The Role of Modified Mediterranean Diet and Quantum Therapy in Type 2 Diabetes Mellitus Primary Prevention

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Abstract: The Authors provide an overview of useful treatments such as 'Modified Mediterranean Diet', CoQ10, melatonin, carnitine and 'Quantum Therapy', testing their effects in Type 2 Diabetes Mellitus (T2DM) primary prevention, performed possibly in the three first stages of T2DM. This is done through 'Quantum Biophysical Semeiotics' biological evaluation, clinically monitoring the results and efficiency of ongoing therapies aimed at improving mitochondrial and endothelial function, when it is impaired in any biological systems. This clinical method allows physicians to bedside assess tissue acidosis, before and during different preventive therapies, testing their respective efficacy and utility.

All the investigated treatments have firstly ameliorated and then normalized tissue microcirculatory pattern, showing a physiological functioning. Furthermore the tested 'Quantum therapy' generates virtuous genetic feedbacks.

'Quantum Biophysical Semeiotics' theory is an extension of medical semeiotics. It is grounded on a multidisciplinary approach that involves chemistry and biology, genetics and neuroscience, chaos theory and quantum physics. It is based on the method of 'Auscultatory Percussion', through which by means of the common stethoscope, it is possible to listen to the signs that the body gives us when appropriately stimulated. The stimuli are used to induce consistent behavior in precise and well defined biological systems of the human body, thus giving local qualitative information on the state of health or disease, whether potential, being developed but not yet evident by usual clinical trial, effective or even in chronic phase. The 'Quantum Biophysical Semeiotics' theory provides very detailed case studies based on the latency time, duration, and intensity of the reflexes, which play a central role in such a diagnostic method.

Keywords: Type 2 Diabetes Mellitus, T2DM Inherited Real Risk, CoQ10, Primary Prevention, Mediterranean Diet, Melatonin, Carnitine, Quantum Therapy, Clinical Diagnosis, Quantum Biophysical Semeiotics.

INTRODUCTION

In a recent paper [1] we have shown the crucial importance of 'Modified Mediterranean Diet' and the important role of 'Coenzyme Q10' in the primary prevention of several diseases. CoQ10 has got a central bio-energetic role in mitochondrial redox metabolism and phosphorylation of ADP. Furthermore, we have highlighted the 'Melatonin Action Mechanisms' in metabolic processes. This is done through 'Quantum Biophysical Semeiotics' bed-side evaluation, which allows physician to bedside assess CoQ10 deficiency.

Quantum Biophysical Semeiotics – QBS - theory, extension of the medical semiotics, is based on the Congenital Acidosic Enzyme-Metabolic Histangiopathy, CAEMH [2], a unique mitochondrial cytopathy, present at birth and subject to medical therapy. According to QBS, physicians can bed-side evaluate, simply using the stethoscope [3], the mitochondrial functionality of their patients in all biological systems.

In the present paper we focus our attention to Type 2 Diabetes Mellitus clinical and pre-clinical diagnosis, bed-side, taking in account the patho-physiology of T2DM, i.e., the five stages of its pathogenesis [4].

Since birth, it is possible to make a diagnosis in order to assess the presence of Inherited Real Risk of T2DM [5], linked to QBS Diabetic "and" Dislipidemic Constitutions, so that an intelligent prevention in subjects with Inherited Real Risk can be implemented. On the basis of QBS constitutions[2] [6], e.g., Osteoporotic Constitution, Oncological Constitution, the onset of more serious diseases such as osteoporosis,

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[1]Cytopathy is the state of suffering of cells, which associated with mitochondria and alterations of mit-DNA, is indicative of diseases in humans, often only potential, as in the quantum biophysical semeiotic constitutions and its related inherited congenital Real Risks. It has been identified several syndromes associated with specific mutations and alterations in mit-DNA, associated with mitochondrial cytopathy, such as cardiomyopathy, hypoglycemia, diabetes, respiratory problems, epilepsy and stroke. One of the authors defines a well determined mitochondrial cytopathy, termed Congenital Acidosic Enzyme-Metabolic Histangiopathy (CAEMH). CAEMH- in his most intensive form, which has got a key role in the semeiotic biophysics, in the clinical microangiology and in the modern medicine.

[2]Quantum Biophysical Semeiotic constitutions, detectable since birth, are the inherited congenital ground or terrain of well defined potential diseases clinically hidden, which can last several years before appearing, in the slow transformation process from potential (pre-metabolic syndrome, pre-clinical stages) to effective pathology (metabolic syndrome).

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diabetes, cancer, ischemic heart diseases, including myocardial infarction, can be prevented, at the condition that their Inherited Real Risks are recognized early, at the best at birth.

The new approach introduced by QBS allows the diagnosis of T2DM, even silent or in the very beginning clinical stages. The existence of pre-metabolic syndrome[3], pre-clinical stage of still potential diseases (evolution to pathology, pre- morbid state or gray area), can also be assessed, so allowing an effective prevention.

According to QBS theory, genome's information are transmitted simultaneously both to parenchyma and related microvessels (technically speaking, to related tissue-microcirculatory-units) , so that mutations in parenchymal cell n-DNA and mit-DNA are *the conditio sine qua non* of the most common human disorders, like diabetes and cancer, bedside recognized by local microcirculatory remodeling[4]. In fact, all these diseases are based on a particular congenital, functional, mitochondrial cytopathy, mostly transmitted through mother, the CAEMH [7]. In addition, parenchymal gene mutations cause a local microcirculatory remodeling, gathering indirect information on inherited modifications of the relative parenchymal cell, since biological system functional modifications parallel gene mutation, according to Angiobiopathy theory [8]. The presence of intense CAEMH – termed CAEMH-α - in a well-defined biological area, involved by gene mutations in both n-DNA and mit-DNA, is the base for one or more QBS constitutions which could bring about, i.e., the congenital Real Risk - RR[5] - of T2DM characterized by microcirculatory remodeling, intense under environmental risk factors.

Whit the aid of QBS, medical doctors are able to do the clinical evaluation of microvascular dynamics [9-11]. The microvessels carry on a motor activity, autochthonous and chaotic deterministic, which represents one of the most remarkable manifestations of microcirculatory hemodynamics, characterized by a *flow-motion* and rhythmically fluctuating hematocrit due to the particular non-linear behaviour [12, 13] of both *vasomotility* and *vasomotion*[6].

Furthermore, the 'Inherited Real Risk' (IRR) of T2DM, characterized by newborn-pathological Endoarteriolar Blocking Devices (EBDs), is associated to endothelial dysfunction[7], which doctor can bed-side assess in an easy and reliable way, at rest as well as under stress tests. As a consequence of the above, briefly referred remarks, according with QBS theory, physicians can observe the presence of typical pathological EBDs[8] in microvessels [14, 15], which play a central role in T2DM 'Inherited Real Risk' (IRR).

QBS method allows physicians to monitor tissue acidosis revealed by the latency time (Lt) of Gastric Aspecific Reflex (G.A.R.) before and during different preventive therapies, comparing them and testing the respective efficacious and utility.

1. State of the Art

a. Type 2 Diabetes Mellitus

Diabetes mellitus, often simply referred to as diabetes, is a condition in which a person has high blood sugar, either because the body does not produce enough insulin[9], or because cells do not respond to the

[3]Metabolic syndrome is a combination of medical disorders that increase the risk of developing cardiovascular disease and diabetes. It is also known as metabolic syndrome X, syndrome X, insulin resistance syndrome, Reaven's syndrome. The pre-metabolic syndrome, as defined by Stagnaro, is the syndrome that precedes the metabolic one, and is linked with congenital real risks and their associated biophysical semiotics constitutions.

[4]The micro-circulatory remodeling is directed by the way of living and working on the parenchyma: if the subject is healthy, the related parenchyma on the microcirculation is healthy too.

[5]Real Risk – RR - means any mutation, limited at level of cells belonging to a well-defined biological system - for example, beta cells of islets of Langerhans, for diabetes - which occurs in one or more cells when ATP decreases strongly for any reason.

[6]In all tissues, a part from their local different architecture, microvessel diameter oscillates rhythmically during time. The term *vasomotility* refers to small arteries and arterioles sphygmicity, according to Hammersen, and *vasomotion* is the subsequent oscillation of capillaries and post-capillaries venules diameter.

[7]There are mitochondria also in endothels, although in small amount. In the lining of the arteries (endothelial cells) and the smooth muscle cells in the walls of the arteries. The endothelial dysfunction is likely to be multi-factorial in these patients and it is conceivable that risk factors such as hypertension, hypercholesterolemia, diabetes mellitus and smoking can contribute to its development.

[8]The Endoarteriolar Blocking Devices (EBDs) are a kind of dam which by opening and closing regulates blood flow in microvessels directed to the parenchyma. If these EBDs are tough, rigid, inelastic, there is a Real Risk of disease. There are EBDs Type I - located in small arteries, according to Hammersen -, and Type II – they can be found in the arterioles that are between small arteries and capillaries -: only type II is ubiquitous, in the sense that it is observed everywhere, in all arteries. Even these physiological types get sick or old. However, the other types, pathological-new-formed, are expressions of the Real Risk of potential disease, they are more occlusive, but through therapy they can be transformed from subtype a) pathological, to subtype b) aspecific, and then to "physiological" type, decreasing gradually their amount. EBDs play a primary role in the regulation of local microcirculatory *flow-motion*: when this is abnormal, there is congenital microvascular remodeling and EBDs bring about impairment of the Microcirculatory Functional Reserve (MFR), which contribute to affect the 'Real Risk' of disorders, like Osteoporosis, whose onset shall possibly occur after years or decades.

[9]Insulin is the principal hormone that regulates uptake of glucose from the blood into most cells (primarily muscle and fat cells, but not central nervous system cells). Therefore deficiency of insulin or the insensitivity of its receptors plays a central role in all forms of diabetes mellitus. Insulin is released into the blood by beta cells (β-cells), found in the Islets of Langerhans in the pancreas, in response to rising levels of blood glucose, typically after eating. Insulin is used by about two-thirds of the body's cells to absorb glucose from the blood for use as fuel, for conversion to other needed molecules, or for storage. Insulin is also the principal control signal for conversion of glucose to glycogen

insulin that is produced. There are three main types of diabetes:

- Type 1 diabetes – T1DM: results from the pancreatic islet β-cell, failure to produce insulin, and presently requires the person to inject insulin.
- Type 2 diabetes – T2DM: results from insulin resistance, a condition in which cells fail to use insulin properly, sometimes combined with an absolute insulin deficiency.
- Gestational diabetes: is when pregnant women, positive for Diabetic Constitution, who have never had diabetes before, have a high blood glucose level during pregnancy. It may precede development of T2DM.

Other forms of diabetes mellitus include congenital diabetes, which is due to genetic defects of insulin secretion, cystic fibrosis-related diabetes, steroid diabetes induced by high doses of gluco-corticoids, and several forms of monogenic diabetes. Both type 1 and 2 are chronic conditions that usually cannot be cured. Serious long-term complications include cardiovascular disease, chronic renal failure, retinal damage, exclusively in patients involved by related inherited real risks, as shown previous [16]. Adequate treatment of diabetes is thus important, as well as blood pressure control and lifestyle factors such as smoking cessation and maintaining a healthy body weight.

In 2000, at least 171 million people worldwide were suffering from diabetes, namely 2.8% of the population.

for internal storage in liver and muscle cells. Lowered glucose levels result both in the reduced release of insulin from the beta cells and in the reverse conversion of glycogen to glucose when glucose levels fall. This is mainly controlled by the hormone glucagon which acts in the opposite manner to insulin. Glucose thus forcibly produced from internal liver cell stores (as glycogen) re-enters the bloodstream; muscle cells lack the necessary export mechanism. Normally liver cells do this when the level of insulin is low (which normally correlates with low levels of blood glucose). Higher insulin levels increase some anabolic ("building up") processes such as cell growth and duplication, protein synthesis, and fat storage. Insulin (or its lack) is the principal signal in converting many of the bidirectional processes of metabolism from a catabolic to an anabolic direction, and vice versa. In particular, a low insulin level is the trigger for entering or leaving ketosis (the fat burning metabolic phase). If the amount of insulin available is insufficient, if cells respond poorly to the effects of insulin (insulin insensitivity or resistance), or if the insulin itself is defective, then glucose will not have its usual effect so that glucose will not be absorbed properly by those body cells that require it nor will it be stored appropriately in the liver and muscles. The net effect is persistent high levels of blood glucose, poor protein synthesis, and other metabolic derangements, such as acidosis. When the glucose concentration in the blood is raised beyond its renal threshold (about 10 mmol/L, although this may be altered in certain conditions, such as pregnancy), re-absorption of glucose in the proximal renal tubules is incomplete, and part of the glucose remains in the urine (glycosuria). This increases the osmotic pressure of the urine and inhibits re-absorption of water by the kidney, resulting in increased urine production (polyuria) and increased fluid loss. Lost blood volume will be replaced osmotic ally from water held in body cells and other body compartments, causing dehydration and increased thirst.

However in 2010, type 2 DM involved 250 million persons, and WHO Members forsee that in 2030 diabetics will rise to 360 milion!

T2DM is by far the most common, affecting 90 to 95% of the World diabetes population. T2DM is one of the most common human diseases, particularly in high developed countries, from the socio-economic view-point, shows a persistent and worrying annual incidence. For instance, although official data are lacking, in Italy there are 2-3 millions of diabetics, with yearly increasing of 6%, including all diabetic types, really different from both aetiopathogenetic and clinical point of view.

In fact, DM represents a *syndrome*, metabolic in origin, very complicated in its aetiopathogenesis, surely genetically based, characterized - in the last two stages (Table **1**) - by relative or absolute insulin-deficiency.

T2DM represents a multi factorial and heterogeneous syndrome, which is characterized by insulin action derangement (insulin resistance) which may be combined with insulin secretion impairment (pancreatic β–cells insufficiency). Insulin resistance is defined as a defect in the ability of skeletal muscle to take up glucose in response to insulin [17]. In fact, skeletal muscle is the major target tissue into which insulin promotes the transport of glucose.

Blood glucose is obviously absorbed also by lever as well as adipose tissue, whose insulin receptors show an abnormal sensitivity to hormone in a highly differentiated manner: lever cell insulin receptors are typically well-functioning in lithyiasic constitution! [18]. This action of insulin is regulated by genetic factors, environmental factors, blood-flow, circulating substances, and insulin signalling pathways [19].

Notoriously, a large number of diseases are associated with hyperinsulinemia-insulin resistance - IIR, such as obesity, particularly the visceral type, where one observes a direct link between insulin resistance, non insulin-dependent diabetes mellitus (NIDDM or T2DM), dyslipidemia, and arterial hypertension [20].

In addition, numerous substances from fat tissue appear to suppress insulin-mediated glucose up-take, including free fatty acids, tumour necrosis factor-alpha (TNF-α) and possibly leptins [21]. Infusion of these factors into normal animals suppresses insulin-mediated glucose up-take [22, 23].

According with the work of one of the authors [6], insulin resistance and insulin-secretion derangement are correlated in a stable manner and both play a pivotal role in the onset of T2DM. In fact, e.g., insulin-secretion is physiologically ruled by insulinemia, by means of a feed-back mechanism, through insulin-receptors localized on the membrane of insular β-cell: the two factors are strictly related each other at large number of different levels. Due to these reasons the clinical on-set of T2DM appears later, because insulin-resistance in liver, adipose cells of the abdomen wall and skeletal muscles during the initial stage, i.e., for years or decades, may be balanced by increasing of the insulin secretion.

Opie [24] described the "hyaline degeneration" of the Langherans pancreatic islets of hyperglycaemic patients, suggesting a possible relation to DM, although in that period amyloid protein was not yet identified as product of insular origin. In 1986, the protein secreted by β-cells was identifies and termed insular polypeptide amyloid [25].

Amyloid protein is composed by dense, interlacing fibrillae, which are coloured by red and are birefrigent to polarized light. These fibrillae are formed by 20 proteins and a large number of them are considered related to specific diseases. Insular amyloid is present in 90 % of diabetic (NIDDM) patients [26], composed of normal proteins, as component of serum P amyloid, and proteoglycans of heparansulfate type, present in both serum and healthy tissues.

The serum P protein component, related to acute phase proteins, may be associated to all amyloid fibrillae, which therefore are protected against proteolysis.

In addition, the experimental evidence shows the importance of this protein in case of amyloidosis "*in vivo*": in gene *knocked-out* rats the systemic amyloidosis on-set is later and its severity is less intense. Insular amyloidosis is related to the loss of approximately 40 -50% of β-insular tissue.

Human insular amyloid polypeptides bring about cytotoxity by a large number of pathological mechanisms, producing amyloid fibrillae. In addition, they undergo to glycation process. Hyperglycaemia causes the production of amyloid both increasing the production of insular amyloid polypeptides and augmenting their fibrillopoietic properties [26].

It is generally admitted that the NIDDM may occur at least 12 years before the clinical diagnosis is made, and retinopathy can develop at least 7 years before the diagnosis. During the time that diabetes is undiagnosed and untreated, complications, that could be avoided, are developing. Therefore, early diagnosis should be established to avoid those complications. In fact, in order to prevent well known diabetic complications, it is extremely necessary that the doctors could use a "clinical" tool reliable in diagnosing early diabetes mellitus, i.e., "since its initial stages" [4, 27, 28]. Until now, unfortunately, diabetes mellitus is too often diagnosed accidentally, e.g., by occasional urinary or blood tests. Furthermore, epidemiologic studies indicate that 50% of individuals with 2-hour post glucose challenge values over 200 mg/dL, a value diagnostic for diabetes, were not previously diagnosed as being diabetic [29].

T2DM is now widely considered to be one component within a group of disorders called the metabolic syndrome[10], both classic and "variant" [28]. Such as syndrome, also known formerly as dysmetabolic syndrome X, is formed by some characteristic factors: abdominal obesity, atherogenic dyslipidemia (elevated triglyceride [TG] levels, small low-density lipoprotein [LDL] particles, low high-density lipoprotein cholesterol [HDL-C] levels), elevated blood pressure, insulin resistance (with or without glucose intolerance), and prothrombotic and proinflammatory states.

b. Patho-Physiology of Type 2 Diabetes Mellitus

Since their birth all diabetic individuals show QBS signs typical of dyslipidemic "and" diabetic constitutions, and all the related Congenital Real Risks, CAEMH dependant, subsequently evolved first into pre-metabolic syndrome and later on into metabolic one under the negative influence of well-known environmental factors: sedentary lifestyle, tobacco smoke, overeating, a diet rich in saturated fats and carbohydrates, weight gain (BMI 25 or more), and so on [6, 8, 30-35]. In Table **1** the natural history of Type 2

[10]Metabolic syndrome, classic and "variant" – is a term used to define a patient with 3 or more of 5 risk factors:

1) abdominal obesity and waist circumference for men greater than 102 cm or 40 inches, and for women greater than 88 cm or 35 inches;
2) elevated triglycerides, defined as equal to or greater than 150 mg/dL;
3) low HDL cholesterol. Overall for the Adult Treatment Panel (ATP)-III guidelines, low HDL cholesterol is defined as under 40 mg/dL; previously it was under 35 mg/dL (for the purposes of the metabolic syndrome, there are different values for men and women: less than 40 mg/dL; for men and less than 50 mg/dL for women);
4) elevated blood pressure, defined according to lower values than those usually used to define hypertension: systolic over 130 mmHg or diastolic over 85 mmHg;
5) fasting glucose equal to or greater than 110 mg/dL.

Table 1: EBD (Endoarteriolar Blocking Devices); ATS (Atherosclerosis), AVA (Arteriovenus Anastomatoses), IIR (hyperinsulinemia-insulin resistance), GAGs (Glycosaminoglycans), an Integral Part of the Extracellular Matrix and Glycocalix; OGTT (Oral Glucose Tolerance Test)

Natural History of Type 2 Diabeyes Mellitus
Stage 1 (individual's birth)
Diabetic "and " Dislipidemic Constitutions
Diabetic Inherited Real Risk (Overt, LATENT or Potential)
Stage II (under 10 years)
Abnormal synthesis of Perivascular GAGs by fibroblasts, pericytes, mioblasts, megacariocytes, a.s.o.; Amiline in the Interstitial Fundamental Substance, glycocalix malfunction in both beta-cells and, peripheral target-organ cells (Location: Capillaries, Small Arteries, Arterioles, AVA type II, group B, cutaneous, EBD, a.s.o.)
Stage III (Second decade of life)
IIR, Microalbuminurie, Initial ATS Plaques , a.s.o.
Stage IV (about third decade of life)
Prediabetes, overt microvascular complications
(OGTT, Iper-Insulinemic-Normo-Glicemic Clamping, Insulinemia)
Stage V
Type 2 Overt Diabetes

Diabetes Mellitus is resumed, i.e., the pathogenesis of T2DM in case of Diabetic QBS Constitution from the moment of birth, which slowly evolves to the pathology after decades.

In fact, not "all" the individuals, even though obese and/or hypertensive, are at risk of diabetes, with the same probabilities.

On the contrary, the individuals with diabetic 'Inherited Real Risk' are all positive to dyslipidemic "and" diabetic QBS constitutions, inherited only from the mother, and associated to the diabetic Congenital Real Risk, *conditio sine qua non* of T2DM [4, 16, 30-35].

2. Diabetic 'QBS Constitution' and IRR of T2DM: Clinical and Pre-Clinical Diagnosis

The objective QBS examination allows physician to bedside recognize and quantify, in a few minutes, the presence of the 'Inherited Real Risk' (IRR) of diabetes or overt T2DM, even initial, through the evaluation of several semeiotics signs, i.e., assessing vasomotility, vasomotion and typical pathological EBDs. In following, we briefly resume the easier way for the diagnosis of this pathology or of the Diabetic Inherited Real Risk: the Gastric Aspecific Reflex (G.A.R.) through the Auscultatory Percussion of the Stomach [36-38].

In a supine healthy subject, psycho-physically relaxed, with open eyes, aiming to lower significantly melatonin secretion, a digital pinch of "mean" intensity, applied upon the skin area of diabetic trigger points brings about G.A.R., whose latency time (Lt), duration (D), intensity and Microcirculatory Functional Reserve (MFR) inform on tissue oxygenation at rest, as well under stress situations [16, 39]. In Table **2** is resumed the study case about G.A.R.

According to clinical and experimental evidences [16], tissue pH is related to the reduction of latency time (Lt) and to the extension of the duration of the G.A.R., which expresses the local Microcirculatory Functional Reserve (MFR), calculated as simply as the disappearing time of G.A.R. before the appearance of the next one [16, 33-37].

In addition, Lt of both caecal and aspecific diabetic reflexes (i.e., caecal and gastric dilation) increases significantly, raising to 24 seconds (negative semeiotic sign, absence of T2DM and of Diabetic Constitution) when digital pinch becomes "intense", hence inducing local metabolic regulation of Tissue Microvascular Unit (T.M.U.), i.e., activating the MFR [6, 7, 16, 33-37].

On the contrary, *Diabetic Constitution's sign* is positive in case of "intense" digital pinch when the reflex appears simultaneously, (Lt = 0), revealing the presence of Diabetic Constitution. In this last case, the G.A.R. is "simultaneous" [4, 16, 40].

In health – in supine position – digital pinch of mean intensity, applied, i.e., on diabetic trigger points (skin projected area of the pancreas, VI thoracic dermathomere), brings about pancreatic G.A.R. after a latency time (Lt) of 12 seconds (Table **2**, first column). Pancreatic G.A.R. lasts less than 4 sec., soon thereafter disappearing for 3-4 seconds. Afterwards, a second reflex occurs. The duration of pancreatic G.A.R. unfolds the MFR activity of related

microvessels, thus correlated with the function and anatomy of the microcirculatory bed, the T.M.U. At this point of investigation, the physician quickly interrupts the digital pressure for exactly 5 seconds. Then, Lt of G.A.R. is evaluated again: Lt raises to 24 seconds, pancreatic G.A.R. lasts less than 4 seconds, disappearing after roughly 4 seconds: these values evidence a *physiological preconditioning* (Table **2**, second column) [16].

In summary, when digital pinching is of mean intensity, physiological Lt of pancreatic G.A.R. is 12 seconds at the first evaluation (*basal-line value*), but increases clearly doubling in the second as well as in the third one, due to the physiological activation of MFR.

In individuals at risk, i.e., of T2DM, *base-line* Lt is physiological during the first evaluation (12 seconds). However, pancreatic G.A.R. lasts 4 seconds or more and disappears for less than 3 seconds. Moreover, preconditioning results "pathological", as Lt is less than 24 seconds: these values give evidence of a *pathological preconditioning.* Interestingly, in patients with T2DM, even clinically silent, the *basal value* of latency time of pancreatic G.A.R. appears to be less than 10 seconds at first evaluation and becomes lower in the second one, in relation to the seriousness of underlying disorder.

In healthy subjects the *preconditioning* brings about, as natural consequence, an optimal tissue supply of material-information-energy, by increasing the local *flow-motion as well as the flux-motion*.

On the contrary, if the 'Inherited Real Risk' of T2DM is present, *preconditioning* data are almost the same as the basal ones, but Lt is a little shorter than physiological one. Finally, in overt disease, *preconditioning* shows an altered and shorter Lt of reflex in relation to the seriousness of the underlying disorders.

At this point, we come back to the former example: in the initial phase of T2DM, which evolves very slowly toward successive phases (Tables **1**, **2**), QBS "basal" data can seem "apparently" normal. However, under careful observation, the duration of pancreatic G.A.R. is equal or more than 4 seconds (the normal value, NN, is less than 4 seconds), indicating a local microcirculatory disorder.

In these cases, *preconditioning* allows in a simple and reliable manner to recognize the pathological modifications, mentioned above, which indicate the altered physiological adaptability, even initial or slight, of the biological system to changed conditions as well as to increased tissue demands. The various QBS parameters, related to a defined biological system, parallel and are consistent with the data of *preconditioning*.

Finally, Siniscalchi's Sign [40] proved to be really efficacious in recognizing in one second Diabetic Constitution, diabetic Inherited Real Risk, and overt diabetes mellitus in a quantitative way.

In health, intense digital stimulation of pancreas trigger points does not bring about simultaneous Gastric Aspecific Reflex.

On the contrary, under identical experimental condition, Gastric Aspecific Reflex appears simultaneously, showing an intensity parallel to the seriousness of underlying disorder: < 1 cm., 1 cm and > 1 cm respectively in presence of DM Inherited Real Risk, evolving, worsening Inherited Real Risk, and finally overt DM.

3. T2DM Primary Prevention and Therapy

'Modified Mediterranean Diet' (a greater amount of fish, i.e., protein and Omega-3 fatty acids, than the normal Mediterranean Diet), together with CoQ10, 'Conjugated-Melatonin' and carnitine, were successfully tested in T2DM primary prevention and therapy[11]. The QBS method and signs were used to monitor tissue acidosis (revealed by the latency time (Lt) of G.A.R.) before and during these preventive therapies.

The combination of these treatments contributes to diminish as far as normalize tissue acidosis and re-equilibrate acid based balance as proved by a longer Lt (Table **2**, fourth column). We explain the properties of these treatments in short as follows.

a. 'Modified Mediterranean Diet Central Role' in Diabetic Prevention

Many studies suggests that Mediterranean diet may be beneficial to health [41], and variants of this diet have improved the prognosis of patients with different diseases, such as T2DM [41-48]. The Mediterranean diet, in general, was associated with increased survival

[11]We enrolled in our research thirty three women and two men, aged from 53 to 67.

among older people, especially when modified adding to it unsaturated acids and omega-3, and suggesting physical exercise, walking about 40 min. day [49].

The 'Modified Mediterranean Diet', we suggest (Table **3**), is characterised by a high intake of vegetables, legumes, fruits, and cereals; a moderate to high intake of fish; a low intake of saturated lipids but high intake of unsaturated lipids, particularly olive oil; a low to moderate intake of dairy products, mostly cheese and yogurt; a low intake of meat; and a modest intake of ethanol, mostly as red wine [41-44]. Furthermore, there are novel actions of vitamin D (i.e., it reduces tissue acidosis and it presents anti-inflammatory properties) and it is useful for the prevention or treatment of degenerative disorders such as T2DM [43-44]. The authors intend the term "diet" in etymological sense, including, i.e., daily physical exercise, whose paramount importance is highlighted as follows, since it works ameliorating endothelial function, as Conjugated-Melatonin does [1-8].

Aadherence to a Mediterranean diet proved to be efficacious in preventing most common and serious disorders, such as T2DM, particularly if personalized, and modified, after therapeutic monitoring [46-48]. However, we have to care an "unique" individual, a "single patient" with particular 'QBS Constitutions', 'Single Patient Based Medicine' [6, 30] is based on. In fact, we must consider accurately in the "single" patient his (her) whole 'QBS Constitutions' [2, 5, 6-8]. Mediterranean diet may prevent T2DM because it contributes to diminish as far as normalize tissue acidosis and re-equilibrate acid based balance [6-8]: firstly it ameliorates and then it normalized the mitochondrial activity, always impaired in case of pathology or congenital risk of disease.

In fact, as evidenced in the first chapter, according to QBS theory, tissue pH is related to the reduction of latency time and to the extension of the duration of the diabetic 'Gastric Aspecific Reflex'. By mean of the above mentioned diet, the latency time of the G.A.R. rises, and the duration of the reflex slows down, both tending to physiological levels.

b. Coenzyme Q10 in Diabetic Therapy

The present literature underlines the clinical benefits of Coenzyme Q10 (CoQ10) in different disorders, as in T2DM therapy [49-56]. Since all common and serious human disorders are based on CAEMH, as mentioned above, ubidecarenone utilization in T2DM primary prevention is justified on the base of its central action mechanism.

The present understanding of the central bio-energetic role of CoQ10 in mitochondrial redox metabolism and phosphorylation of ADP was well demonstrated [52, 57-58].

Analogously to Conjugated-Melatonin[12] multiple action mechanisms, Coenzyme Q10[13] ameliorate mitochondrial function, impaired in some biological systems in individuals positive for CAEMH. As a consequence, the use of both drugs has shown to be really efficacious in a lot of disorders [59-64], including Type 2 Diabetes Mellitus, especially when administered in earliest stage, i.e., in individuals apparently healthy, but positive for T2DM 'Inherited Real Risk' [6-8, 30].

Anti-aging effect of the antioxidant containing foods and various anti-oxidants, such as coenzyme Q10, was studied just in animals [65]. A clinical study aimed at evaluating the therapeutic efficacy of C0Q10 for primary prevention of osteoporosis in humans was done by one of the author. In spite of the small number of subjects treated (only 5) the results obtained are evidence of the efficacy of this agent which had never before been used in the therapy of osteoporosis. The possible mechanisms of action CoQ10 are discussed in the light of an original interpretation of the etiopathogenesis of this very complex bone disease [58].

c. Melatonin Action Mechanisms in Cell Metabolism

In previous monographs, new action mechanisms of melatonin were described by one of the authors [66, 67]. In several researches melatonin proved to be really useful in ameliorating metabolism and tissue oxygenation, reducing tissue acidosis and normalizing the microcirculatory flow-motion in humans. The results obtained by other Authors indicate that melatonin treatment improve metabolism and it is useful for the treatment of diabetic disorders [68-71].

According to Stagnaro's [67], such as action mechanism of melatonin in ameliorating metabolism impairment is more complex than generally admitted, including also both the positive effect on adiponectin synthesis and than its efficaciousness on lever, skeletal muscle, and parietal wall. As a matter of fact, adiponectin have showed a protective effect on metabolism in patients with type 2 diabetes mellitus

[12]We use melatonin conjugated with adenosine as prepared by Dr. Ferrari and Dr. Di Bella.

[13]We use UBIMAIOR 50, twice per day; no important side effects observed. The dose were controlled by bedside evaluation of Co Q10 Deficiency Syndrome [23-26].

[49, 72], corroborating the results in individuals with predisposition to degenerative pathologies and under different conditions [1-8, 73].

d. The Role of Carnitine in T2DM Primary Prevention

One of the authors have described 'Carnitine Deficiency Syndrome', from the clinical view-point, bedside diagnosable in a quantitative way [74-76], in accordance with the role of carnitine deficiency in patients with diabetes mellitus evidenced by other studies [77, 78]. Regarding carnitine action mechanisms, the principal function of the L-carnitine in the organism is to facilitate the metabolism of the fats for the securing of energy. The fats are metabolized inside the cellular mitochondria in the so-called process beta oxidation. So that the fatty acids could penetrate in the mitochondria, a system of specific transport is needed composed for carnitine and three enzymes [74].

The initial activation necessary for the conversion of the fatty acids of long chain to Acetil-CoA takes place in mitochondria and in the most external membrane of the same one. But, the Acetil-CoA of long chain cannot penetrate in the most internal membrane to be oxidized ("burned") in the case of carnitine deficiency syndrome [75].

The carnitine, therefore, acts as a system of transport, like a "shuttle". Joined the carnitine as Acetil-carnitine, the Acetil-CoA can cross the internal membrane of the mitochondria. Without the carnitine, the fats cannot be burned as fuel. Since they will be stored in the cells in the shape of lípids and triglycerides, insulin receptors sensitivity lowers pathologically, bringing about insulin resistance [76].

4. A New Way of Therapy: The Quantum Biophysical Approach

Recent clinical experiments about quantum therapy in EHF (Extremely High Frequency) and BRR (Body Resonance Recording) regime showed to be useful in patients with diabetes. The most important therapeutic effect of EHF-therapy for diabetes mellitus of the 1st and 2nd types is stabilization of blood sugar level, which permits to select dose of insulin or other antidiabetic medicines more precisely and to compensate and maintain blood sugar at a stable level. The more expressed therapeutic effect was observed in patients with diabetic angiopathies – the lower extremity vessel angiopathy, retinopathy, nephroangiopathy, and polyneuropathy [79].

QBS tools are not only useful for diagnostic purposes, but also for therapeutic advices, because they are able to measure the microcirculatory activity before and after each preventive therapy's treatment, in order to understand the effectiveness of remedies.

Quantum Biophysical Semeiotics allows an accurate and direct study of condition and functioning of microvessels and only indirectly of the related parenchyma[14]. If the way of being and functioning of the microcirculation improves, it means that also the way of being and functioning of its parenchyma has improved.

Treatment and prevention, according to QBS, must be geared to improve and normalize metabolism, tissue oxygenation and mitochondrial respiratory chain function, expression of the normal operation of mitochondrial oxidative phosphorylation. Indeed, the mitochondrial functional cytopathy (CAEMH) is the *conditio sine qua non* of the more frequent and severe human diseases, like CAD, type I and II DM, and Cancer.

QBS has recently tested some treatments not yet experimented for preventive purposes as the quantum treatment mentioned above and the water thermal therapy [80, 81]. We consider, among the several diagnostic parameters provided from QBS, the Latency time (Lt) of G.A.R., as illustrated in Chapter 2. In this case the physiological Lt is 12 seconds (NN = 12). If the basal value is less than 12 seconds, then there is Diabetic Constitution and Inherited Real Risk of T2DM (Table **2**, first column).

Under a continuative preventive therapy based on the combination of Modified Mediterranean Diet,

[14]The micro-circulatory remodeling is directed by the way of living and working on the parenchyma: if the subject is healthy, is healthy the related parenchyma on the microcirculation (see angiobiopathy theory, dealing with diseases of blood and lymph vessels in accordance with QBS). Certainly a loss, rheumatism, immune, infectious, can act both directly and indirectly. See [http://www.semeioticabiofisica.it/microangiologia/common.htm]. It may be that in the long run re-organization becomes difficult or impossible because the flow decreases more, and then are built up of feedback mechanisms for which are to activate dormant cancer cells. Aging with free radicals that accumulate contributes to further damage both micro vascular and parenchymal: even endothelium (cell layers lining the inner surface of blood vessels and heart chambers) and smooth muscle cells possess mitochondria. Remodeling micro circulatory type cancer is an expression of mutations of genes within cells in that forum: any change in gene expression - cell finds its expression in the parallel alteration of its microcirculation (tissue microvascular units): the tissue here is around the vessels, interstitial, not the parenchyma! If these processes are blocked, stops the entire organization. Very important is that if there are congenital abnormalities, genetically transmitted through the mother (see CAEMH, mitochondrial cytopathy or mitochondrial functional pathology in the site www.semeioticabiofisica.it) amending the unfolding vital physiological processes occur the most serious human diseases, and not, now real epidemics. Autopoietic networks must therefore regenerate themselves continuously in normal and physiological way, to maintain its organization.

Table 2: Latency Time Under Different Preventive Therapies

Latency time (Lt) in seconds	Latency time after preconditioning (pause of 5 sec.)	Diagnosis	Latency time during a combined treatment of Mediterranean Diet, CoQ10 and Melatonin	Latency time during (and after) quantum therapy	Latency time during (and after) sulphurous thermal water therapy
Lt = 12	Lt = 24	Health	==========	==========	==========
Lt = 12	Lt < 24	Inherited Real Risk of T2DM	Lt = 16	Lt = 20 (16)	Lt = 20 (16)
9 <Lt <12	18 < Lt < 24	Inherited Real Risk of T2DM in evolution	Lt = 16	Lt = 20 (16)	Lt = 20 (16)
Lt ≤ 9	Lt < 18	Type 2 Diabetes Mellitus	Lt = ↑	Lt = ↑	Lt = ↑

Legend: Lt (Latency time); ↑ = Lt increases from baseline pathological level.

CoQ10, 'Conjugated-Melatonin' and carnitine the Lt rises to 16 seconds, so that the Inherited Risk of T2DM becomes residual (Table **2**, fourth column) [1-8, 16, 82, 83]. By this way tissue oxygenation and mitochondrial activity are improved, mitochondria are running well, but the genetic alteration of mit-DNA still remains (CAEMH and Diabetic Constitution are still positive). The news is given by the quantum therapy just mentioned, as follows.

We capture, i.e., the pancreatic trigger points' radiations for one minute by means of a quantum device working in BRR mode[15], then we apply the device's crystals with the customized frequencies, on the same trigger points for 10 minutes. At this point the experimental and clinical evidences provided by QBS diagnosis and monitoring on more than 30 subjects at Risk of T2DM confirm that the diabetic 'QBS Constitution' disappeared [83]. From this moment we observe a very high Microcirculatory Activity never seen before, denoted by a Lt of 20 seconds, which lasts for 7 days.

After a re-structuring period of time (7 days) the Lt slows down to 16 seconds, more than physiological one (Table **2**, fifth column). All QBS parameters from the beginning of the single unique application, till the time-out of genetic re-structuring time, and all QBS monthly diagnosis monitoring confirm the negativity of diabetic Constitution. After 9 months from the day of the unique device's application, the Microcirculatory Activation stops: this is the time-out of the normalization period. From this moment in time there are not anymore biological evidences of quantum treatment in progress, and the diabetic 'QBS Constitution' continue to be negative [96, 98].

Furthermore, we discover that hot springs have great therapeutic properties: by the same way of the quantum treatment above mentioned, after drinking sulfuric thermal water the diabetic 'QBS Constitution' disappears, and the QBS parametrical values are similar than those induced by the quantum treatment: Lt during the genetic re-structuring length of time rises to 20 seconds, before slowing normalizing to 12 seconds after 9 months (Table **2**, sixth column) [82].

Recent experiments [83], undertaken with the same group above mentioned, have shown that quantum therapy in BRR mode and sulfuric thermal water are able to act and feed back to higher levels, directly on the causes of the diseases, such as healing the alteration of maternal mit-DNA and 'QBS Constitutions', in accordance with the Principle of Recursive Genome Function - PRGF by Pellionisz [84, 85] who argues the chance of a direct bi-directional communication's feedback between DNA and proteins. QBS clinical and experimental evidences have been analyzed and related to PRGF, in order to understand if the genetic alterations of mit-DNA could be reversed, due to the recursive energy, information and communication feedback between DNA, RNA and downstream structures such as tissues, cells, mitochondria and proteins. These evidences [86] are consistent with and fully confirm the above mentioned Principle.

Pancreatic Gastric Aspecific Reflex - mean intensity digital pressure on VI thoracic dermathomere (pancreas skin projected area- pancreatic trigger points).

CURRENT & FUTURE DEVELOPMENTS

Mediterranean Diet, CoQ10, 'Conjugated-Melatonin' and carnitine were successfully tested in T2DM primary

[15]'Quantum therapy' in this paper stands for capturing radiations from the body trigger points for 60 seconds, modulated at 10 Hz, and re-transmitting the same modulated frequencies for 10 minutes in the same place. BRR mode works with a semi-conductor of microwaves (millimeter waves) whose frequencies are in the range 35 – 70 GHz.

Table 3: An Example of Modified Mediterranean Diet

1st Day	2nd Day	3rd Day	4th Day	5th Day	6th Day	7th Day
200 gr. Mixed Fresh Salad with Olive Oil	150 gr. Pasta with Olive Oil	200 gr. Mixed Fresh Salad with Olive Oil	200 gr. Mixed Fresh Salad with Olive Oil	150 gr. Pasta with Olive Oil	200 gr. Mixed Fresh Salad with Olive Oil	200 gr. Mixed Fresh Salad with Olive Oil
100 gr Fish	100 gr. Meat	100 gr Fish	100 gr Fish	100 gr. Meat	100 gr Fish	100 gr Fish
100 gr Legumes	200 gr. Mixed Fresh Salad with Olive Oil	100 gr Legumes	100 gr Legumes	200 gr. Mixed Fresh Salad with Olive Oil	100 gr Legumes	100 gr Legumes
150 gr. Fresh Fruit	150 gr. Fresh Fruit	150 gr. Fresh Fruit	150 gr. Fresh Fruit	150 gr. Fresh Fruit	150 gr. Fresh Fruit	150 gr. Fresh Fruit
150 gr. Yogurt	150 gr. Yogurt	150 gr. Yogurt	150 gr. Yogurt	150 gr. Yogurt	150 gr. Yogurt	150 gr. Yogurt
100 gr Cereals	100 gr Cereals	100 gr Cereals	100 gr Cereals	100 gr Cereals	100 gr Cereals	100 gr Cereals

prevention and therapy, according to QBS theory. They are able to reduce tissue acidosis improving tissue oxygenation and mitochondrial activity, but the genetic alteration of mit-DNA still remains (CAEMH and 'Diabetic Constitution' continue to be positive). Recent positive clinical and experimental evidences provided by a quantum therapy able to capture and re-transmit customized frequencies from pancreatic trigger points suggested us to test the preventive effectiveness of this treatment through the assessment of QBS parameters. This quantum therapy allows to improve mitochondrial and endothelial function, and furthermore to heal the 'Diabetic Constitution'. The water therapy by means of sulfuric thermal water provides similar results as well as those offered by the quantum treatment.

According to QBS remarks, a new efficient Primary Prevention of T2DM can be performed, on very large scale in individuals, involved both by Dyslipidaemic and Diabetic 'QBS Constitutions' "and" 'Inherited Real Risk' of T2DM, which have to undergo the above-mentioned treatment, rationally prescribed, and bed-side monitored.

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