

# **Predictive and Preventive Care: Metabolic Diseases**

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#### ABSTRACT

South Asians have a very high incidence of ischemic heart disease and stroke. In addition, they also have a very high incidence of metabolic diseases such as prehypertension, hypertension, visceral obesity, metabolic syndrome, prediabetes, type-2 diabetes, and its clinical complications. Currently, there are over 75 million diabetic subjects in India and an equal number of prediabetics. Republic of China has taken over India as the diabetes capital of the world, with over 115 million diabetics. Modern medicine is disease focused and has failed to address the prevention of these chronic diseases. According to the reports from the United Nations (Millennium Development Goals [MDGs], the World Health Organization, Global Health Initiatives, and the non-communicable disease risk task force), obesity has increased by 2-fold and type-2 diabetes by 4-fold worldwide. Experts in this field predict that chances of meeting the MDGs set by the UN members of reducing the incidence of these diseases at 2025 to the level of 2020 are very little. Western medicine has failed to reduce or reverse the trend in the incidence of these diseases. We feel that an integrated approach to health care may be a better option, to reduce the disease burden in developing and resource-poor countries. Having said that, one cannot prevent something that one is not aware of, as such it is the need of the hour for us, to develop a robust predictive and preventive health-care platform. In an earlier article, we presented our views on reducing or reversing cardiometabolic diseases. There is great enthusiasm among the health-care providers and professional bodies that integration of emerging technologies will help develop personalized, precision medicine, as well as reduce the cost of health-care worldwide.

Key words: Metabolic risks, risk prediction, preventive care

## INTRODUCTION

Success of IBM-Watson as a knowledge platform helped to develop a superb game show like Jeopardy and influenced the technologists, to use the ability of this platform, and to learn the diagnosis and effective management of dreaded diseases such as cancer and non-communicable diseases. 4 years ago, Memorial Sloan-Kettering and IBM Watson formed a partnership, to develop Watson for Oncology, a cognitive computing system, that can analyze large volumes of data including medical literature, patient health records, and clinical trials, to offer personalized, evidence-based treatment recommendations for cancer patients. Currently, Watson for Oncology is in use at a number of hospitals worldwide, including Bumrungrad International Hospital in Bangkok, Thailand, Manipal Hospitals in seven cities in India, and Memorial Sloan Kettering in New York. Since our interest is metabolic diseases, I will discuss the use of big data in the management of these diseases. The American Heart Association (AHA) announced recently the launch of its new Workplace Health Achievement Index and a collaboration to build upon it with IBMs Watson and the health management company, Health and Welltok, to transform heart health. Simply put, AHA's science-based metrics and health assessments with cognitive analytics are delivered on Welltok's Health optimization platform.

Heart disease is the leading global cause of death, accounting for over 17 million deaths per year, a number that is expected to grow to more than 24 million by 2030.<sup>[1-12]</sup> Unless effective

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prevention strategies are implemented, the total cost of cardiovascular diseases is projected to exceed \$1 trillion by 2030 in the U.S. alone. As Watson is trained on heart health goals and measures, it aims to help employers better design, tailor and deliver health programs, and ultimately provide employees with more customized coaching for those wanting to achieve ideal heart health. Yet another application is Sugar. IQ, a new app from Medtronic Inc., that uses IBM Watson computing power for collecting and computing realtime data from continuous glucose monitors (CGMs) and insulin pumps, to find patterns and then offer personalized insights to the end users. Just recently (June 2018), Food and Drug Administration (FDA) of the USA approved Israel's DreaMed Diabetes App., an Advisor Pro, for managing diabetes treatment with CGMs for type-1 diabetics. These are high end, high tech approaches to improve or manage the health care.

How about the low end or run of the mill approaches to health care? Availability of inexpensive sensors and software analytical capabilities and smart platforms such as iPads and smartphones has created a flurry of activities to develop mobile health care and management applications. What started as wellness apps have now become part of National and International studies. One such application is the use of Fitbit activity tracker, by the prestigious National Institutes of Health, USA, to track sleeping patterns. Fitbit the leading global wearables brand has been selected for use in the National "All of Us" Research Program established by the White House in the US. This National level research program is aiming to get 1 million Americans, to eventually enroll in the program. The Scripps Translational Science Institute will be using Fitbit devices for looking into how individual characteristics can affect health and disease treatment. The program will collect genetic information from participants and use wearable devices to track health-related metrics including heart rate and sleep patterns. Recent developments in mobile health applications, global shift toward precision medicine, and health metrics that can be generated through wearables have the potential to provide cost-effective, highly personalized, sustainable health-care solutions. Smart vascular stents with sensors that can monitor blood flow have been developed and are under clinical evaluation for further validation and possible replacement of the conventional bare metal and drug-eluting stents. If these sensors are capable of measuring the fluid dynamics of the circulating blood, then they would be the first one of kind sensors, to monitor in real time, the thrombotic or hemorrhagic status of the circulating blood.

We at Bengaluru, India, the IT capital of India, have been trying to establish a consortium of experts including members of the academia and industries to integrate emerging technologies for the development of affordable and sustainable health care. In August 2015, we organized an International workshop on, "Preventive Medicine through Contemporary Advances in Interdisciplinary Engineering" in Bengaluru, India, under the aegis of National Design Research Forum (DRDO), Institutions of Engineers, Bengaluru. We are currently working on various pieces of this "public health puzzle." As and when we develop new and useful technologies, we will report our findings. Now that, we have briefly described the role of big data, machine learning, artificial intelligence (IBM-Watson), and the usefulness of wearables in improving wellness and health-care delivery, we will discuss the couple of clinical applications with "novel methodologies," where integration of available technology has made a difference. We will also discuss the strengths and weaknesses of such approaches. A report by Carolyn Johnson in today's issue of Washington Post (June 21, 2018) titled, "Gawande to head health-care venture of Amazon, Berkshire, and JP Morgan" supports our suggestion that integration of emerging technologies, will help to develop personalized, precision medicine, as well as reduce the cost of health-care worldwide. At least that is the anticipation of this powerful team.

With the help of Dr. Pratiksha G. Gandhi, Chairperson, IPC Heartcare Centre, Mumbai, (www.ipcheartcarecentre.com), we developed collaboration with Dr. Albert Maarek (LD Technologies, Miami, Florida), who has developed a unique platform to evaluate endothelial dysfunction, metabolic syndrome, insulin resistance, cardiac risk assessment, and autonomic risk factor (RF).<sup>[13-15]</sup> It is of great interest for those of us, who are trying to develop integrated health-care systems, to validate and appreciate the ingenuity of this noninvasive diagnostic platform. Basic devices integrated in this system or systems are oximeter, blood pressure monitor, and a galvanic skin response monitor as shown in Figure 1, under the heading LD Products. Dr. Albert Maarek's system is sold by the LD Products of Miami, Florida, under the name of TM-OXI, EC-GS, and ES-GS systems. In India, when these systems were obtained by Mr. Ashok Jain, he put them together on a console and established "Lifespan" diagnostic centers. In the initial stages, Dr. Gandhi was facilitating the distribution of this system. Currently, it is marketed by Magus Biotech Pvt., Ltd. (www.magusbiotech.com).

As mentioned earlier, the device integrated in these various system is standard time-tested FDA approved devices such as oximeter, blood pressure monitor, and galvanic skin response monitor (used for lie detection). The engineers and software experts have used the data generated from these devices and with the help of clinical data, come up with diagnosis of various risks, clusters of such risks, and risk scores for cardiometabolic disease (CMD). At personal level, I have tested this system in the USA, as well as at our IPC clinic in Mumbai. I would say with certainty, it does a fairly good job in determining the state of one's health. What we have to remember hear is to appreciate the ingenuity of the developers that the data generation, algorithms, and analytics drive the final outcome and generate the results [Figure 4]. The oximeter which is extensively used for obtaining oxygen saturation in intensive care units is used here in this system, to obtain pulse waveforms [Figure 2].

As shown in Figure 2, the pulse waves generated by the oximeter provides three types of data: Heart rate variability as a response to the autonomic nervous responses, systolic interval time as it relates to blood pressure, and change in the blood volume as it relates to the arterial stiffness.

Using plethysmography of the waveforms, software analytics generate the type of information clinicians are looking for. Similarly, plethysmography of the waveforms is used for developing information about autonomic nervous system imbalances [Figure 3]. Using the clinical data from various sources, they have developed a correlation between the type of data generated using these devices and various known risks of CMDs. What are some concerns in using this non-invasive diagnostic platform? By and large, clinicians, diabetologists, and endocrinologists manage diabetes using parameters such as fasting blood glucose, postprandial glucose, or  $HBA_{1,.}$  The health-care providers are not familiar with the risk analysis algorithms used by these kinds of platforms or with the terminology used for risk scores and how they were derived. Independent validation of the data generated by this system, as well as addition of emerging technologies such as Dexcom G6 or LIfeStyle Libre Free Pro, to monitor glucose, will enhance the acceptance and use of such devices. Having said that, we would like to underscore the importance of this innovative platform, as it is one of a kind non-invasive diagnostic platform, wherein, the innovators have very cleverly used three well-accepted devices to develop a variety of risk indicators,



Figure 1: Sudo-Path System and Tm-Oxi System Courtesy: Albert Maarek, LD Technologies.



Figure 2: Plethysmography tracings of pulse waves. Courtesy: Albert Maarek, LD Technologies

Rao: Metabolic disease risks



Figure 3: Autonomous nerve system responses. Courtesy: Albert Maarek, LD Technologies

Symptoms	✓ Disease	✓ Treatme	ent	✓ Lab Tests	~
B. ANS Activity SDNN 28 ms R R S S S B. ANS Activity 28 ms 34 Teower 528 534 528 534	B. ANS Balance	Lipid Markers FM 2531 36.3 BMI 18.5.249 27.7 kgm2 AI PTG 0.50 %	Sys.A 110   10:140 110   mm/g 0   Dias.A 69   syr.A 1483   opniscm2 1483	IR - IGT Markers*	CMR S. Nomal Range <= 4 7 S C ANR S. Nomal Range <= 4
Sudo Test ESR N0 → #83 → #00 ESR Cl - 524 → #100 - mV Latency ≤ Sec 	Symp. Test SPRV2 -20-40 mmHg SPRV4 10-20 0 mmHg 10 -11 mHg	Parasymp. Test	Syst. Time I.   LVETi 3888   700-420 3888   PEP 90-110   99 120   99 0.36   0,35 0.36	Endothelial Test RI 45 90 916 I 39.5 192 PTG R 42.3 192 2.3 192 90 90 90 90 90 90 90 90 90 90	Navigation ANS Baseline PTG Wave ANS Testing BP Analysis Profile Scores Color Code Serves Risk Moderate Risk Moderate Risk Moderate Risk Moderate Risk Besults Color Code
SMR S. SMR S. Normal Range < 2	str. s. 2 Normal Range < 2	PTR S. 2 Normal Range < 2	<sup>6</sup> STI S. 2 Normal Range < 2	EndoTS. 4. Normal Range < 2	Severe Increased Moderate Increased Mild Increased Normal Range Mild Decreased

Figure 4: Metabolic risk factors (RFs), RF clusters, and risk scores. Courtesy: Albert Maarek, LD Technologies





risk clusters, and risk scores for monitoring CMDs. Since we emphasized the importance of monitoring blood glucose for the management of the severity of the disease and to prevent the development of clinical complications associated with the Type-2 diabetes, we will discuss some of the options available from the perspective of integration of emerging technologies. Continuous monitoring of glucose has great advantages.

According to Rebecca Voelker's report in the recent issue of JAMA Network (May 2018), the US FDA has approved a

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 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 sensor just beneath the skin. The sensor measures glucose levels and a transmitter inside of it sends readings wirelessly every 5 min, to a receiver or



Figure 6: Ambulatory glucose profiles are generated from the composite data collected several days or weeks, plotted according to time they occurred over the 24-h period



Figure 7: Glucose profile of a patient with no medications: High HBA1c 9.8%. Courtesy: Abbott Diabetes Care



**Figure 8:** Glucose profile of a patient 80 years old, diabetic for 20 years, under medical care *HBA1c* 7.2% (personal studies). Courtesy: Abbott Diabetes Care



**Figure 9:** Data plot for  $HBA_{tc}$  versus fasting blood sugar (n = 100,000)

a compatible smartphone or smartwatch. With a mobile app, users can share readings with up to 5 people. No finger sticks are needed for calibration or diabetes treatment decisions. In two trials, 324 adults and children aged 2 years or older with diabetes used the Dexcom G6 for 10 days. During multiple clinic visits, their readings were compared with laboratory test results that measured their blood glucose levels. An FDA statement indicated that no adverse events were reported during the studies. We would be glad to validate these sensors in India, if the manufacturers provide them for our clinical evaluation in India.

Abbott Diabetes Care has launched their Ambulatory glucose monitor (AGM) FreeStyle Libre Pro in India. This system

also uses a transdermal sensor, which is easy to apply with an auto applicator. Manufacturers sell a reader, which can read the real-time data, and at the end of the study (12–15 days), will consolidate the composite data into readable charts. The individual mean glucose value for every reading is also provided for developing further information.

Mean glucose values for the 12 days study period are shown in Figure 5 these bar graphs. Mean glucose value is 156 and there is variation of a high of 29 and a low of 26. This composite data come from over 1152 recordings (close to 100 readings per graph). In view of the fact that the mean glucose value is a collective value of so many individual readings, this type of data collection brings a great degree of confidence and reliability compared, to single point measurements, by currently used glucose monitoring methodologies. In the area of hypertension management, importance of ambulatory measurements was recognized much earlier. Yet the US health-care payers do not pay for such valuable services. It is time, the global health providers recognize the importance of this kind of monitoring and subsidize preventive care. Ambulatory glucose profiles are shown in Figure 6.

Figure 7 shows a glucose profile for a 12-hour period. Dark blue line represents the mean glucose value. Hemoglobin value is computed, and in this patient, it is 9,8%. In Figure 8 glucose profile a patient who is on medication is graphed. HBA1c is 7.2% which is close to the recommended level for elderly individuals.

Since software provides flexibility to look at composite data for 1-day measurements and 1-week or 2-week measurements, this method of monitoring glucose can be used for following single drug treatment, combination of drugs, or the effect of even dietary or lifestyle changes. Since this device also is FDA approved, both the Dexcom G6 (CGM) and Abbott flash glucose monitor (AGM) are useful tools, for monitoring glucose in Type-1 as well as Type-2 diabetic patients. Type-1 patients and Type-2 patients on insulin can take advantage of hypoglycemia alerts to adjust their medications. Similar to the Dexcom G6, if the Abbott Diabetes Care develops connectivity to various smartphone apps, it would be very useful. We, in India, are trying to validate the FreeStyle Libre Pro (AMG) at two independent sites. Specific goals are as follows: (1) To find correlation between blood glucose levels and interstitial glucose levels, (2) to determine the usefulness or otherwise of this methodology for managing real-time, post-meal glucose levels, and (3) to use it as a tool to screen indigenous drugs and their combinations, dietary supplements, and complementary therapies for managing post-meal glucose levels.

Manufacturers claim that *HBA1c* values generated using FreeStyle Libre Pro correlates well with finger prick measurements. Shown below in Figure 9 is a data plot of

individual values for fasting blood sugar against  $HBA_{lc}$  for a total of over 10,000 individuals monitored at two independent sites (Patna, Bengaluru) in India. One can visualize quite a scatter of the individual values (data points) and the reasons for such deviation need explanation. This is yet another area, where we would like to validate these devices for their specificity and accuracy, compared to the conventional blood glucose values. Dr. Mohan and associates at the Madras Diabetes Research Foundation, Chennai, India, have done a multicenter real-life study on the effect of flash glucose monitoring on glycemic controls in patients with type-1 (T1D) as well as type-2 (T2D) diabetes and have demonstrated significant reduction in  $A_{lc}$  levels in both T1D and T2D patients.<sup>[16]</sup>

## DISCUSSION

Since I am writing this "point of view" article for the Journal of Clinical Research in Diabetes and Endocrinology, I would like to initiate a debate on the benefits or otherwise of clinical studies versus clinical trials, in providing the needed information for developing cost-effective affordable, predictive, and preventive care. Let us examine for instance the results of clinical trials on fish oil supplements. In April issue of JAMA, as part of Medical News and Perspectives, Jennifer Abbasi describes findings of fish oil supplementation as, "Another Nail in the Coffin for Fish Oil Supplements."<sup>[17]</sup> The findings of 10 clinical trials are at odds with the advice from the AHA, including a 2017 science advisory recommendation, to consider fish oil supplementation for patients with a recent myocardial infarction or heart attack.<sup>[18]</sup> We and others, decades ago had demonstrated, that fish oil supplements do not interfere with the conversion of arachidonic acid to prostaglandins or with platelet function.<sup>[18]</sup>

Now, let us examine a few examples of clinical studies (not clinical trials), which have demonstrated safety and efficacy of complementary therapies. It is a well-known fact that oxidative stress, free radicals, tissue injury, and inflammation play a very important role in promoting metabolic diseases. The transcription factor Nrf2 (nuclear factor erythroid-2related factor-2, Nrf-2), for instance, a master regulator of detoxification, antioxidant, anti-inflammatory, and other cytoprotective mechanisms is raised by health-promoting factors. This transcription factor activates the transcription of over 500 genes (so-called survival genes) in the human genome, most of which have cytoprotective functions. The most healthful diets such as Mediterranean and Okinawa are rich in Nrf2 raising nutrients. Recent studies have demonstrated that induction of Nrf2 and Ho-1 expression by Protandim (a mixture of five phytochemicals; Ashwagandha, Indian Bacopa, Indian Green Tea, China Milk Thistle, and China Turmeric) is associated with a reduction in oxidative stress and fibrosis, preservation of the RV microcirculation, and RV function.<sup>[19]</sup> Studies by the pioneer scientist, professor

McCord and Fridovich, on the effect of Protandim on various pathways have shown, significant modulation by Protandim not only of pathways involving antioxidant enzymes but also those related to colon cancer, cardiovascular disease, and Alzheimer's disease.<sup>[20,21]</sup>

In a recent study, Rossman and associates have shown that chronic supplementation with a mitochondrial oxidant (MitoQ) improves vascular function in healthy older adults.<sup>[22]</sup> They studied the effect of oral supplementation of 20 Mg/day MitoQ for 6 weeks in healthy older individuals with impaired endothelial dysfunction, as measured by the brachial artery flow-mediated dilation. In these subjects, post-treatment, brachial artery flow-mediated dilation was higher; aortic stiffness was lower, and plasma oxidized lowdensity lipoprotein, a marker of oxidative stress was lower, suggesting the beneficial effects of MitoQ. In a separate study, 6 weeks of 500 mg twice daily of nicotinamide riboside (NR) chloride (NIAGEN) seems to boost the level of nicotinamide adenine nucleotide (NAD+) and reverses the physiological signs of aging and kick starts the same key chemical pathways responsible for its health benefits including the activation of enzymes called sirtuins, which are largely credited for the beneficial effects of calorie restriction.<sup>[23]</sup> Studies from the University of Minnesota have demonstrated that D-ribose, a commonly used supplement, can indeed provide quick energy and reduce oxidative stress at the cellular and organ levels.<sup>[24]</sup>

Several seminal studies have demonstrated that management of modifiable risk factors (RFs) significantly reduces the development of acute vascular events.<sup>[25,26]</sup> In spite of this observation, we know that there are many other metabolic risks, if not controlled in time, contribute significantly to the progress of these metabolic diseases, and promote acute vascular events. Just to name a few metabolic risks, they include oxidative stress, free radical injury, inflammation, blood flow alterations, hypertension, endothelial dysfunction, hardening of the arteries, subclinical atherosclerosis, excess weight, subcutaneous obesity, visceral obesity, metabolic syndromes, and type-2 diabetes. It is rather time consuming and extremely costly to do clinical trials, to find appropriate therapeutic interventions for all of these known metabolic risks. However, if we develop a multifunctional platform, to validate the efficacy and safety of complementary therapy, it is possible to screen many therapeutic modalities and develops evidence-based data in a cost-effective manner in a relatively short time period. For instance, we have validated the safety and efficacy of mulberry green tea as well as 1-arginine using TM-Oxi systems at the IPC Clinic in Mumbai, India.

We are currently facing an "epidemic or tsunamis" of metabolic disorders and time to act is now. In view of the time constraints and economic constraints, we suggest that simple clinical studies should be encouraged for developing complementary therapies to reduce, reverse, or prevent the growing menace of metabolic diseases. In a short overview like this, it is hard to cover all aspect of this very important topic, but we encourage readers to refer to original articles, reports, and reviews on the "Integration of emerging technologies for cost-effective, affordable health care."<sup>[3-6,27-33]</sup>

## CONCLUSIONS

Metabolic diseases such as excess weight, obesity, metabolic syndrome, and type-2 diabetes have reached epidemic proportions worldwide. To create awareness, develop educational and preventive strategies, we started a professional society at the University of Minnesota, in 1993. Since that time, we have been working on issues related, to the early diagnosis of the risks for various metabolic diseases, and development of novel integrated technologies, to manage the observed risks. In spite of the fact that global organizations such as the World Health Organization, United Nations, and non-communicable risk task force have been developing reports on the increase in the incidence of metabolic diseases, no country has reduced, reversed, or prevented the increase in the incidence of the twin epidemics, obesity, and type-2 diabetes.

On the other hand, major clinical trials have demonstrated the beneficial effects of managing the modifiable RFs, in reducing the incidence of acute vascular events. When it comes to reducing or reversing the twin epidemics of obesity and diabetes, we still have a long way to go.

Clinical trials are time consuming, expensive, and at times unpredictive. In this review, we have raised the possibilities of developing cost-effective clinical studies, which can provide evidence-based information on the safety and efficacy of complementary therapies at the shortest possible time. We also have provided examples for developing integrated platforms for risk assessment, risk prediction, and risk management, using integrated emerging technologies. We also recommend that new emerging technologies should undergo clinical evaluation and validation by independent sources other than manufacturer-sponsored studies.

We have discussed some examples of complementary drug development, which may prove to be safe and effective in reducing the impact of additional RFs, other than the known modifiable RFs for cardiovascular disease. It is our viewpoint that the future health-care providers will use every possible emerging technologies, to reduce the cost of the services and improve the quality of care. At the clinician's level, there will be more emphasis on personalized and precision care. The need of the hour is in our opinion, development of a robust predictive and preventive health-care platform.

## ACKNOWLEDGMENTS

The author wishes to thank Dr. Sadhana Sharma, Professor, Head, Department of Biochemistry, All India Institute of Medical Sciences, Patna, and Dr. M.A. Shekar, the Director, Karnataka Institute of Endocrinology and Research, Bengaluru, India, for their inputs. Dr. Pratiksha Gandhi, the Director, IPC Heartcare, Mumbai/USA, and Dr. Albert Maarek, the Director, LD Technologies, Miami, Florida, USA, for their collaboration in clinical studies of TM-Oxi and Sudo-Path Systems. Dr. Navneeth Selvan (Southern Region) and Dr. Silpi Bardhan (Eastern Region), Regional Scientific Directors (Abbott Diabetes Care), for their help in these studies and Ms. Smitha Bopanna, the Director, Noesys Software Pvt., Ltd., Bengaluru, for her help in the analysis of data.

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**How to cite this article:** Rao GHR. Predictive and Preventive Care: Metabolic Diseases. Clin Res Diab Endocrinol 2018;1(1):1-8.