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Review Article

Risk Prediction, Assessment, and Management of Type-2 Diabetes

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Abstract

Twin epidemics of obesity and type-2 diabetes are on the rise worldwide. No country has been able to reverse this trend in the increase of cardiometabolic diseases (CMDs). In spite of the fact that these diseases are preventable, very little is done at the national level to develop awareness, introduce educational, and preventive strategies. Western medicine is disease-centric whereas, traditional medicines practiced in India and China seems to be holistic in their approach to the management of lifestyle disease. Several recent studies have demonstrated the beneficial effect of diet, exercise and lifestyle changes in the reduction, reversal, or prevention of metabolic diseases. We feel strongly, that development of integrated approach to healthcare may provide a better management option for the reversal of this observed trend in the increase of metabolic diseases. In view of these observations, we started a professional society, South Asian Society on Atherosclerosis and Thrombosis (SASAT) in the USA, to address these issues of great public health importance. In recent years, we have established collaboration with other professional platforms to develop novel approaches to the early detection and better management of CMDs. Major contributors for CMDs are hypertension, excess weight, obesity, oxidative stress, and metabolic syndrome. In this overview, we have expressed our point of view on the early diagnosis and management of type-2 diabetes. We have just described few salient observations in this short review as they relate to the incidence of cardiometabolic diseases, early detection of risk factors, and the management of the observed risks.

Keywords: *Type-2 Diabetes; Cardiometabolic Diseases (CMDs); Obesity; South Asian Society on Atherosclerosis and Thrombosis (SASAT)*

Introduction

Incidence of excess weight, obesity and type-2 diabetes is rising worldwide in epidemic proportions. In an article in 2014, we wrote that according to a World Health Organization (WHO) report, India leads the world with the largest number of diabetic subjects with over 65 million diabetics [1-4]. Just four years later, we report that China has taken over as the world leader with over 114 (American Medical Association estimation) million diabetics. The Non-communicable Disease (NCD) Risk Factor Collaboration Group (NCD-Risk), in their seminal article in The Lancet (April 2016) concluded that, "if the post-2000 trends continue in the incidence and rise of type-2 diabetes, the probability of meeting the global target of halting or reducing the rise in the prevalence of type-2 diabetes by 2025 to 2020 levels worldwide is lower than one percent" [2-4]. According to the Institute for Health Metrics and Evaluation (IHME), currently 2.1 billion people are either obese are overweight. Since 1980, obesity has increased worldwide by two-fold and diabetes by four-fold [5,6]. Major contributors for the development of this chronic metabolic disorder are inflammation, atherosclerosis, oxidative stress, endothelial dysfunction, hyperglycemia, insulin resistance, dyslipidemia, hypertension, obesity, and metabolic syndrome. Some of the early symptoms related to altered glycemia include polydipsia, polyphagia, polyuria and changes in the vision. In this overview, we will discuss briefly some on-going studies related to risk prediction, assessment, and management strategies.

Risk Prediction:

Framingham heart study (FHS) is a project of the National Heart, Lung, and Blood Institute (NHLBI) of National Institutes of Health (NIH) and Boston University [7]. According to their web site(https://www.framinghamheartstudy.org), in 1948, Framingham heart study scientists and participants embarked on an ambitious project to identify risk factors for heart disease. Today, the study remains a world-class epicenter for cutting-edge heart, brain, bone and sleep research. The FHS leaders are Vasan Ramachandran, MD, the Boston University School of Medicine (BUSN), and Daniel Levy, the NLHBI Director, and their co-investigators. The Original Cohort, founded in 1948, consisted of 5209 men and women. The Offspring Cohort in 1971 was a second-generation study, where children of the Original Cohort were eligible. Over 1000 medical articles have been published related to the FHS. Based on the results of this on-going study, the 10-year cardiovascular risk of an individual can be estimated with the Framingham (https://www.mdcalc.com/framingham-coronary-heart-disease-risk-score) Risk Score [8]. The Framingham Risk Score is computed, based on findings of the FHS about various risk factors associated with the heart disease [7,8]. Various professional organizations such as American Heart Association, Mayo Clinic, and many other independent sources, have developed heart disease risk calculators.

More than a decade earlier to the Framingham Heart Study, CSI (Church of South India) Holdsworth Memorial Hospital (HMH) in Mysore, India, had started preserving its obstetric records in hard copy from 1934 to the present [9]. From 1993 to 2001, in a collaborative study with the Medical Research Council Environmental Epidemiology Unit, University of Southampton, UK, the birth records at HMH were used to trace people born in the hospital between 1934 - 1966. The first study (n = 1069, 1993-2003) examined associations of size at birth of babies with adult cardiometabolic disorders (hypertension, insulin resistance, dyslipidemia, type-2 diabetes and heart disease) and lung function. According to an NIH summary, the main basis of the Barker hypothesis is that under nutrition in pregnancy impairs fetal growth or promotes disproportionate fetal growth, and as a trade-off these adaptations that promote survival in adverse conditions, lead to limited physiological functions and development of adult diseases of fetal origin. In spite of over six decades of research on this topic, very few interventions have been developed to reduce or prevent the conditions that promote fetal origin of adult diseases. India and China have the highest incidence of low birth weight children. Even to this day more than 30% of (over 8 million) children born in India are of low birth weight and as such they are at high risk for developing cardiometabolic diseases (CMDs) [4].

Dr. Robert Freishtat and his colleagues from the Children's National Memorial Hospital (CNMH) Washington DC, have described exosomes as "biological tweets" (that is expression in terms of short messages) shed by cells that allow for intercellular communication and alter gene expression. In their studies, they have demonstrated that adipocytes that exist in large quantities of visceral fat, "tweet" signals that cause down regulation of proteins impacting two key signaling pathways; TGF-β and Wnt/β catenin, associated with controlling chronic inflammation and fibrotic diseases throughout the body [10]. Since South Asian phenotype is characterized by increased presence of visceral fat, these observations become very important for exploring their role if any, in the initiation and promotion of CMDs in this population. With this specific goal/objective in mind we have facilitated the development of a bilateral study between the CNMH and KEM Hospital, Pune, India.

Preliminary studies done at this center (KEM) are encouraging and currently we are exploring funding for further studies from the prestigious National Institutes of Health, USA. This type of early detection of gene expression could be really a game changer for millions of South Asians who are at risk for developing CMDs and other obesity-related clinical complications. If these investigations (CNMH/KEM) develop a strong correlation between the maternal adipose tissue signals and the development of altered metabolism of the children from obese mothers, then one has to consider various strategies for the prevention of this well-known phenomenon of the fetal origin of adult diseases. Interventions at the gene expression level or using microRNA technology or gene therapies may not be cost-effective or affordable considering the huge population of individuals with excess weight, obesity, metabolic disease and type-2 diabetes in the two "Asian Giants", India and China. In one of our earlier articles we have discussed the possibility of using a dietary supplement to alter gene expression profiles. In brief, the study we have referred in that article is that of Professor Joe McCord and associates on the effect of Protandim (a herbal supplement) on Nrf2, a master transcription factor, that activates the transcription of over 500 genes (so called survival genes) (Hybertson BM., *et al*: Mol. Aspects of Med. 32: 234-46, 2011).

Now that we have discussed the earliest risk prediction (low birth weight children), let us examine the status of excess weight, altered metabolism and pre-diabetes. A recent article in the New England Journal of Medicine (2018), by the Swedish researchers involving 62,565 Danish individuals has demonstrated that childhood overweight is associated with an increased risk for developing type-2 diabetes in adulthood [11]. Obesity prevalence has increased during the past 30 years. In 2012, in the USA, 35% of the adults and 17% of the children and adolescents ages 2 - 19 years, and 8% of infants and toddlers were obese. In children, oxidative stress and adipokine levels worsen throughout the continuum of obesity and especially in the presence of the metabolic syndrome. Overweight children with components of the metabolic syndrome may be at higher risk for future cardiovascular events. (https://doi.org/10.1111/j.1559-4564.2006.05758.x). Kelly and associates at Minnesota conducted a study to assess subclinical inflammation, fasting insulin, and endothelial dysfunction before and after exercise in overweight children. They found in the overweight children and adolescents, inflammatory marker C-reactive protein was an independent component, compared with fasting insulin. Eight weeks of exercise, improved fitness, HDL-cholesterol, and endothelial dysfunction in this group [12].

In a recent article in the Journal of American College of Cardiology Professor Valentin Fuster (Director, Zena and Michael A. Weiner Cardiovascular Institute, The Mount Sinai Hospital, New York), and his associates demonstrated that after age and male sex, LDL- Cholesterol was the main predictor of the presence of arterial atherosclerotic plaques. Using the latest non-invasive imaging technology they demonstrated that, "atherosclerotic plaques were present in 50% of the middle-aged individuals with no classical risk factors and they also had hardened arteries. Researchers of this study concluded that, "these findings could help improve cardiovascular risk prevention in the general population even before the appearance of conventional risk factors, an example of primordial prevention". This sub-analysis of the PESA study (Progression of Early Subclinical Atherosclerosis) evaluated 1779 study participants who had no classical risk factors. This observation by Professor Fuster and associates brings back the immediate need for the development of non-invasive cost effective tests for determining the subclinical atherosclerosis, hardening of the arteries, endothelial dysfunction, and altered blood flow dynamics in non-symptomatic or asymptomatic individuals [13].

At the University of Minnesota Rasmussen Center for the prevention of cardiovascular diseases, Professor J Cohen and associates established comprehensive screening of asymptomatic population with 10 tests designed to detect early vascular and cardiac abnormalities and blood tests to identify potential targets for risk prediction and intervention. Authors of this study further modified their screening methodology and developed a set of 7-vascular tests, which included, large and small artery elasticity, resting blood pressure and exercise blood pressure, optic fundus photography, carotid intimal-media thickness, and micro albuminuria, and 3 cardiac tests (electrocardiography, N-terminal pro β-type natriuretic peptide and left ventricular ultrasonography [14,15]. These and other similar studies demonstrated the importance of endothelial dysfunction as an early marker for detection of hardening of arteries, alterations in the flow dynamics and the beginning of vascular diseases. Studies on the structural morphology, physiology, flow velocity and function of blood vessels demonstrated that alteration or dysfunctions of these parameters leads to subclinical atherosclerosis.

Several studies have demonstrated the usefulness of monitoring health of the blood vessels by using techniques that measure, Intima-Media Thickness (IMT), Pulse Wave Velocity (PWV; Genesis Medical System, Hyderabad, India), Ankle-Brachial Index (ABI), Carotid Duplex Ultrasound (CDU) Index, and Vessel Wall Plaque Volume (3D Carotid Ultrasound). Although many methodologies are available for early detection of altered vascular function, the most widely used method is monitoring aortic Pulse Wave Velocity (PWV). With the advance in technologies, now it is possible to use multiple technologies and build a comprehensive risk assessment platform [16]. Having said that, it is very important to remember that in majority of the countries, individuals do not get a preventive health check-up or screening. When discussing early detection of risks, education of the clinicians, caregivers, patients and even the "so called" healthy individuals becomes very important.

Now that we have discussed fetal origin of adult diseases, childhood obesity, endothelial dysfunction, we will move on to discuss the health of adolescent and adult individuals. A collaborative study between the staff of the University of Minnesota and Madras Diabetes Research Foundation (MDRF), Chennai, India, concluded, that compared to the US, the waist-hip ratio is significantly higher in men and women from India. The results support the hypothesis that South Asians are particularly predisposed toward central abdominal adiposity. This unusual distribution of visceral fat in South Asian phenotype needs further extensive studies [17]. These studies also gave rise to a simple anthropometric test to determine the individuals with metabolic syndrome (Waist/Hip ratio). Furthermore, these studies for the

first time demonstrated that monitoring Waist/Hip ratio was superior to measurements of Body Mass Index (BMI), which has been used as the gold standard for determining excess weight and in cardiovascular risk score algorithms. A recent study, based on the data from the National Health and Nutrition Examination Surveys (NHANES) between 1988 to 2014, examined the cardiovascular and renal burdens in adults with prediabetes over time and found that renal risks and vascular disease have become highly prevalent in adults with prediabetes, irrespective of the definitions used. Identification of people with prediabetes might increase the opportunity for cardiovascular and renal risk reduction [18].

Just recently (May 7th 2018) Dr. Francis Collins, the Director of National Institutes of Health, USA, announced an ambitious program called "All of US", which aims at seeking DNA and information on health habits of one million subjects, a massive historic study, aimed at accelerating the prevention and treatment of lifestyle-related metabolic diseases. Although the announcement by Dr Collins is one of the most recent one on this topic, an article in the Genetic Engineering six years ago (June 18, 2012), highlighted the partnership between the Population Genetics and Oxford University, on biomarkers for myocardial Infarction, diabetes and metabolic diseases. Under this agreement, the University will have access to Population genetics, Genome Pooling and Reflex Technologies. One of the first studies by this group will evaluate 74 exons from 12 genes across 1,000 genomic DNA samples, to try to identify genetic variations associated with diabetes and metabolic disease. As early as in 2003, Khoury., *et al.* speculated that physicians in the era of genomic medicine will have the opportunity to move from intense, crisis-driven intervention to predictive medicine by screening the entire populations or specific groups for genetic information in order to target interventions to individual patients that will improve their health and prevent disease [19].

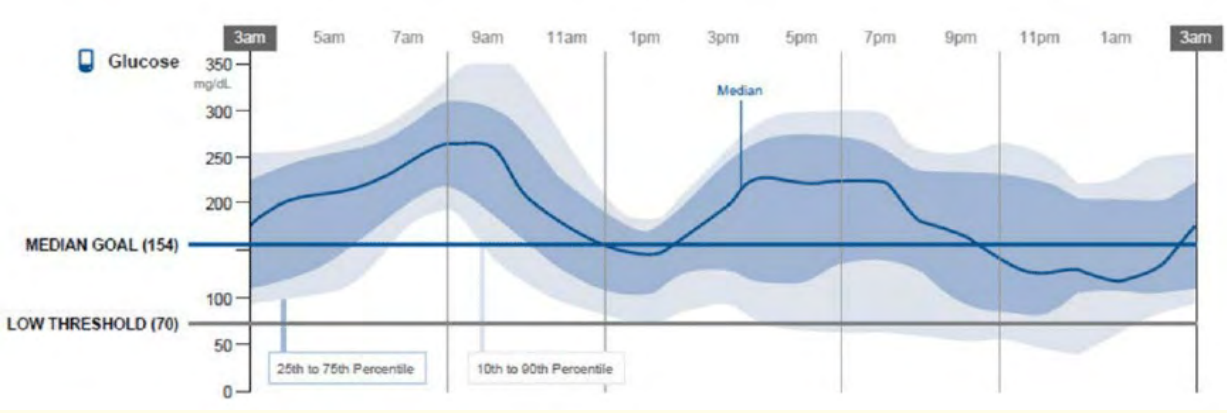
In the introductory paragraphs, we discussed the seminal studies of the Framingham heart study group. Collaborators of this pioneering study, Massachusetts General Hospital (MGH) have followed the offspring of this historical study to look at possible molecular biomarkers, which are indicative of the risk for developing type-2 diabetes. They found that elevations in just five amino acids- isoleucine, leucine, valine, tyrosine and phenylalanine, were significantly associated with the later development of type-2 diabetes. On further analysis they found combination of several metabolites, as opposed to single amino acid, improved risk prediction [20]. Authors concluded that, "These findings underscore the potential key role of amino acid metabolism early in the pathogenesis of diabetes and suggest that amino acid profiles could aid in diabetes risk prediction and assessment". As a part of our discussions on early diagnosis and risk prediction, we have briefly discussed the role of intrauterine alterations leading to the fetal origin of adult disease, childhood obesity and its role in inflammation, oxidative stress, endothelial dysfunction, importance waist/hip ratio vs. BMI in risk assessment, prediabetes, risk factors in asymptomatic patients, molecular biomarkers, genomic and population based studies. In the next few paragraphs we will discuss some novel methodologies for the risk assessment and management of type-2 diabetes.

Risk assessment and Management

In view of the fact that South Asians have the highest incidence of cardiometabolic diseases, we started a professional society called, "South Asian Society on Atherosclerosis and Thrombosis (SASAT) at the University of Minnesota in 1993. Under the aegis of SASAT and India Heart Watch, we conducted a 21-state lifestyle survey in India, to follow the regional variations in cardiovascular risk factors [21]. The pioneering case-control studies (INTERHEART/INTERSTROKE) have identified that the common risk factors account for more than 90% incidence of myocardial infarctions and stroke. A recent study from the University of Texas has demonstrated that nutrient-deficient diet may be a major factor contributing to the excess incidence of cardiometabolic diseases (CMDs) in South Asians living in the USA [22]. In spite of the fact that a variety of methods are under investigation to determine the various risks for the early detection and effective management of diabetes and its clinical complications, by and large at most clinics, detection and management of this disease is limited to monitoring and management of blood glucose levels. Various professional organizations have developed guidelines for effective management of type-2 diabetes [23]. Recent guidance statement from American College of Physicians (ACP) are as follows: 1) Clinicians should personalize goals for glycemic control in patients with type-2 diabetes on the basis of a discussion of benefits and harms of pharmacotherapy, patients' preferences, patients' general health, and life expectancy, treatment burden, and costs of care. 2). Clinicians should aim to achieve an *HBA1c* level between 7% and 8% in most patients with type-2 diabetes. In this section we would like to discuss some novel approaches that SASAT and IPC Heart Care Center (www.ipcheartcentre.com), Mumbai are using for risk assessment and risk management.

According to Rebecca Voelker's report in the recent issue of JAMA Network (May 2018), the US-Food and Drug Administration (FDA) has approved a continuous glucose monitor (CGM) that can work in tandem with mobile medical apps and automated insulin pumps to help people with diabetes manage their interstitial sugar more easily. The Dexcom G6 (www.**dexcom**.com/**G6**-CGM· Dexcom) is the first CGM approved as both a stand-alone device and one that can be integrated into automated insulin dosing systems. According to the manufacturer, Dexcom Inc. of San Diego, California, its newly approved CGM has an easy-to-use auto applicator that inserts a small glucose sensor just beneath the skin. The sensor measures glucose levels and a transmitter inside of it sends readings wirelessly every 5 minutes to a receiver or a compatible smartphone or smart watch. With a mobile app, users can share readings with up to 5 people.

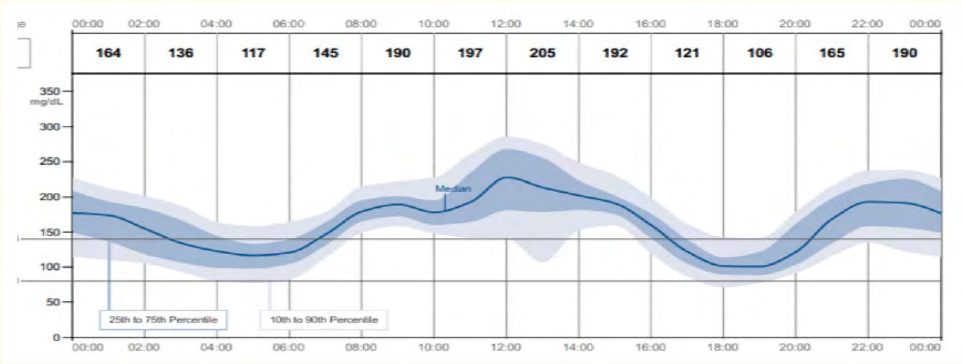
Abbott Diabetes Care also has launched an FDA approved continuous glucose monitor (www.freestylelibre.us) in India, called FreeStyle Libre Pro, with a similar easy to use sensor and a reader. However, they do not have the connectivity to smart apps other than their proprietary reader. A typical 12-hour composite glucose profile of a newly identified diabetic patient is presented below.



HBA1c 9.8%

Twelve-hour glucose profile of a newly diagnosed individual with type-2 diabetes.

The composite glucose profile shown above shows mean glucose value collected and computed from the sensor at 15 minutes intervals. Suggested mean glucose level is to bring it down to 150 or less and *HBA1c* to between 7% and 8%. Shown below is a profile of an 80-year old individual who is under medication for over 20 years. With a combination of anti-glycemic drugs, it is possible to manage glucose profile of diabetics over a long period of time. *HBA1c* level is within the range of ACP recommendations.



HBA1c 7.2

Twelve-hour glucose profile of an 80 year old: with medication, for 20 years.

Availability of easy to use disposable glucose sensors will revolutionize the detection and management of type-1 and type-2 diabetes. Ability to monitor real-time data with smart applications helps patients, their family and care givers in keeping track of changes in glucose constantly. We have initiated preliminary studies at two independent sties in India to validate these sensors for their specificity, accuracy, and correlation with blood glucose levels. We feel that such real-time measurement will enable us to follow changes in post meal increase in glucose levels. These sensors may also help us in setting up screening studies to follow the effect of new anti-glycemic drugs, dietary supplements, herbal products and life style changes on overall glucose profiles. We feel strongly, that just the detection of increased blood glucose or interstitial levels of glucose is not enough to manage chronic metabolic diseases.

There is a great need for the development of non-invasive diagnostic platforms for the early detection of cardiometabolic risks such as hypertension, endothelial dysfunction, abdominal obesity, metabolic syndrome, prediabetes, type-2 diabetes, heart disease, and stroke. Dr. Pratiksha Gandhi, the Director IPC Heart Care, Mumbai, India, introduced a new novel platform in India for screening clusters of risks associated with cardiometabolic diseases. Dr. Albert Maarek, founder CEO of LD Technologies, Miami, Florida, USA (www.ldteck.com) designed and developed this novel, noninvasive diagnostic platform to assess clusters of cardiometabolic risks. Dr. Gandhi has validated extensively this system in her specialty clinic, IPC Heart Care, to screen heart disease patients for risk factor clusters and provide them non-invasive preventive care. One of her patients, Mr. Ashok Jain obtained the rights to use this platform in his new diabetes diagnostic clinics called, "Life Span" clinics (www.lifespanindia.com). Their website claims that they are the largest chain of diabetes management clinics in India. They have clinics in ten major cities and have screened over 100,000 out patients. They claim that R.I.S.C™ Test screens 30 vital cardiometabolic health indicators.

With TM-Oxi and SudoPath systems used (same platform as R.I.S.CTM) at IPC heart care, Mumbai, India, Dr Gandhi and associates have determined 14 clusters of cardiometabolic risks. Various risks are color coded from low (green) moderate (yellow/orange) to high (red). The results computed are presented as digitized values as well as bar graphs for easy reading and interpretation. The diagnostic platform developed by the LD Technologies uses three simple FDA approved devices, Pulse Oximeter, Blood pressure monitor and a galvanic skin response monitor. Based on the data generated, autonomic nervous system (ANS) tests, Heart Rate variability (HRV) tests, SudoPath System (TM-Oxi System) tests are performed. Proprietary algorithms and analytics developed by the researchers convert the data generated by these devices into clinically useful risk scores. TM-OXI and SUDOPATH status report summary provides the details of the response of all markers used for risk calculation. Provides patient details, physician details and explains clinical context of the markers studied, and the range of values obtained (Goal, Borderline, Abnormal, Normal ranges).

Risk analysis is a composite score of various measurements made during the examination. For instance, ANS function will be assessed by overall ANS activity, sympathetic activity, parasympathetic activity and balance between these activities. Similarly, endothelial function (EF) score will be developed based on the measurements of arterial stiffness, blood flow marker, and autonomic nerve marker. Vital signs monitored includes, heart rate average, oxygen saturation, systolic pressure while sitting, diastolic pressure while sitting, systolic pressure while standing and diastolic pressure while standing. Using appropriate responses, cardiometabolic risk score (CMR) as well as cardiac autonomic risk score (CARTs) are calculated.

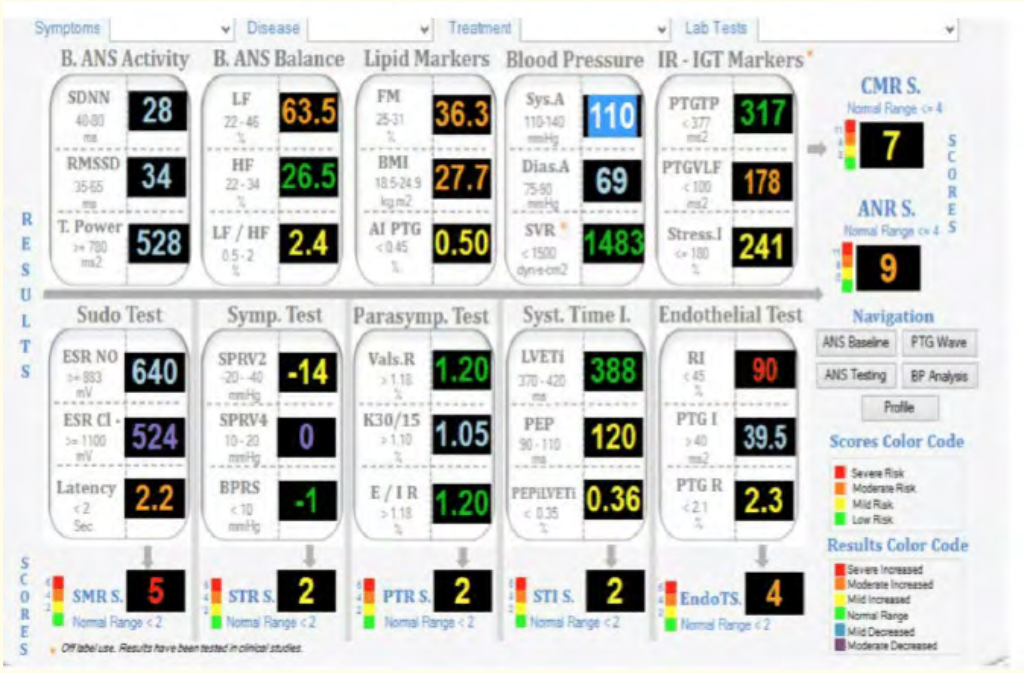


Figure 3

Typical results from one of the studies are presented above. Risk scores computed for various functions tested are digitized and color-coded. Abbreviations used in the following summaries of results include: ANS; Autonomic nervous system, BMI: Body mass index, CAN: Cardiovascular autonomic neuropathy, DAN: Diabetic autonomic neuropathy, CMRS: Cardiometabolic risk score, CVD: Cardiovascular disease, DVP: Digital volume pulse, ESRNO: Electric skin response to nitric oxide, FFT: Fast Fourier transform, FFTPTG: Frequency spectrum of PTG data, FGP; Fasting plasma glucose, GHB: Glycosylated hemoglobin, HRV: Heart rate variability, PNS: parasympathetic nervous system, PTG: Photoplethysmograph, PTGHF: Component associated with R-R changes during the phases of breathing, SNS; Sympathetic nervous system. For additional information about the use of these devices for monitoring cardiometabolic risks readers are urged to refer to our earlier publications [24-31]. In the result summary presented above 10 different risk clusters are presented. Each risk is provided with normal range, variations, and a digital score as well as a color code.

Digital data also can be presented as bar graphs for simple interpretations and patient education. Results of two studies representing the patient profile at an initial visit and a follow up visit, post medications are presented as bar diagrams below.

Figure 4

The bar graph above represents values for the fourteen risk clusters monitored. Cardiometabolic risk score is computed form the values derived by fat mass, spectral analysis of the pulse wave and the blood pressure (Systolic) data. The cardiometabolic risk (CMR Score) is quite high [15] hence shown in red. Individual risk factors that contribute to the overall increase in the CMR also are shown in the bar graph as red.

In the bar graph shown below results of an ongoing study of a patient is presented in bar graphs. A change in life style, diet, and use of medication (metformin) has lowered all cardiometabolic risks except endothelial dysfunction.

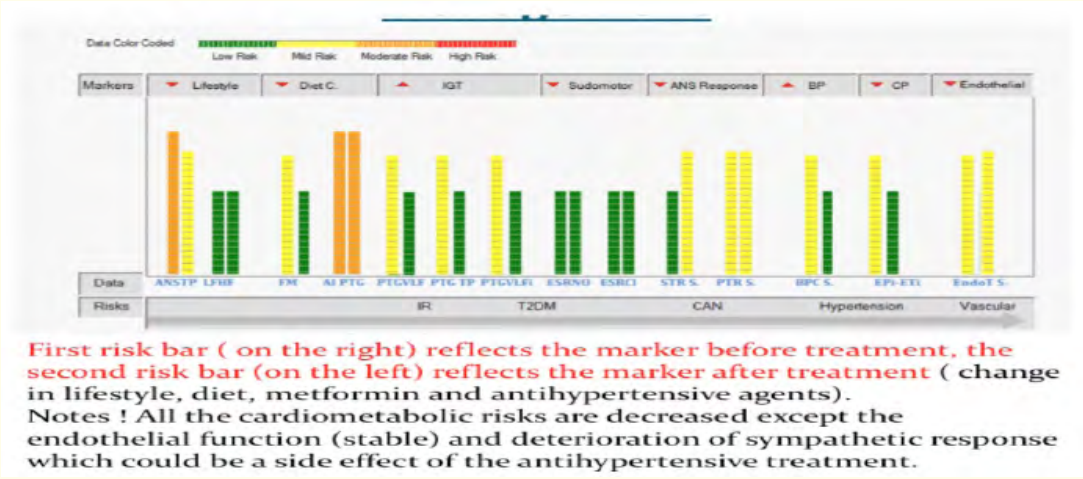


Figure 5

In a separate study (not shown here) we were able to demonstrate the reduction in the endothelial dysfunction following several weeks of oral supplement containing l-arginine, a substrate for the nitric oxide production.

Using such analysis, Dr Gandhi and associates in India have followed the changes in the metabolic risks in hundreds of patients who are seen in the preventive heart care clinic in Mumbai, India. Markers used to identify autonomic, sudomotor and endothelial dysfunction reliably distinguish diabetic population form non-diabetic populations [27-30]. Similar studies have been done by Dr Lewis and associates at the Miami Miller School of Medicine. They have demonstrated the usefulness of this novel device to detect diabetes with endothelial and autonomic nervous system markers. They concluded that this novel system shows promise as valid, convenient, and non-invasive diagnostic method for monitoring clinical complications of type-2 diabetes such as autonomic neuropathy, endothelial dysfunction and cardiometabolic risks [27,30].

Strengths of this novel system are it gives a risk score for dozens of known cardiometabolic risks. Having said that, we have to inform the readers that as in any device or software driven diagnostic results, it will be physician's responsibility to make proper diagnosis and develop personalized care. Usefulness of such emerging technologies will depend upon the awareness of the existence of such novel non-invasive systems, development of robust clinical data to support and validate the sensitivity and specificity of the data. This system is in use in several commercial diagnostic centers in India and at various research facilities in the USA.

Conclusions

In summary, in this short overview, we have briefly described early detection of cardiometabolic risks (genetic and epigenetic alterations of intrauterine fetal growth and physiology, childhood obesity, oxidative stress, insulin resistance, endothelial dysfunction, hypertension, metabolic syndrome, pre-diabetes and molecular markers for altered metabolism). We also have introduced some novel techniques and emerging technologies to aid the early detection and better management of CMRs. Use of novel non-invasive technologies to determine, Fat mass, Body mass index, Waist/Hip ratios, oxidative stress, insulin resistance, endothelial dysfunction, pre-diabetes enables physicians to personalize the care of the patients. Earlier studies have demonstrated the beneficial effects of life style change, exercise and diet on the progress of these metabolic diseases [31]. There is considerable interest in the low- carbohydrate diet, Mediterranean diet, Ketogenic diet as well as dietary supplements in the management of CMDs [32,33].

What the readers have to understand is that just risk factor management may not prevent the occurrence of acute vascular events. Each risk factor reduction may offer some degree of protection. Having said that, it is important to remember that even when all the risk factors are robustly managed the acute vascular events may occur. The reasons for these discrepancies between the expectations and limitations are obvious. Our knowledge of the mechanisms that underlie these metabolic diseases is to some extent incomplete. In view of these observations, all our attempts are aimed at reduction of the observed risks. For instance, the acute events that we all dread most are the heart attacks and stroke, which are to a great extent precipitated by the activation of coagulation pathways. Thrombotic state of the blood is dictated by the hyperfunction of platelets as well as activation of coagulation pathways. There are no specific assays to monitor the thrombotic state of the blood at any given time. Hence, most of the risk prediction algorithms cannot compute contribution of this pathway when computing the risk for a future acute vascular event.

Diabetes is a chronic metabolic disease and is rapidly increasing worldwide in epidemic proportions. It is not just the increase in the blood sugar that makes this a complex disease, but the clinical complications associated with the progress of this disease. Just about everywhere, diabetes is managed by controlling the fasting blood sugar, post meal increase of sugar or by *HBA1c* levels. Recent guidelines recommend that in addition to blood sugar control, the treatments be customized to prevent the clinical complications associated with type-2 diabetes. India and China have the largest number of diabetic subjects in the world. In the absence of a population based early screening program early detection, reduction, reversal, or prevention is not in place in many countries. By the time risk factors are diag-

nosed by using current diagnostic methodologies, the disease will have made sufficient progress. As we have discussed earlier, even pre-diabetics seem to have significant renal and vascular damage. Affordable multifunctional diagnostic platforms will facilitate the detection of various risk factors associated with the CMDs at the earliest stages of the disease. Effective integrated management of the known risks will slow or reduce the disease burden. In this short overview, we have expressed our point of view on the diagnosis and management of type-2 diabetes. We have just described few salient observations related to cardiometabolic diseases, early detection of risk factors, and the management of the observed risks; readers are urged to consult original articles, comprehensive reviews, editorials, and monographs on the subject for additional information [1-4,16,34-41].

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