particular the SST-RH, is described in this paper.

From the first decade of life, at about five years old, typical functional alterations of glycocalyx in neuronal centers are observed by QBS in individuals with Inherited Real Risk of Cancer dependent on Oncological Terrain. As is known, structure and function are the two poles of the same equation: it is impossible to change one without affecting the other.

Also the normal endothel glycocalyx is composed by glycosaminoglycans (GAGs), proteoglycans and glycoproteins fully integrated into a functional layer attached to the vascular endothelial luminal surface. The shredding of the glycocalyx appears as an essential initial step in the pathophysiology of atherosclerosis and microangiopathic complications of T2DM: the degradation of the glycocalyx enables an abnormal protein filtration at glomerular level and a progressively worsening disorder of the endothelium. These abnormalities underlie both the appearance and progression of the diabetic micro-angiopathy (DMA) (53-56) A number of early microvascular changes with loss of the glycocalyx, before clinically apparent vascular complications, were observed in a population of children affected by type 1 diabetes mellitus. These results disclose the glycocalyx as a possible monitoring measurement for earlier detection of DMA and may provide a basis for new diagnostic and therapeutic strategies aiming at protection or restoration of the glycocalyx. This reinforces the importance, starting from the first decade of life, of a proper and timely assessment of the glycocalyx and the microvascular compartment. In the present paper wprevious articles, my disciples and I havee explored a pathophysiology of T2DM resumed in five-stages suggested by a clinical diagnosis, based on the Auscultatory Percussion (AP) of organs and viscera, and termed Quantum Biophysical Semeiotics (QBS).

This novel technique allows an early assessment of the clinical and preclinical stages of T2DM. Our research is based on a case series observational study run by me, between 1982 and 2012. The inclusion criteria were the patient's age (< 40 y.o.), an already established clinical T2DM diagnosis and the absence of the clinical signs of the DMA. The exclusion criteria were the patient's age (> 40 y.o.) and the presence of already well known complications related to the DMA. A total of 250 patients were recruited and evaluated using the QBS diagnostic method based on the spatial (cm) and temporal (sec) reflexes' parameters which can be observed during the AP. The following outcome measures were adopted: (1) to establish the variations over time (mean follow-up 10 years) of the parameters appreciated during Overview Mitochondria dysfunctions, blood-brain barrier impairments, endothelial and glycocalyx evaluations are novel insights into the pathogenesis and early diagnosis of type 2 diabetes mellitus (T2DM). T2DM is characterised by a localised endothelial cell dysfunction that underlies the development of both the micro and macrovascular complications of the disease. Various theoretical models and experimental approaches provide data about changes to the structure and functions of the glycocalyx under various types of inflammatory conditions. These alterations are suggested to promote inflammatory processes in the vessels and local parenchyma.

Interestingly, to demonstrate the central role played by the Constitution-dependent, Inherited Real Risks, during the Reconstructing Mitochondrial Quantum Therapy, first of all the signs of microcirculatory remodeling disappear and after those of inflammation.

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