MINI REVIEW

Diagnosis of Early Risks, Management of Risks, and Reduction of Vascular Diseases

Gundu H. R. Rao

Emeritus Professor, Department of Laboratory Medicine and Pathology, Director, Thrombosis Research, Lillehei Heart Institute, University of Minnesota, USA

ABSTRACT

In a recent issue of the Journal of Circulation, American Heart Association has published a scientific statement, related to the excess heart disease and acute vascular events in South Asians living in the USA**.** The same group of experts, also have published a complementary article in Circulation titled**,** "call to action: Cardiovascular disease (CVD) in Asian Americans."I being a South Asian immigrant living in the USA, have always wondered as to why we do not have the same benefits as the other resident Americans in terms of the advantages of living in a highly advanced country? According to a study done in 2013, cardiovascular mortality has declined and diabetes mortality has increased in high-income countries. The study done in 26 industrialized nations, estimated the potential role of trends in population, for body mass index, systolic blood pressure, serum total cholesterol, and smoking, the modifiable risk factors identified as the promoters of CVD, and acute vascular events, by the Framingham Heart Study (FHS) group. We the founding members of the South Asian Society on Atherosclerosis and Thrombosis (SASAT) have been debating the reasons, why there is this observed excess of CVD events in the South Asians living abroad. During our various national and international conferences, some of the experts have suggested quite often, that the lifestyle and work-related stress may be one of the causes contributing to this excess incidence of CVD events. A recent article in the Lancet (June 2018), reports the findings of a multicohort study, which assessed the effect of work stress on the risk of morality, using the data from the individual-Participant Data Meta-analysis in Working Populations (IPD-Work) consortium. According the Global Burden of Diseases Study, CVDs remain a major cause of health loss, for all regions of the world. Based on the findings of FHS, several investigators have conducted clinical trials, to validate the effect of a robust management of modifiable riskson the development of acute vascular events. Over the past 25 years, there has been a gradual decline in CVD in industrialized nations, but not much of a decline in CVD-related deaths in other regions of the world. In view of this observation, we feel strongly that there is a great need to evaluate the role of all the know metabolic risks, especially early markers such as oxidative stress, inflammation, and endothelial dysfunction rather than just the modifiable risks of FHS, in order to improve CVD risk scores. In this overview, we will discuss the role of emerging technologies in the early diagnosis of risks for various metabolic diseases and their impact on the disease progression, precipitation of acute vascular events, and some strategies for effective management of the perceived risks.

Key words: Vascular diseases, risk management, diagnosis of CVD risks

INTRODUCTION

Several recent scientific reviews, have reported a rapid increase in the incidence of metabolic diseases like hypertension, excess weight, obesity, type-2 diabetes, and vascular diseases worldwide.[1-10] American Heart Association in a scientific statement has reviewed the excess heart disease, and acute vascular disease events, in the South Asian Populations living in the USA.[1,2] We the members of the South Asian Society on Atherosclerosis and Thrombosis

Address for correspondence:
Gundu H. R. Rao, 12500 Park Potomac Ave, Unit 306 N, Potomac MD 20854, USA. E-mail: gundurao9@gmail.com

have discussed this issue in several national and international conferences. In view of the fact that several studies have demonstrated, that management of modifiable risk factors, significantly reduce the CVD events, we have wondered whether any ethnic-specific risks, or lifestyle, or work-related risk underlies this excess CVD burden in the South Asians living in the USA?.[5] In industrialized nations, there is a significant decline in the CVD-related deaths, whereas there is considerable increase in the diabetes-related deaths in these countries.[3] According to experts 80% of the worldwide CVD deaths occur in low and middle- income countries. Although majority of members of the United Nations have agreed to lower the metabolic disease burden by 2025, meeting that Millennium Development Goal seems, unlikely in most of the developing countries. No major comprehensive report has come up with any definite plan of action, that can alleviate this global disease burden. In this mini overview, we have discussed some novel ideas for the detection of early risks for metabolic diseases, and the management of observed risks, with integrated emerging diagnostic technologies.

Future of medicine, especially the precision and personal medicine, lies in clinicians gaining much more detailed information about the patient, the underlying causes of the disease, the knowledge of the emerging technologies and their applications, to deliver personalized or precision treatment, with a better outcome. Since my area of interest is cardiometabolic diseases, let me try to discuss how this is done at an academic setting. At the University of Minnesota Rasmussen Center for Cardiovascular Disease (CVD) Prevention, they have developed a philosophy, which focuses on treating the disease itself, rather managing just the risk factors. How is it done? What really constitutes a metabolic disease? How can one develop clinical tests to find out the earliest alteration in the normal metabolic state? These are some important questions that come to my mind, when I think of efforts to reduce, reverse, or prevent metabolic diseases. At the University of Minnesota, they use a ten-point clinical test package, to grade or score the disease progress. This center was founded by the World-renowned cardiologist, Professor Jay N Cohn. The non-invasive tests include monitoring resting blood pressure, retinal-eye blood vessel analysis, and electrocardiogram (EKG), measurement of large and small artery elasticity (endothelial dysfunction), ultrasound of the heart (left ventricle), ultrasound of the carotid (neck) artery thickness, walking treadmill exercise test, and blood chemistry (cholesterol panel, glucose, C-reactive panel, NT-proBNP, microalbumin). They have developed a scoring system, which will grade the stage of atherosclerotic disease in the patients. By placing patients in three different risk categories, the Rasmussen score is able to tell the patient what they should be doing for their health. Scores can range between 0 and 20 with 0–2 as evidence of no disease, 3–5 as evidence of early disease, and 6 and above as evidence of advanced disease. Probably, all major academic medical centers have such heart disease prevention programs and offer their own customized package of tests.

Although the 26-countries study referred to above showed a decline in the cardiovascular deaths, it also showed that deaths related to diabetes was on the increase.[3] According to Dr. Margaret Chan, Ex-Director, World Health Organization (WHO), "over three-quarters of deaths from heart attacks and strokes occur in low- and middle-income countries." At the population level, the Global Hearts Initiative (2018) will be initially rolled out in the following countries; Barbados, Benin, Colombia, Ethiopia, India, the Islamic Republic of Iran, Jordan, Nepal, Nigeria, Philippines, Sri Lanka, Tajikistan, Thailand, and Uganda - and will be open to all countries wishing to participate. FHS group developed a list of modifiable risk factors that are supposed to promote the development of CVDs. Over 70 years of research by this group has produced massive data on various aspects of CVDs in this cohort. However, the data generated by FHS by and large, is based on the information obtained by studying Caucasian communities living in this area. Underlying causes may or may not be the same for each demography or ethnicity. For instance, the South Asians living in the USA, who are socioeconomically much better than other ethnic minority groups, still have a much higher rate of incidence of CVDs and type-2 diabetes. Conventional risk factors such as smoking, high blood pressure, lipid abnormalities, and elevated glucose do not fully account for the difference in the risk between various ethnic groups.

At the level of individuals, by and large in majority of the clinics, the health-care providers pay for the tests approved by the health insurance companies or the National Health Services. Metabolic risks that modulate or promote the vascular diseases include oxidative stress, inflammation, endothelial dysfunction, hardening of the arteries, subclinical atherosclerosis, elevated blood pressure, excess weight, metabolic syndrome, obesity, and type-2 diabetes. Currently, no health-care provider will recommend all these tests routinely. For instance, it is very well established that ambulatory monitoring of blood pressure and blood glucose is superior to single-point measurements done at the clinics. Yet, neither clinic offers these services routinely nor any health-care provider pays for it. The ten-point test that is offered at the University of Minnesota has been recommended for asymptomatic individuals every 5 years. Except at the University of Minnesota, I do not see such rigorous tastings offered or recommended anywhere. In view of the fact that diabetic subjects are at a greater risk for acute vascular events, researchers have felt a greater need for early detection of silent CAD in these subjects. In addition to exercise EKG test, recent emerging non-invasive CAD screening modalities include stress echocardiography, stress radionuclide perfusion imaging, coronary artery calcium scoring (CACS), and computed tomography coronary angiography. In a series

of articles published recently (2014–2018), in the European Heart Journal-Cardiovascular Imaging, on the topic related to the benefits of non-invasive imaging, researchers concluded that, "The addition of coronary computed tomography angiography improved category-free net reclassification of major adverse cardiovascular events."[11-14]

In a recent article in the Journal of American College of Cardiology, Professor Fuster *et al.* at the Mount Sinai Hospital, New York, reported their findings of a study that closely looked at the clinical features of the participants from the progression of early subclinical atherosclerosis. The specific objects of this study were to seek to identify predictors of subclinical atherosclerosis, in cardiovascular risk-free individuals. The authors of this study demonstrated that, after age and male sex and low-density lipoprotein (LDL)-cholesterol was the main predictor for the presence of the atherosclerotic plaques, suggesting a great correlation between LDL-cholesterol and levels of atherosclerosis.[15] Using the latest non-invasive imaging technology, they demonstrated that plaques were present in 50% of the middle-aged individuals with no classical risk factors. Furthermore, these individuals also had hardened arteries showing the altered morphology and dysfunction of the vessel walls. They 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." In spite of the seminal findings of this important study, we find no revised guidelines recommending these procedures for early detection of vascular diseases.

We already have discussed the ten-point test that is being offered by Professor Cohn *et al.* associates at the University of Minnesota. One of the tests they rely heavily to detect subclinical atherosclerosis is endothelial dysfunction, which indicates the hardening or stiffening of the arteries. Several clinical studies have established the importance of endothelial dysfunction as an early marker for detecting hardening of the arteries, alterations in the flowdynamics, and the beginning of vascular diseases. Similar to the studies of Professor Valentin Fuster of Mount Sinai Hospital, New York, Cohn *et al*. at the University of Minnesota also have been performing non-invasive tests in individuals, with no history of CVD and have demonstrated the superiority of their ten-point test, in detecting the presence and progress of subclinical atherosclerosis in asymptomatic patients.[15] In majority of the clinical settings, measurement of intima-media thickness (IMT) is used mainly to study the atherosclerosis progression. However, advances in imaging capabilities have provided clinicians the ability to monitor changes in the vessel wall morphology at the carotid and femoral artery bifurcations. It has been shown that half the cases in which plaques are found by this technique had normal IMTs.[16] Researchers at the Robarts Laboratory at the University of Western Ontario, Canada, have developed three-dimensional (3D) ultrasound imaging, capable of measuring plaque volume instead of luminal volumes by the two-dimensional (2D) ultrasound.[17] Schroeder *et al.* have studied subclinical atherosclerosis in asymptomatic patients using a multimodality assessment. They found that carotid ultrasound measurements and computed tomography angiography were significantly more sensitive than CACS.[18]

Professor Wang *et al*. reported in their comprehensive review that arterial stiffness is a sensitive and useful biomarker of cardiovascular risk, because of the underlying pathophysiological mechanisms. This test is becoming an emerging earlier biomarker for reflecting risk stratification of patients for assessing pharmacodynamic effects and efficacy in clinical studies.[19] According to Minnesota researchers even in children, oxidative stress and adipokine levels worsen throughout the continuum of obesity. Kelly *et al*. in Minnesota conducted a study to assess subclinical inflammation, fasting insulin, and endothelial dysfunction, before and after exercise in overweight children. The researcher of this study found that just 8 weeks of moderate exercise, improved overall fitness, lowered high density lipoprotein cholesterol, and restored endothelial function.[20] Ashor *et al.* in the UK studied the effects of exercise modalities on arterial stiffness and wave reflection. Based on their review and meta-analysis of randomized clinical trials, they concluded that "aerobic exercise improved arterial stiffness significantly and that the effect was enhanced with higher aerobic exercise intensity and in participants with greater arterial stiffness at baseline."[21] We at the IPC Heartcare, Mumbai, India, demonstrated the benefits of oral supplementation of l-arginine, a substrate for nitric oxide (NO) synthesis, in improving endothelial dysfunction (personal communications). Studies in which the presence of a plaque determines subclinical atherosclerosis, although are very important, are not really the earliest tests for atherosclerosis. By the time a plaque is recognized in any artery, the disease of the vessel has already progressed for a long period.[22]

When developing strategies for the early diagnosis of complex and chronic diseases, such as hypertension, excess weight, obesity, type-2 diabetes, and vascular diseases, it is important to discuss, how early is really early? In our opinion, the diagnosis and management of fetal origin of adult diseases would be the earliest? For instance, in the majority of Asian countries, even to this day, more than 30% of the children are born with low birth weight.[23] These low-birth weight children, as they grow to adulthood develop metabolic diseases.[24] Studies from Harvard Public Health School has demonstrated that this condition could be prevented by providing pregnant women with micronutrient supplements.[25] Metabolic risks have been identified in children with excess weight or obese as well as in prediabetes conditions. What then are the early metabolic risks? Apart from the modifiable risks that were

developed by the FHS Group, a simple list of few known metabolic alteration includes oxidative stress, inflammation, altered flow dynamics, endothelial dysfunction, hardening of the arteries, and subclinical atherosclerosis.[26,27] In spite of the fact, we know that these are the early signs of atherosclerotic disease progression, no early diagnostic or preventive measures are planned at the population level.

Researchers at the National Children's Memorial Hospital (CNMH), Washington, DC, have demonstrated that visceral adipocytes shed exosomes (miRNAs), which "tweet" signals capable of regulating end-organ transforming growth factor-β and Wnt/β-catenin. They have shown that fat cells from obese people send messages to other cells that worsen metabolic function. By further analysis of the messages sent by the miRNAs, researchers hope to develop treatments to reverse metabolic problems. In view of these findings, we have facilitated a bilateral study between the staff of CNMH and that of the staff of Diabetes Clinic, KEM Hospital, Pune, India, to study the cellular signaling processes through adipocytes of obese pregnant women and lean pregnant women. Several earlier studies indicate that birth weight is not determined by genetic variation but by prenatal environment. There are some speculations that adaptations to prenatal environment include interaction with the genes, which control a variety of metabolic, cellular, and organ functions. Since the Asian phenotype has excess visceral fat, as well as excess incidence of metabolic diseases, proposed bilateral studies will be very important. This type of early detection for metabolic risks could really be a game changer for millions of Asians, who are at high risk for developing heart disease as well as other diabetes and obesity-related complications.

FHS group, which has completed 70 years of meticulous work on CVD-related research, recently reported that alterations in amino acid metabolism, could predict the development of type-2 diabetes in later life.[28] According to their report, five branched-chain amino acids had highly significant associations with future diabetes: Isoleucine, leucine, valine, tyrosine, and phenylalanine. A combination of three amino acids predicted future diabetes with a five-fold higher risk for individuals. With a similar approach to the early diagnosis, Wurtz *et al* from Finland also have reported that the elevation of branched chain amino acids in the blood, similar to the earlier findings of FHS group in Boston, Mass., could be used as biomarkers for the development of insulin resistance in the young.[29] The authors concluded that the association of branched-chain amino acids with the risk of future diabetes is at least partly mediated through insulin resistance. These and other studies indicate that plasma free amino acid (PFAA) profile is elevated with visceral obesity, hyperinsulinemia, and diabetes. Yamakado *et al.* from Tokyo, Japan, also have reported that PFAA profiles, predict 4-year risk of developing diabetes, metabolic syndrome, dyslipidemia, and hypertension in Japanese population.[30] They suggest that PFAA profiling can be potentially used for evaluating the future risk of developing lifestyle-related diseases.

Swedish researchers involving over 62,000 Danish individuals have demonstrated that childhood overweight is associated with an increased risk for developing type-2 diabetes in adulthood.[31] According to a recent report by the Centers for Disease Control and Prevention, 50% of the adults in the USA are pre-diabetic (84 million). It is a well-known factor that the individuals with diabetes have a several-fold higher risks for developing vascular disease.[32] High incidence of pre-diabetes is not unique to the USA. Having said that, we would like to refer the readers to a study on metabolic profiles of young-onset type-2 diabetes in South Asians. In this study the researchers found following profile of incidence in young-onset diabetes: from Hong Kong (15,431), India (9107), Philippines (7712), China (5646), South Korea (1751), Vietnam (705), Singapore (385), Thailand (275), and Taiwan (107), representing one in five individuals studied with young-onset diabetes. The authors concluded that "in view of the risk conferred by the long-term suboptimum metabolic control, the findings of this study suggest an impending epidemic of young-onset diabetic complications."[33] In the recent years, cardiovascular and renal risks have become highly prevalent in adults with pre-diabetes, irrespective of the definitions used. Identification of people with pre-diabetes might increase the opportunity for cardiovascular and renal risk reduction.

Now that we have briefly discussed some of the early diagnosis of the principle promoters of metabolic diseases, let us discuss some additional less known risk factors that also significantly contribute to the acceleration of the disease, as well as promotion of acute vascular events. One of the dramatic findings of that nature is the recent report from Professor Paul Ridker's laboratory for the Canakinumab anti-inflammatory Thrombosis Outcome Study (CANTOS) Clinical Trial Group. The authors conclude that "Anti-inflammatory therapy targeting the interleukin-1β with canakinumab, a monoclonal antibody significantly lowered the recurrent cardiovascular events, independent of lipid-lowering.[34] CANTOS trial was designed by this group, to test directly the role of inflammation in atherothrombosis. According to his own words, (Professor Paul Ridker, Director of the Center for CVD Prevention at Brigham and Women's Hospital, at Boston), "for the first time, we have been able to definitely show that lowering inflammation independent of cholesterol, reduces cardiovascular risk." The study was conducted with over 10,000 patients, who had previous heart attack and had persistently high levels of high sensitive C-reactive protein (hsCRP), a marker of inflammation. The drug tested was Canakinumab, a monoclonal antibody, that neutralizes interleukin 1β signaling, thereby suppressing inflammation. Hypothesis for a significant role for inflammation in precipitating acute events was developed

based on the fact that of the patients on high statin therapy, there were still a significant proportion of those who had increased hsCRP, a biomarker of inflammation. A new concept of "residual inflammatory risk" was developed based on this observation. These evidence-based observations, led to the development of CANTOS trial, which represents a seminal study from biomarkers to molecular mechanism relevant for the development of therapeutic strategies.

Inflammatory mechanisms participate in many different aspects of the pathogenesis of atherosclerosis including early cell adhesion, lesion propagation, matrix and collagen degradation, smooth muscle proliferation, development of subclinical atherosclerosis, heightened platelet reactivity, stability of or vulnerability of the atherosclerotic plaque, and thrombosis. The question then is, at what stage in the injury phase, should one interfere, to reduce or modify the influence or inflammation, in atherosclerosis promotion? It is well established that hyperlipidemia elicits enrichment and promotion of pro-inflammatory subset of monocytes. In fact, any injury to the biological system to some extent initiates inflammatory response, including the very process of wound healing. Harvard group have strongly promoted the role of low-grade chronic inflammation, as measured by the elevation of hsCRP, as a risk of atherosclerotic complications. In view of this observation, the CANTOS trial and the positive results observed gives some credibility to their long-held views about the definitive role of hsCRP in the development of acute events associated with thrombotic events. Just to illustrate the complexity of the role of inflammation, I will describe a recent finding in which another antibody used to treat skin disease, psoriasis has been found to be effective in reducing the aortic inflammation, a key marker of future risk for major cardiovascular events, according to the researchers at Perelman School of Medicine at the University of Pennsylvania.

Just like inflammation plays a role in some of the natural physiological processes, oxidative stress and reactive oxygen species (ROS) also play an important role in cell signaling and homeostasis. According to the researchers on this topic, oxidative stress has a central role in the pathogenesis of atherosclerosis.[35-41] In fact, increased generation of ROS in the vessel wall and a reduction in the production of vasodilator like NO will lead to an imbalance in the ratios of vasoconstrictor to vasodilators, and thus initiate endothelial dysfunction, which we consider is the earliest sign of vascular disease. In addition, they can also trigger several redox-sensitive transcriptional pathways, shifting cellular, molecular response and gene expression profile, toward proatherogenic state. Thus, they can accelerate formation, accumulation of lipid peroxidation products, and modulate pro-inflammatory genes. The transcription factor Nrf2 (nuclear factor erythroid-2-related factor-2, Nrf-2) for instance, a master regulator of detoxification, anti-oxidant, 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. Modern diets are deficient in such nutrients. Recent studies, however, 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 right ventricular (RV) microcirculation and RV function.[42] Studies by McCord *et al.* 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, CVD, and Alzheimer's disease.[43,44]

We already have discussed the importance of diagnostics and the progress that has been made in imaging technologies. Since we have highlighted the importance of endothelial dysfunction, we would like to elaborate a little further on this procedure. At the University of Minnesota, they use CV-Profiler (hypertension diagnostics [HD], Minneapolis, Minnesota), whereas in India researchers use Periscope, arterial stiffness measuring system (Genesis Medical Systems, Hyderabad, India). LD technologies of Miami, Florida, have developed a multidiagnostic platform, that uses an oximeter, blood pressure monitor, and a galvanic skin response monitor, to conduct a variety of tests aimed at computing cardiometabolic risks (CMR), cluster of metabolic risks, as well as risk scores. In 2016, we organized an International Symposium at Bengaluru, India, to discuss ways and means to integrate emerging technologies for developing IT-supported, web-enabled affordable health-care platform. We also obtained funding from the Indian Council of Medical Research) to develop a prototype of non-invasive glucometer. We have established a consortium of Academia-Industry experts, to work on devise development as well as on the possible integration of available technologies to improve the health care.

In collaboration with the medical devise industries and academia, we are exploring possibilities of developing a hand-held ultrasound applicator for monitoring flow dynamics in peripheral arteries and veins. Once we have calibrated the conventional 2D ultrasound imaging devices, we would like to develop hardware and software, to convert 2D data to 3D. We also are exploring possibilities of using piezoelectric flexible pressure sensors, to obtain pulse waveforms at various pulse pressure points. Analysis of flow at these pulse points using wearables will provide data on the flow dynamics of regional vascular beds. For additional information on these ideas, we urge readers to refer to our earlier publications on these topics.[45-47] In addition to the research and development

work that we have initiated on the development of non-invasive diagnostics, we also are validating the data from emerging technologies in relevant fields of cardiometabolic applications. We have done some preliminary studies on the ambulatory glucose monitor (AGM) that has been launched in India by Abbott Diabetes Care.

Figure 1 shows a glucose profile for a 12-h period. Reading are taken every 15 min.

Currently, Dexcom G6 and LifeStyle Libre Pro (Abbott) devices are available for continuous monitoring interstitial glucose. Dexcom G6 uses an easy to use applicator for placing transdermal sensor, which provides glucose reading every 5 min. It also has developed Apps that can be used by caregivers, patients, or parents to get real-time data on the glucose levels. Whereas, Abbotts, AGM provides 15 min readings and can be used for 2 weeks at a time. It requires a reader provided by the manufacturers. Although there are some smartphones with near frequency communication packages that can read the real-time data. Both the devices are available for patients with prescription.

Figure 2 shows the summary reading of a typical test run. The data is color-coded. Green being low-risk and red being high-risk, yellow and orange as mid-range scores. Total of ten tests are summarized with separate individual risks, collective risks, as well as score for overall CMR score.

We are also validating the TM Oxi system, and Sudo-Path system, of LD technologies of Miami Florida. These systems which are designed by Dr. Albert Maarek uses three standard diagnostic devices to generate the digital data. The components are oximeter, blood pressure monitor, and a galvanic skin response monitor. Data generated by these three devices are collected and processed to generate, a variety of clinical risk indicators. The software package includes information about the interpretation of the data generated. Having said that, it will be the responsibility of the physicians to use this data appropriately to manage the observed risks. We are quite impressed with the ingenuity of this approach, as much of the information generated, is based on analytics and software derived. In other words, these devices for instance are not measuring directly the risks for lipid markers, IGT markers, or for that matter CMR markers. However, using the digital data and the clinical data obtained by independent studies, appropriate algorithms are developed to compute the scores expressed on the output. We are excited about the development of emerging non-invasive and minimum invasive diagnostic technologies, which use sophisticated analytics, algorithms, to compute new and useful clinical data. We would like to see that these entrepreneurs work with the clinicians in developing such integrated technologies, develop risk assessment, and risk prediction that are user- and clinician-friendly. We also would like to see independent validation of these new technologies for their specificity and efficacy.

Figure 3 shows risk scores, risk score for clusters, and cumulative risk score for cardiometabolic risk score are presented as bar graph. Risk scores are graded by color, green being low-risk and red, representing high-risk

Figure 4 shows the CV-Profiler of HD does waveform analysis and measures C1-large artery elasticity and C2-small artery elasticity and computes arterial stiffness or hardening of the arteries. http://www.hypertensiondiagnostics.com/.

According to the manufacturers HD-technology, a low C2-small artery elasticity is an indication of endothelial dysfunction, subclinical atherosclerosis, vascular disease progression, and a predictor of cardiovascular events. In spite of the fact, this device has been in use for decades, at the University of Minnesota and few other institutions, it is not used extensively worldwide. We at Bengaluru, India, with the Academia-Industry collaboration, are trying to develop handheld devices capable of generating information on blood flow dynamics, altered flow patterns, hardening of the arteries and subclinical atherosclerosis, using modified ultrasound imaging, and pulse waveform analysis technologies. Unlike the clinical devices, these low-cost handheld devices would be useful for conducting population-based studies. We have already demonstrated in our earlier studies with LD-technology systems, that using oximetry, blood pressure monitors, and plethysmography, we can develop data on endothelial dysfunction. Data generated from such measurements are used for computing endothelial risk score as well as CMR score in the TM-Oxi system [Figures 2 and 3].

When we talk about the integration of emerging technologies, we are talking about the development of non-invasive diagnostic platforms with multiple diagnostic capabilities. For instance, using the same approach as that of Dr. Albert Maarek's TM-Oxi and Sudo-Path systems (LD -Technologies), we can add to their diagnostic platform, capabilities to monitor glucose, blood flow dynamics, sleeping patterns, alerts about malfunction of systems, and a variety of useful analytics. It will be like a computerized diagnostics system of an automobile engine performance. For instance, studies are underway to use sensors on implantable coronary stents that can monitor changes in the blood flow. Researchers at the University of British Columbia have developed smart stents that can monitor hemodynamic changes in the artery and warn clinicians of restenosis at its earliest stages. If such sensors on medical implants can relay the real-time data to a smart platform, then we will know any malfunction of the system immediately. In the near future, technologies will be developed to follow the physiology and function of various organs and systems in real-time, thereby

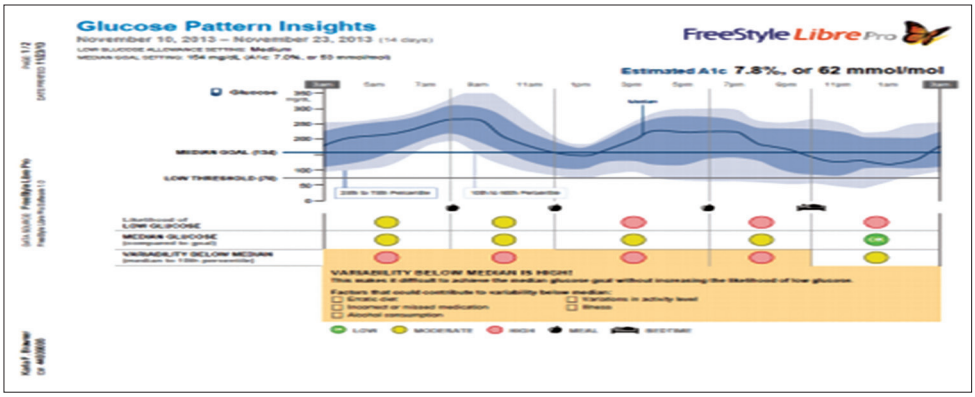

Figure 1: A glucose profile for a 12-h period. Readings are taken every 15 min. Mean glucose values are represented as solid blue line
Courtesy: Abbott Diabetes Care

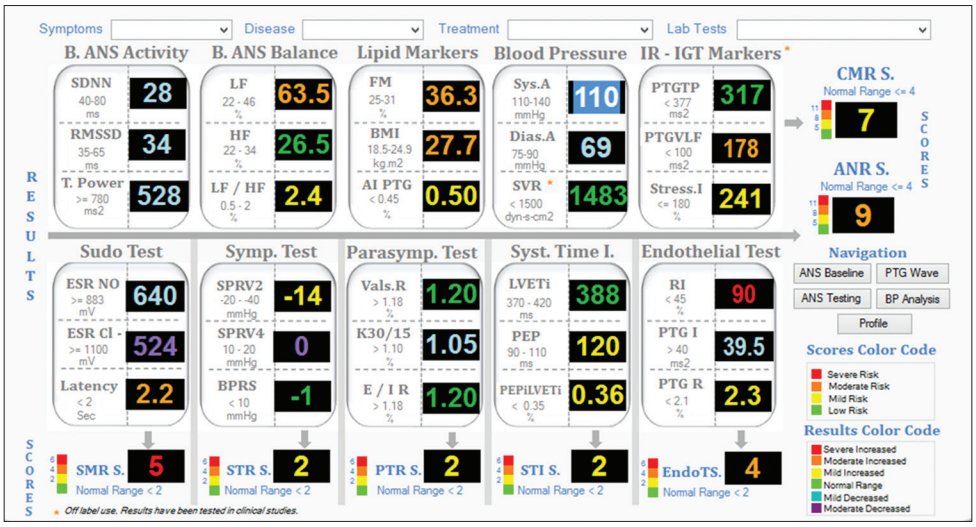

Figure 2: Risk factors, clusters of risk factors, and risk scores
Courtesy: LD Technologies, Miami, Florida

improving our diagnostic capabilities immensely. In a short overview, it is not possible to give details of all the possible applications related to the improvement of clinical studies and integration of emerging technologies for the development of better diagnostics and validation of therapeutic protocols. Readers are urged to consult original articles, reviews, and monographs on these topics.[45-61]

We have discussed early diagnostic markers in a variety of ways, and it is time for us to discuss yet another marker, which plays a very important role but has been neglected or left out in majority of our risk assessment calculators. We are referring to the role of risk associated with lifestyles and work-related. In a recent study, which was reported in the journal Lancet Diabetes and Endocrinology, the researchers examined the data on 102,633 men and women living in Finland, France, Sweden, and the UK, who participated in one of seven studies examining the relationship between work and stress and mortality.[7] This study was led by Mika Kivimaki, a professor at the University College of London and Helsinki. Researchers found that work-related stress was harmful for those with CVDs, metabolic diseases such as diabetes, heart disease, and stroke. What was really surprising in their findings was that this excess risk was independent of the conventional risk factors such as smoking, high blood pressure, or high cholesterol concentration. The authors concluded that chronic work-related stress corrodes health in two major ways: By affecting the nervous system and psychological systems that control heart rhythms, blood vessels, blood clotting, inflammation and other factors and indirectly by affecting coping mechanisms, which may promote unhealthy lifestyle. We feel strongly that such studies should be conducted with appropriate biomarkers, so that level of work-related stress could be scored and appropriate interventions developed. For instance, salivary cortisol, blood cortisol, or hair cortisol could be used as biomarkers

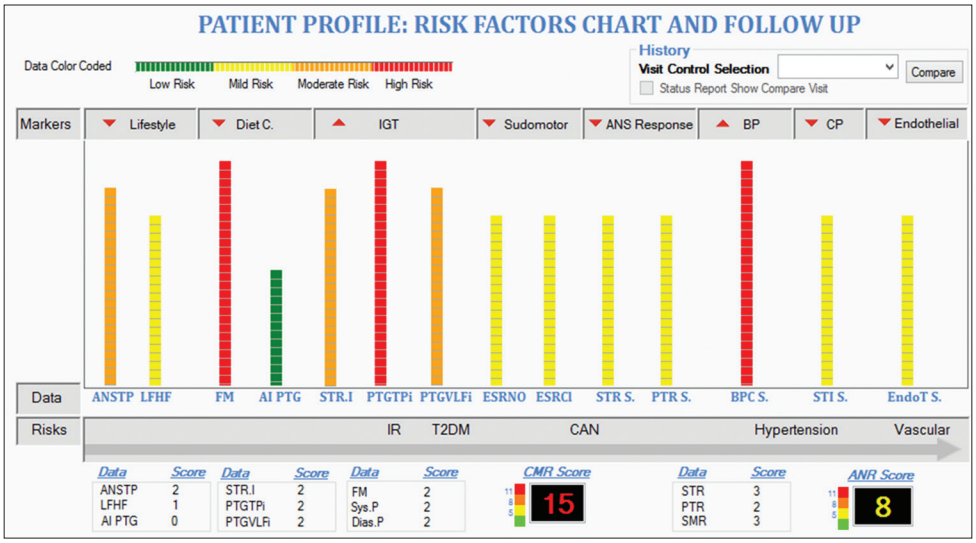

Figure 3: Risk profile for various tests and risk scores expressed in bar graphs
Courtesy: LD, Technologies, Miami, Florida

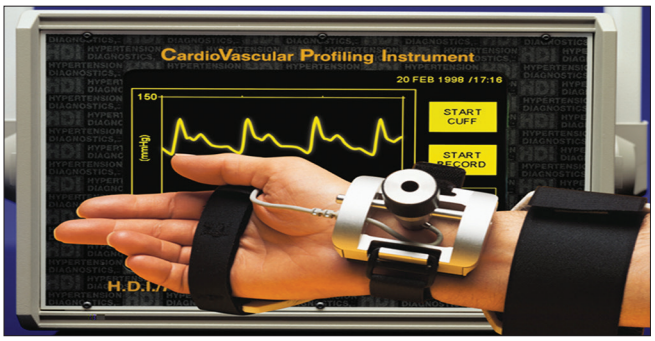

Figure 4: The CV-Profiler - MD 3000, hypertension diagnostics, Minneapolis, Minnesota
Courtesy: Hypertension Diagnostics, Minnesota

for acute and chronic stress levels. Chronic, low-grade stress and inflammation associated with it are underlying causes in most of metabolic diseases, such as excess weight, abdominal obesity (visceral), metabolic syndrome, type-2 diabetes, and vascular diseases.[34-41] These conditions also are well recognized as the central features of obesity and metabolic syndrome. As these conditions are asymptomatic, such as elevated blood pressure and blood sugar, it may take years or even decades, before first symptoms are diagnosed. However, it is possible to monitor the levels of adipocytokines such as, interleukin (IL)-1, IL-6, IL-8, interferon-γ, tumor necrosis factor-α, leptin and resistin, which are pro-inflammatory factors.

DISCUSSION

All of the known metabolic risks such as, oxidative stress, inflammation, altered blood flow dynamics, endothelial dysfunction, arterial stiffness, hardening of the arteries, and subclinical atherosclerosis, play a role in the development of major metabolic diseases, promote the progress of the atherosclerotic vessel wall diseases, and contribute significantly for the development of acute vascular events. Major metabolic diseases such as hypertension, excess weight, obesity, metabolic syndrome, and type-2 diabetes have reached epidemic status worldwide. In spite of the great progress made by the FHS Group, National Institutes of Health, USA, and various other global health-care organizations, even to this day, vascular disease ranks number one in all-cause mortality. Having said that, it is worth noting that preventive strategies developed by various policy-making bodies, guidelines by professional societies, indeed have contributed significantly to the observed decline in deaths due to CVDs in industrialized nations. To a very great extent, this observed decline in CVD-related events is attributed to robust management of modifiable risk factors such smoking, blood pressure, blood glucose, cholesterol, diet, and physical activity. In recent years, there is increased interest in testing the benefit or otherwise of interventions aimed at lowering other less known risk factors, such as oxidative stress, inflammation, and endothelial dysfunction in improving the results of the final outcome. Case in point to illustrate such approach is the CANTOS study, by Professor Ridker and associates, at Harvard on the effect of a monoclonal antibody on the final outcome of their randomized clinical study.

In this overview, as an invited article for the Journal of Clinical Cardiology and Diagnostics, we have discussed the advantages of initiating novel approaches for studies on clinical studies of lesser-known risk factors, as well as improvements in the integration of emerging technologies for development of newer multifunctional diagnostic platforms for risk assessment, risk prediction, and risk management. What are some of the early biomarkers, Which could be the

game changers in the reduction, reversal, and prevention of metabolic diseases? We have briefly discussed possible role of adipocyte-derived exosomes (miRNAs) in the modulation of fetal gene expression profiles. We also have discussed the role of branched-chain aromatic amino acids in the pathogenesis of diabetes. In connection with possible ill effects of excess weight and obesity, we have briefly discussed the role of lipids in oxidative stress, free radical pathology, and chronic low-grade inflammation. It is well known that altered fatty acid metabolism or free-radical pathology may lead to alterations in the synthesis by the vessel of vasodilators (PGI_2, NO) and cellular vasoconstrictors (PG endoperoxides and thromboxanes). Such imbalanced production of bioactive molecules at the vessel environment could induce alterations in the blood flow dynamics, initiate endothelial dysfunction, stiffening or hardening of the arteries, and subclinical atherosclerosis.

CONCLUSIONS

Metabolic diseases such as hypertension, excess weight, obesity, metabolic syndrome, and type-2 diabetes have reached epidemic status worldwide. According to the World Health Organization reports, obesity has increased by two-fold and diabetes by four-fold. On a personal note, according to my observations, in the last three decades, the incidence of diabetes in China has increased 17-fold.[61] In spite of several reports suggesting a significant decline in the deaths due to CVDs, this cluster of diseases are the leading causes of deaths worldwide. Even in the countries where the CVD-related deaths have declined, it has been noted that deaths related to diabetes and metabolic diseases have increased. In view of these observations, researchers are exploring the management of other associated risks such as oxidative stress, inflammation, altered flow dynamics, endothelial dysfunction, hardening of the arteries, and subclinical atherosclerosis. In this overview, we have described these classes of risks as markers of early risk, for the development and progress of vascular diseases. We have briefly described other conditions such as intrauterine disturbances, childhood excess weight, and pre-diabetes, also as contributors for the promotion of the metabolic diseases. We also have discussed possible interventions for these observed risk promoters. For instance, we have suggested supplementation of micronutrients for preventing clinical complications associated low-birth weight. We have suggested the use of anti-inflammatory therapies for the prevention of complication-related pro-inflammatory and oxidative stress-related mechanisms. We also have discussed the role of moderate exercise, high-intensity exercise, and l-arginine supplementation in lowering the ill effects of endothelial dysfunction. In view of the fact that most metabolic diseases have reached epidemic proportions, we have suggested developing simple clinical studies (not clinical trials) to validate safety and effectiveness of complementary therapies at the shortest possible time.

We also have provided examples for developing proof of concept of such therapies, the use of emerging technology integrated platforms. We have advocated the use of ambulatory blood pressure monitoring, AGM, as well as multifunctional testing platforms such as TM-OXi and SudoPath systems of LD-technologies. We have emphasized the importance of collaboration between the clinicians and device developers for developing user-friendly, patient-friendly diagnostic platforms. Having said that, we also have emphasized the need for independent validation of such devices to demonstrate, reliability, specificity, and superiority of such tests in providing new and useful information. Using the LD-technology platform as a model we have suggested how many other diagnostic tools, tests, and methodologies could be added to such a non-invasive platform. We feel strongly that integration of emerging technologies and the use of smart platforms, sophisticated software, improved algorithms, and analytics, will be the future of diagnostics. We also feel that development of simple validation methods for developing proof of concept, for early diagnostics as well as for therapeutics will go a long way for providing observation-based evidence, for safety and efficacy of these newer methodologies.On a personal note, according to my observations, in the last three decades, the incidence of diabetes in China has increased 17-fold.

What are the take-home messages of this overview? Discovery of the modifiable risks for CVD and effective management of these risk factors have contributed significantly to the decline in the deaths, due to CVDs in industrialized nations. In spite of this observed decline in deaths due to CVDs, these diseases collectively are responsible for highest numbers of all-cause mortality worldwide. In addition, the metabolic diseases that contribute the development of CVDs have reached epidemic proportions. In view of these observations, there is an immediate need for developing short term, cost-effective clinical studies, to validate complementary therapies for intervention of all the metabolic risks. Furthermore, there is an immediate need for developing integrated diagnostic technologies, for risk assessment, risk prediction, and risk management. Studies at the Mount Sinai Hospital, New York by Professor Valentin Fuster and associates on the presence of subclinical atherosclerosis and hardened arteries in middle-aged, asymptomatic adult patients led them to conclude, "these findings could help improve cardiovascular risk prevention in the general population even before the appearance of conventional risk factors, an example of primoradial prevention." Similarly, studies done at the University of Minnesota by Professor Jay Cohn and associates for over two decades, with asymptomatic adult patients, led them to hypothesize, that in the absence of endothelial dysfunction, there is no progression of atherosclerotic diseases. We would

like to conclude this overview, with a slight modification of our title for this article, "Diagnosis and management of early risks such as oxidative stress, inflammation, and endothelial dysfunction will reduce or reverse metabolic diseases."

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