ORIGINAL ARTICLE

Diabetes-related Clinical Complications: Novel Approaches for Diagnosis and Management

Gayathri Choda[1], Gundu H. R. Rao[2]

[1]Aarca Research Pvt. Ltd., Bengaluru, India, [2]Laboratory Medicine and Pathology, Thrombosis Research, Lillehei Heart Institute, University of Minnesota, USA

ABSTRACT

Metabolic diseases such as hypertension, obesity, diabetes, and vascular diseases have reached epidemic proportions worldwide. In the past four decades, childhood and adolescent obesity has increased four-fold worldwide. During the same period, obesity in adults has doubled and diabetes has increased by four-fold. In China, India, and the USA, the number of prediabetes is more than diabetics. This population is at considerable risk for developing diabetes, its clinical complications, and acute vascular events. The management of modifiable risks for cardiometabolic risks has improved considerably. Several major studies have demonstrated, that robust management of modifiable risks for cardiovascular diseases (CVDs), significantly reduces premature mortality from CVDs. Considering the progress made in the risk assessment, risk management, we feel strongly, that not much progress is made in the areas of primary prevention and early risk assessment, for clinical complications associated with metabolic diseases, in particular, diabetes. The majority of the clinical complications associated with diabetes are due to dysfunction of the vascular system or nervous system. Complications include vasculopathy leading to subclinical atherosclerosis, heart attacks, and stroke. Other clinical complications include peripheral artery disease, and peripheral neuropathy, the leading cause of functional impairments of the two lower extremities, hands, and limbs. Apart from these complications, uncontrolled diabetes leads to dysfunctional kidneys and ultimately end-stage renal disease and kidney failure. Vascular dysfunction in diabetes also leads to glaucoma and diabetic retinopathy. Prestigious Mayo Clinic of Rochester, Minnesota, has listed following conditions as clinical complications associated with diabetes: Nerve damage (neuropathy), kidney damage (nephropathy), eye damage (retinopathy), foot and limb damage, skin conditions, hearing impairment, and Alzheimer's disease. In this overview, we have discussed some of these issues as well as described available non-invasive technologies for the early detection of clinical complications related to diabetes.

Key words: Clinical complications, diabetes, diagnosis, management

INTRODUCTION

Diabetes as a disease was known to Egyptians, at least from 1500 BC. The ancient Indian physicians, Sushruta and Charaka (400–500 AD), were able to identify the two types; Type-1 and Type-11 as a manifestation of the same disease.[1] Countries with a large population, China and India are competing for the number one position, when it comes to the ranking as "Diabetes Capital" of the world, a dubious distinction. The number of prediabetes exceeds the number of individuals with diabetes in China, India, and the USA. Probably, the situation may be the same in most of the other countries. Since 1980, age-standardized diabetes prevalence in adults has increased in every country.[2-10] Childhood and adolescent obesity worldwide have increased by ten-fold in the past four decades: A new study by the Imperial College, London, and World Health Organization (WHO).[2] Professor Ezzati, the lead author of the study says, "These worrying trends reflect the impact of food marketing and policies across the globe, with healthy nutritious foods too expensive for poor families and communities. The trend predicts, a generation of children and adolescents, growing up

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

obese, with at a greater risk of diseases, like diabetes." Apart from the known symptoms like increased thirst or urination, by and large, the disease is recognized clinically by increased blood sugar levels. According to the International Federation of Diabetes (IDF), and the WHO, diagnostic criteria for diabetes are fasting sugar >7.0 mmol/l (126 mg/dl) or 2 h post-prandial glucose 11 mmol/l (200 mg/dl).

Complications associated with diabetes may include; vasculopathy and neuropathy. Heart attacks and stroke are 2–4 times more common in people with diabetes. High blood pressure affects two out of three individuals with diabetes. It greatly raises the risk of diabetes-related complications, heart attack, stroke, kidney failure, and blindness. Periodontal disease occurs more often in people with diabetes. Diabetes is the leading cause of blindness (retinopathy or glaucoma). Diabetes is one of the major contributors to end-stage renal disease (ESRD). More than half of individuals with diabetes have some form of nerve damage (neuropathy). In Type-1 diabetes, ketoacidosis is quite common. Vascular diseases are one of the main causes of erectile dysfunction in men with diabetes. Diabetes is a group of metabolic disorders characterized by hyperglycemia. All awareness programs should emphasize the importance of protecting the body from hyperglycemia. The direct and indirect effects of the human vascular tree are the major source of morbidity and mortality in both Type-1 and Type-2 diabetes.[2] The injurious effects of hyperglycemia manifest as macrovascular complications (coronary artery disease, peripheral arterial disease, and stroke) and microvascular complications (diabetic nephropathy, neuropathy, and retinopathy).

Diabetic retinopathy (DR) may be the most common microvascular complication, which depends on both duration and the severity of hyperglycemia. Development of DR was associated with both the severity of hyperglycemia and hypertension in the UK Prospective Diabetes Study.[11-13] DR is the most common microvascular complication, responsible for over 10,000 new cases of blindness every year in the USA alone. Diabetes retinopathy may begin to develop as early as 7 years before the diagnosis of diabetes in individuals with diabetes. Therefore, this condition may go unnoticed for several years. As to the mechanism of cell injury by excess sugar, high glucose level seems to increase the flux of sugar molecules through the polyol pathway, increasing sorbitol levels. Increased osmotic stress from accumulated sorbitol seems to be the major contributor to diabetic microvascular complications. Furthermore, high glucose concentrations can promote the formation of advanced glycation end products. Oxidative stress may also play an important role in hyperglycemia mediated cell injury. Besides, growth factors (endothelial growth factor) and transforming growth factors also have been implicated in the pathogenesis of diabetes-related retinopathy. Small vascular dilation occurs in the retina as an early sign of retinopathy. In addition to microaneurysms, which induce such vascular dilation, small spot hemorrhages occur, which are described as "dot hemorrhages."

Diabetes nephropathy is a leading cause of chronic kidney disease and renal failure worldwide.[14] Diabetic nephropathy is kidney damage that results from having uncontrolled diabetes for a long duration. High blood sugar damages that part of the kidneys that filter the blood. The damaged filter becomes "leaky" and lets protein into the urine. It is diagnosed in clinics by the presence of microalbumin, leading to "microalbuminuria." Like the retinopathy, this condition also seems to manifest several years before the diagnosis of diabetes. However, experts predict that peak incidence usually occurs in persons having diabetes for 10–20 years. The overall prevalence of microalbuminuria and macroalbuminuria in Type-2 diabetics is 30–35%. ESRD is the major cause of death. Patient education seems to be the key to prevent nephropathy. There is a great need to identify and clarify the role of biomarkers in clinical practice.

Diabetes peripheral neuropathy (PN) is accompanied by the presence of symptoms or signs of peripheral nerve dysfunction in people with diabetes. Clinical diagnosis includes a test to determine loss of touch, vibration, and temperature sensitivity. Patients, who have lost 10-g monofilament sensation, are at considerable risk for developing foot ulceration. About 60–70% of all people with diabetes will eventually develop PN, although not all suffer pain. Numbness is the most common symptom of nerve damage due to diabetes. People who lose sensation are the ones most likely to get ulcers on their feet and end up needing amputations.[15-17] Diabetic PN has been defined by the Toronto Consensus Panel on Diabetic Neuropathy, as a "symmetrical, length-dependent sensorimotor polyneuropathy, attributable to metabolic and microvessel alterations, as result of chronic hyperglycemia exposure and cardiovascular risk covariates."[16] Since the loss of sensation is a subtle change that occurs over a long period, there is a great need for the development of novel noninvasive methodologies to follow microvascular dysfunction.

DISCUSSION

In spite of the fact, diabetes is managed worldwide by monitoring glycemic load, some experts feel that diabetes is a disorder of lipid metabolism. Abnormal lipid environment seems to be responsible for the devastating vascular complications associated with uncontrolled diabetes, including chronic inflammation that promotes vascular disease. Hyperglycemia and insulin abnormality seems to be the underlying causes for all vascular disease in diabetes although the exact molecular mechanisms responsible for this vascular injury are poorly understood. Endothelial and vascular smooth muscle cell dysfunction contributes

significantly to atherosclerosis and its complications. Several studies have shown that endothelium-dependent vasodilation is abnormal in patients with diabetes.

Monitoring glucose for management of diabetes

The concentration of glucose is highest in the arterial blood. Laboratory analysis of blood glucose is done usually in venous blood samples. Glucose concentration may be determined in whole blood, plasma, or serum. Although clinical diagnostic laboratories still use venous blood samples for glucose analysis, introduction three decades ago, self-monitoring of blood glucose using finger stick blood samples, test strips, and portable meters, has significantly aided diabetes management. The WHO has approved the use of point-of-care-testing devices for hemoglobin A1c (HbA1c) diagnostic tests traceable to the International Federation of Clinical Chemistry reference method. The Quo-Test analyzer by Entwicklung, Konstruktion und Fertigung Diagnostics, directly measures HbA1c in minutes using a 4 ul sample of blood from a simple finger stick.

The use of this method in resource-poor countries is limited. We have been working on the development of a portable non-invasive method for monitoring blood glucose for quite some time. Senior author, Gundu H.R. Rao was funded by the Indian Council of Medical Research, India, for developing prototypes of non-invasive glucometers (NIGM). We used near infrared (NIR) sensors for the detection of blood glucose (Antony Aneel Joseph and Gundu H.R. Rao: Indian Patent number 2756/CHE/2012 A). The NIR emitter used was a 940 nm IR light-emitting diode and the detector was a photodiode chip, with 1100 nm wavelength (https://www.diabiqik.com). The NIGM is currently undergoing productization and clinical validation. Continuous glucose monitoring (CGM) from the interstitial fluid is a new technology that is used by the Abbott Diabetes Care as well as Dexcom G-6 (www.dexcom.com). The Food and Drug Administration (FDA) of the USA has approved both these systems. We and others have validated the FreeStyle Libre Pro in India, for Type-1 as well as Type-2 diabetes management.

None of the existing home monitoring devices directly determine HbA1c. Since it is very important to know the HbA1c values to manage glycemic load effectively, we prefer the use of FreeStyle Libre Pro or Dexcom-G6 devices. Figure 1 shows a plot for fasting glucose done by Abbott (Courtesy Abbott Diabetes Care) device, compared to a commercially available device using the fingerstick method. The data show a strong linear relationship between blood glucose and interstitial fluid glucose values.

Since HbA1c values are more reliable for robust management of blood glucose, we did a population-based study of over 10,000 individuals in a hospital setting. Data presented as a dot-plot in Figure 2 show a wide scatter of values at HbA1c 7.0, ranging between 100 and 200 mg/dl. Because of this

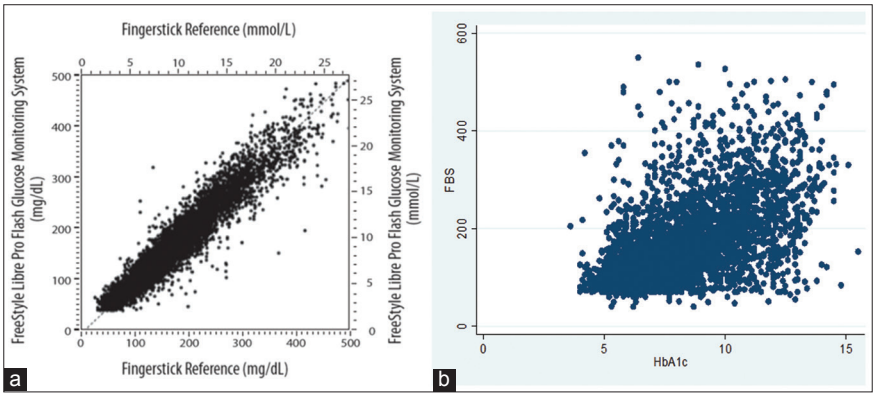

Figure 1: (a) Fasting glucose: CMG versus fingerstick (b) Fasting glucose versus hemoglobin A1c (n = 10,000)

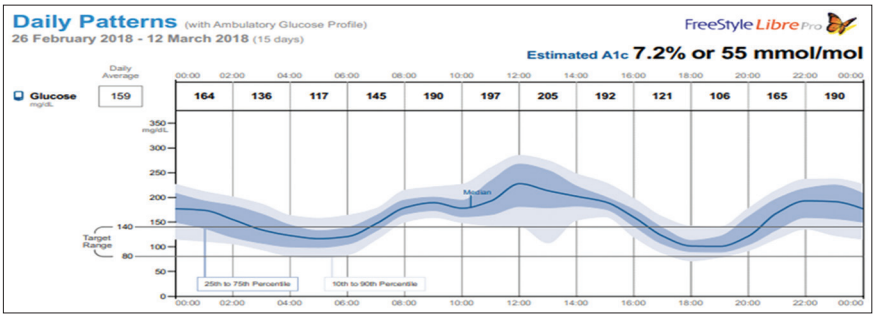

Figure 2: Glucose profile of a diabetic patient on medication for over 20 years. Source: Personal data

observation, we feel strongly that one should not go by the HbA1c values alone, but conduct additional tests to diagnose early signs of diabetes-related clinical complications. Given the fact, that CGM devices are available.

Individuals should be encouraged to use such devices. Figures 2 and 3 show the glucose profiles of a diabetic individual, who is on medication. Despite having diabetes for over 20 years, the patient seems to have a well-controlled glucose profile, with mean glucose of 156 and HbA1c of 7.2. However, in the absence of a further test, it will not be possible to predict, whether or not any diabetes-related complications are already in the early stages of development. The trend in glucose profile makes it easy to detect ups, downs, night-time lows as well as postprandial peaks and recovery times.

Early diagnosis of risk factors for vascular diseases

The ability to scan many times, as well as the accumulation of data frequently over several days, allows one to better understand the impact of actions such as food intake, exercise, and lifestyle changes. These devices can be customized to send reminders, alerts and add your notes, thus, it empowers the users for improving their health.

Primary prevention of cardiovascular disease (CVDs) has been aimed at early risk factor identification and robust management of the modifiable risks (American College of Cardiology/American Heart Association Guidelines: J Am Coll. Cardiol 17: epub. 2019). At the University of Minnesota, a center was established for comprehensive screening of an asymptomatic population with ten tests designed to detect early vascular and cardiac abnormalities using a scoring system from 0 to 20, 48% of the population screened exhibited scores >5, indicative of early vascular disease. One of the tests used for monitoring endothelial dysfunction was pulse wave analysis using Cardiovascular Profiling Instrument developed by Hypertension Diagnostics of Minneapolis, Minnesota [Figure 4].

Hypertension diagnostics of Minneapolis, Minnesota, has developed a method for noninvasively measuring the elasticity of large and small arteries, providing an early assessment of CVDs. According to experts including Professor Jay Cohn of the University of Minnesota, alterations in the small artery elasticity are the earliest and most sensitive marker of CVDs. For use at the population level, we need a simple cost-effective hand-held monitor to detect vascular dysfunction or hardening of the arteries. We are trying to develop a wearable device using flexible piezoelectric pressure sensors.

Imaging of carotid intima-media thickness is widely used for monitoring subclinical atherosclerosis. However, an Imaging Research Laboratory in Ontario, Canada, has developed a three-dimensional (3D) imaging of the carotid arteries. On the left side [Figure 5] is a relatively healthy artery with no visible signs of plaque buildup, whereas, in the photo on the right side, clear atherosclerotic plaque is seen. Proprietary software and analytics will provide plaque volume and other characteristics needed for following progression, or regression

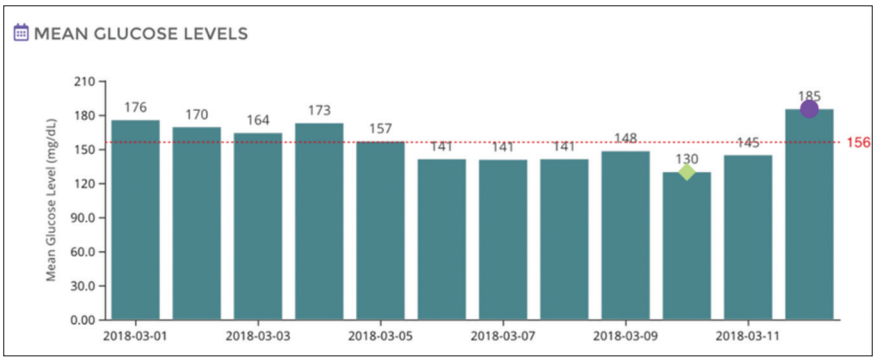

Figure 3: Mean daily glucose values for the same patient shown in Figure 2, plotted as a graph. Source: Personal data

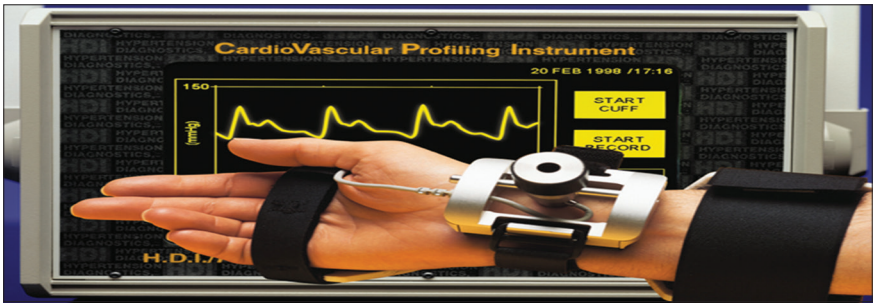

Figure 4: Cardiovascular - Profiler. (Courtesy: Hypertension Diagnostics, Minneapolis, USA)

of plaque before and after treatment. In collaboration with the Medical Electronics Group at Bengaluru, India, we are trying to develop a cost-effective carotid 3D scanning device.

Early diagnosis of risk for DR

There is a great need for the development of cost-effective, reliable, easy-to-use, portable fundus cameras for evaluating retinopathies, responsible for childhood, and adult vision loss. The Pictor Plus (Volk Optical, Mentor, OH) is an FDA approved, commercially available portable system that shows utility for determining optic disc edema and DR.[18,19] Retinal fundus photography is the most common DR detection method globally. Forus Health Technology, Bengaluru, has developed "The 3nethra classic," a compact, portable, easy to use nonmydriatic digital imaging device to acquire, display, store, and transmit images of the posterior and anterior surface of the human eye. Photographs indicating retinal hemorrhages, hard exudate, and microaneurysms can be obtained easily by non-clinician healthcare workers. Fundus photographs serve as a reference standard in early detection and for following the progression of DR.

Shown in the Figure 6 are the color photographs of an eye of a normal individual (left side), and that of a smoker (right side). The inventors claim that their state-of-the-art imaging and telemedicine system is fully equipped to improve diagnostic accuracy and minimize screening time. Furthermore, once images are captured, the system grades, in real-time, and identifies images have DR. Then patients are advised to consult the specialists, for further clinical tests and management. Fundus autofluorescence imaging has been effectively used as a non-invasive tool for the detection of calcium emboli, as well as atherosclerotic plaques in the retinal artery. NIR imaging

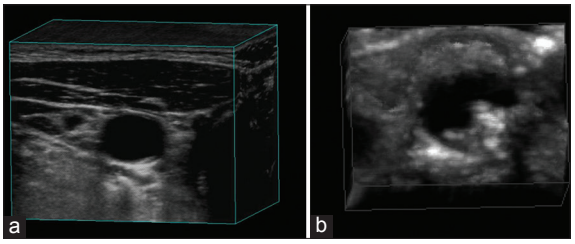

Figure 5: (a) Carotid scans (Carotid artery by three-dimensional ultrasound. Courtesy: Dr. Fenster). (b) Imaging Research Laboratories, London. Ont. Canada

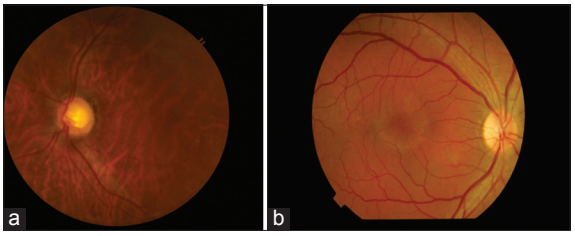

Figure 6: The color fundus images (Normal and that of a smoker. Courtesy: Shaym Vasudev Rao, Forus Health, Bengaluru)

modality is being widely used for the detection of lipid content in coronary plaques. These two simple non-invasive techniques, fundus autofluorescence, and infrared fundus imaging have been used for detecting asymptomatic or atypical emboli, even before vascular occlusion occurs.[19] We are very much interested in developing devices that can follow the flow dynamics in the blood vessels of the eye using IR imaging systems. We also are interested in using confocal microscopy as well as optical coherence tomography, non-invasive imaging techniques, to follow the morphology of blood vessels of the eye as a means to study subclinical atherosclerosis and its progression.

Early diagnosis of peripheral vasculopathy (PV) and neuropathy

Lower extremity diseases, including PN and peripheral vascular disease, are leading causes of disability worldwide.[20] The early detection of PN and PV, with appropriate counseling, seems to be the best strategy for preventing dysfunction of the two lower extremities. We and others (SUDOSCAN) have used monitoring Sudo Path System to monitor sudomotor function for the detection of diabetic neuropathy.[21,22] Apart from the measurement of c-fiber response to stimuli, there are many other methods available for early detection of PN/PV. Corneal nerve fiber density, cold perception threshold, intraepidermal nerve fiber density, peroneal motor nerve conduction velocity, sural nerve action potential, sural nerve conduction velocity, vibration perception threshold, and warm perception threshold can be followed using appropriate devices. Corneal nerve fiber density determined by corneal confocal microscopy (no/mm20). The non-invasive vascular screening device, -VP 1000 plus (Omron Healthcare), is capable of detecting ankle-brachial index, toe-brachial index, pulse wave velocity, and vascular age in 5 min. It also can detect R-R interval heart rate variability. On the other hand, IR thermal imagers are useful for recording thermograms, which provide temperature variation in subjects with multicolor graphs. When connected to software, the software helps to generate multiple patient report charts.

Forward-looking infrared radar (FLIR) - E6-XT 43.2 (240 × 180) pixel infrared detector, with built-in Wi-Fi, allows to quickly connect with the FLIR - tools Mobile app, for sharing images and sending reports easily from any location. FLIR systems (Wilsonville, Oregon) are the leading manufacturers of IR imaging systems for a variety of applications. FLIR TG 165 Spot Thermal Camera with image storage capabilities features innovative lepton IR imaging engine with 80 × 60 resolution, 150mK sensitivity, and 9 hz refresh rate 4800 IR pixel resolution. At Aranca Research Laboratory, Bengaluru, India, we use FLIR-E85 series thermal imaging camera to obtain thermal scans of body surfaces for monitoring thermal variations [Figure 7].

For population-based screenings, we may use a portable smartphone camera (Therm-App), similar to the one, as shown in Figure 7. In a routine thermal imaging process,

we shoot the video at 30 frames/s for 1 min and capture 1800 frames of data. The data thus collected are computed and processed further, using proprietary software to obtain patterns of thermal variation, and graded for risk with 1–10, one being no risk and increases in the numbers indicating higher risk. Figure 8 shows a thermal scan of a low-risk individual with an even distribution of temperature. The subject is an 83-year old, male individual with 20-years of diabetes, under medication: Metformin (2 g), Glipizide (10 mg), Januvia (100 mg), Carvedilol (6.25 mg), Lisinopril (20 mg), and Atorvastatin (10 mg). Shown in the Figure 8 are thermal scans of the hands of a low risk individual (left side), and that of a high risk individual (right side) with uncontrolled diabetes. The scan shows thermal asymmetry for both hands.

Figure 9 shows thermal scans of the foot of a low-risk individual and a high-risk individual. In the low-risk individual with 20 years of diabetes, the thermal activity is evenly distributed, but for a slight difference in the left foot, compared to the right foot. In the high-risk individual (shown on the right side), the thermal activity is quite uneven and shows some unusual focal pattern (light yellow) on the right heel.

Earlier in the article, we described observations made by experts that diabetes-related complications may develop even

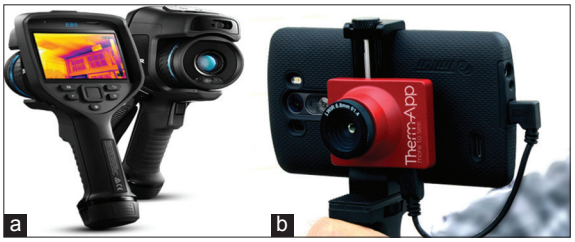

Figure 7: (a) Forward-looking infrared radar-E85 thermal image camera. (b) portable thermal camera for smartphone

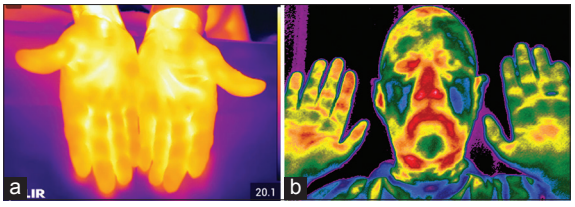

Figure 8: (a) Low risk (even thermal symmetry). (b) High risk (Uneven asymmetry)

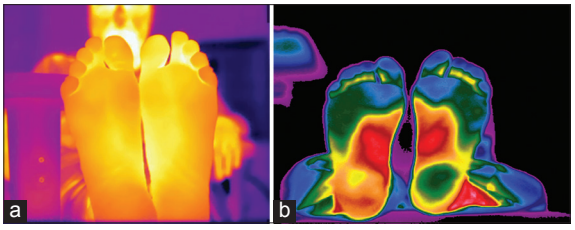

Figure 9: (a) Low risk (Even thermal activity). (b) High risk (Thermal asymmetry)

before the disease is diagnosed. Because of such observations, it is essential to scan individuals often enough, to observe early signs of vasculopathy. For instance, in the case we have discussed above, despite well-controlled diabetes, and a reasonably acceptable HbA1c of 7.2 [Figure 2], the individual shows early signs of vascular dysfunction as evidenced by regional thermal variations in the foot (Figure 9 left side). In the preliminary clinical studies, we have done the technique of thermal imaging with appropriate software analytics seems to be of great value to follow thermal variations in the two lower extremities, which are the body parts most liable to develop vascular dysfunction and PN in individuals with diabetes. We are developing other non-invasive technologies as well, to follow the blood flow dynamics of regional vascular beds. The results of our clinical validation of these emerging technologies will be reported in the near future.

CONCLUSIONS

Metabolic diseases have increased in the incidence and prevalence, to epidemic proportions worldwide in the past four decades. Hypertension, excess weight, obesity contribute significantly to the comorbidities of diabetes, and vascular diseases. It has been very well established that the coexistence of diabetes and hypertension worsens clinical outcomes. The interdependency of metabolic diseases is so complicated that having hypertension appears to increase the risk for Type-2 diabetes, and having Type-2 diabetes increases the risk of hypertension. Having both conditions increase the risk of various complications such as heart attack, stroke, kidney disease, neuropathy, and retinopathy. Close to 70% of deaths occur in diabetes due to macrovascular complications, such as myocardial infarction and stroke. Being overweight or obese, increases the chances of developing Type-2 diabetes. The number of obese adults is forecasted by the experts, to rise by 73% over the next two decades. The relationship between obesity and diabetes is again interdependent and as a result, a new term, “diabesity” has been coined by experts to describe this condition. Major factors that contribute to this condition include overconsumption of energy-dense food, altered lifestyle, genetic predisposal, and altered fat metabolism, leading to adipose tissue dysfunction. Visceral fat content seems to serve as an independent predictor of insulin resistance. According to experts, 80% of diabetics are obese. Having said that, we should inform the readers about the Asian phenotype, which is characterized by an increase in visceral fat (central abdominal obesity). Therefore, in this population, waist/ratio is a better indicator of metabolic syndrome, than body mass index, the gold standard for obesity.

As we have described in this preliminary study, diabetes-related clinical complications are far less common in people who have well-controlled blood sugar levels. Therefore, maintaining glycemic control in patients with diabetes prevents many

of the microvascular and macrovascular complications associated with diabetes. Macrovascular complications of diabetes are primarily diseases of the coronary arteries, peripheral arteries, and cerebrovascular arteries. Early-onset of vasculopathy begins with the hardening of the artery or with altered blood flow, resulting in endothelial dysfunction, the earliest signs of vascular dysfunction. Early macrovascular disease is associated with the development of subclinical atherosclerosis. Earlier studies have demonstrated the presence of subclinical atherosclerosis even in asymptomatic individuals. DR, on the other hand, presents as two different types: Non-proliferative retinopathy with venous loops, retinal hemorrhages, hard exudates, and soft exudates. Whereas, proliferative retinopathy is marked by the presence of new blood vessels, with or without vitreous hemorrhage. Diabetic nephropathy is defined as persistent proteinuria, which can progress to kidney dysfunction and, ultimately ESRD. Diabetic neuropathy is quite heterogeneous and is associated with vasculopathy as well as nerve pathology.

In view of the fact, that diabetes-related clinical complications are far less common in patients who have well-controlled blood sugar levels, we have discussed the importance of using emerging technologies to monitor blood or interstitial fluid glucose levels. We also have emphasized, that we should not be dependent on fasting blood glucose values or the HbA1c values alone for the success of interventions, but conduct tests for early markers of various know clinical conditions. We have described available methods for monitoring endothelial dysfunction or hardening of the arteries. We also are trying to develop simple, easy to use cost-effective mobile devices, to monitor endothelial dysfunction, which is considered to be the earliest sign of vascular disease. We have described emerging technologies to monitor atherosclerosis in carotid arteries. Currently used diagnostic methods for monitoring altered vascular pathology of the carotid artery are; ultrasound scanning for measuring intimal media thickness (IMT), and the use of Doppler Ultrasound for visualising bloodvolume flow dynamics. Its two-dimensional grayscale can be used for measuring intimal-media thickness. However, the method that we have described being 3D gives a better idea about plaque volume as well as plaque morphology.

For early diagnosis of DR, we have described portable fundus cameras that are available with modern software analytics, for the detection of eye conditions such as glaucoma, non-proliferative as well as proliferative conditions. Furthermore, these platforms can collect, analyze the data real-time, and send reports to the clients as well as health providers. We also have described that fundus autofluorescence imaging has been effectively used as a non-invasive tool for the detection of calcium emboli, as well as atherosclerotic plaques in the retinal artery. NIR imaging modality is being widely used for the detection of lipid content in coronary plaques. Continuing in the same lines of thinking, we have described a newer application, thermal imaging for monitoring diabetes-mediated vasculopathy and PN. At present, we are testing the new technology under clinical conditions, to validate the superiority of this method, to other methods in use for the detection of vascular insufficiency and resulting body surface temperature variations. We will present the results of our studies using thermal imaging, in some important clinical cases, in our future articles.

Finally, we would like to inform the readers that we have no clue whatsoever, at this time of writing, as to how the molecular mechanisms (altered lipid and carbohydrate metabolism, gene expressions, and micro RNAs), drive the progress of the disease to any of the complications we have discussed in this article. It is a great topic of interest for us, for our future exploratory studies.

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