Management of Diabetes, Metabolic Syndrome and Cardiovascular Complications Using A Novel Diagnostic Platform

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Abstract

Metabolic diseases such as hypertension, excess weight, obesity, type-2 diabetes and vascular diseases, have become epidemic worldwide. In the last three decades, obesity has increased by two-fold, and diabetes by four-fold globally. In spite of the decline in cardiovascular disease (CVD) related deaths in industrialized countries, CVD has remained the number one killer for over a century. With scientific discoveries, it is recommended, that once the risks for metabolic diseases are recognized, the only choice we have, is robust management of observed risks. Metabolic risks usually develop as cluster of risks, and act in concert to promote the pathogenesis of atherothrombotic state and contribute significantly to the premature mortality and co-morbidities. There is considerable debate in the scientific community, as to what metabolic risks constitute, "metabolic syndrome". Furthermore, there is no clear-cut guidelines or guidance for the most effective management of metabolic diseases, and resulting clinical complications, more so in preclinical or subclinical states. In view of these observations, we are trying to validate various diagnostic tools, for the development of a noninvasive integrated platform, for the early diagnosis of cardiometabolic risks and management of observed metabolic and cardiac risks. In this overview, we describe the use of a novel integrated platform called, TM-Flow, put together by Dr. Albert Maarek and his team at LD Technologies (www.ldteck.com), Miami, Florida. The integrated diagnostic platform, uses time-tested devices such as, oximeter, photo and volume plethysmography, blood pressure monitor with central aortic systolic pressure, , and a galvanic skin response monitor, to elicit a variety of hemodynamic body signals, representing physiopathology of the test subjects, and a proprietary software which analyzes, computes, and correlates with clinical diagnosis of the various risks and cluster of risks, indicating the progression of metabolic and cardiac diseases. In this review, we will introduce this novel diagnostic tool, and discuss the advantages or usefulness of this system in the early diagnosis, risk stratification, guide to therapy and post-therapy management of the progression or regression of the observed risks and risk-clusters.

Introduction

According to the Global Burden of Disease Study, and the NCD Risk Factor Task Force, metabolic diseases such as hypertension, childhood obesity, adolescent and adult obesity, prediabetes, type-2 diabetes, and vascular diseases, have reached epidemic proportions worldwide [1-17]. Management of modifiable risk factors, and a healthy life style, has contributed significantly to the decline in CVD related deaths in industrialized nations, yet there seems to be increases in diabetes related deaths, in low- and middle-income countries [12-17]. With the rapid progress in emerging technologies, and improved diagnosis, the list of metabolic risks, that promote metabolic disease and vascular disease are increasing by the day. Just to mention a few; oxidative stress, low grade chronic inflammation, altered blood flow dynamics, endothelial dysfunction (hardening of the arteries), prehypertension, insulin resistance, prediabetes, infant, childhood and adolescent obesity, subclinical atherosclerosis and many more. Having said this, it is important to note, not many of these metabolic risks are assessed are treated in day to day practice of preventive medicine.

When it comes to diagnosis of metabolic risks, some are easy but many or complex issues. For instance, diagnosis of elevated blood pressure requires just a blood pressure (BP) monitor. However, if one were to use a continuous blood pressure monitor (ambulatory BP monitor), management of BP would be much more efficient, than the current practice of monitoring one- time measurements at the doctor’s office. Diagnosis of excess weight, obesity is also easy. Once can measure height, and weight of patients, calculate the body-mass index (BMI) or measure waist, hip circumferences, and calculate Waist/Hip ratio. Usual diagnostic methods for prediabetes and diabetes include, measurement of fasting glucose, impaired oral glucose tolerance test, glycosylated hemoglobin A1c (HBA1c), insulin sensitivity. In most clinics, worldwide, diabetes and hyperglycemia are managed by just measuring fasting glucose or at the most the half yearly measurements of HBA1c. There are newer emerging technologies available, for predictive and preventive medicine. For instance, Japanese researchers recently presented their findings, about early prediction of future diabetes occurrence,
in Berlin, Germany, in an international meeting at this year’s European Association for Study of Diabetes (EASD) conference. They measured the trajectories of fasting glucose, BMI, and insulin sensitivity in individuals. Their findings showed that on average, several risk factors were more common among individuals, who went on to develop type 2 diabetes compared with those who didn’t. In particular, BMI, fasting glucose, and insulin resistance, were increased up to 10 years before diagnosis, and these differences widened over time. Yet another emerging technology is measurement of plasma free amino acids (PFAA) as predictors of future occurrence of diabetes [18-20]. Although these are useful discoveries, may not be suitable for population-based studies or at low- and medium-income countries.

**Novel Diagnosis of Diabetes and Cardiometabolic Risks**

The TM-Oxi system, takes measurements from a blood pressure (BP) device and a pulse oximeter. The SudoPath system, measures galvanic skin response to assess the SudoMotor pathway function. Spectral analysis of the photo plethysmograph (PTG) waveform, and electrochemical galvanic skin response, allow the TM-Oxi and SudoPath systems, to calculate several homeostatic markers, such as the PTG index (PTGi), PTG very low frequency index (PTGVLFi), and PTG ratio (PTGr). The focus of these studies was to evaluate these markers (PTGi, PTGVLFi, and PTGr) in CVD patients against a control group, and to calculate an independent cardiovascular risk factor score, diabetes and the diabetes-related neuropathy [21-23]. We have articulated the use of this methodology for the diagnosis of cardiometabolic risk, in many of our recent articles [21-26]. In the present study, we have used a new software developed by the LD Technologies, and the results of these studies are presented in Figure 1-4 as TM-Flow Reports. The TM-Flow is a Medical Device Data system, that measures hemodynamic body signals, using photo and volume plethysmography, and galvanic skin response test. The system has integrated software, and calculates the mathematical analysis of the signals, and provides markers for diagnosis of cardiometabolic disease and associated cardiovascular and autonomic system dysfunctions.

**Figure 1:** Autonomic nervous system markers are presented: (sudomotor function), heart rate variability, para sympathetic and sympathetic tests.

**Figure 2:** Vascular function markers are presented: Endothelial function (Stress Index), upper large artery (pulse pressure), and lower large artery (pulse wave velocity).
Figure 3: Lifestyle markers and suggestions: Diet markers (BMI), fitness markers (fitness level, mental stress, exercise tolerance, biologic oxygen saturation, heart rate).

Figure 4: Cardiometabolic score: suggests that the treatment management is not effective.

In a typical TM Flow Report, which includes microvascular and autonomic assessment, Sudo-Motor tests include: left foot nitric oxide peak and right foot nitric oxide peak, representing response of skin microcirculation; left foot sweat response and right foot sweat response, representing C-fiber density. Parasympathetic tests include: markers of the parasympathetic baroreceptor sensitivity, markers of cardiovascular innervation, and cardiac function, while standing. Sympathetic reflex tests include: adrenergic response during standing, norepinephrine response during standing, and markers of the sympathetic beta-baroreceptor sensitivity. Blood pressure responses include: brachial systolic pressure when heart contracts, BP when heart relaxes delta minus diastolic pressure, and markers of the pressure of the aorta.

Markers of artery stiffness include: peripheral small artery tone, aortic stiffness, and lower extremity stiffness (pulse wave
velocity). Lower artery markers include: right and left leg artery stiffness (Brachial, left ankle and right ankle: systolic and diastolic). Vascular and endothelial homeostatic markers include: marker for insulin resistance, marker for glucose control, marker for fibrinogen, marker for inflammation and marker for LDL-cholesterol. Body composition markers include: dry lean mass, fat mass as percent of the total weight. Autonomous nervous system (ANS) markers include: marker for the ANS activity, parasympathetic activity at rest, marker of mental stress, marker for the VO2 max.

From the clinical point of view, early stages of sudomotor dysfunction includes, C-fiber inflammation, micro circulation disorder and reduced C-fiber density. ANS and Vascular Factors Score includes; endothelial chart, body composition chart and fitness chart. Whereas, TM-Flow cardiometabolic score report, summarizes the major clinical findings. For instance, if the mild inflammation is detected, appropriate interventions are recommended. In this section of the report, comments include; vascular and ANS risk factors, and hemodynamic risks. In each section of the flow chart, the first column reports the raw data, followed by diagnosis in the next column, in terms of “abnormal, borderline, or normal,” color-coded green to red, to indicate, low to high risk. Each section also contains, a final risk score in percent of overall risk for each category or cluster of risks. Having described the old version (TM-Oxi), as well as the new version, TM-Flow data systems, we will present a typical case history. After making the diagnosis the patient was treated with appropriated interventions, including anti-glycaemic therapy. Although the therapy lowered the blood glucose level and made the patient normo-glycaemic, clinical complications related to diabetes were not significantly altered, suggesting the need for further therapeuic interventions to reduce, reverse, or prevent the development of acute vascular events or end organ failure.

Preliminary Diagnosis

59-year-old male, with Type 2 DM diagnosed more than 20 year ago. Upon initial consultation, his medications included Novolin 70/30 and glyburide 10mg daily. He is intolerant to metformin due to worsening GI side effects. He was not on any specific healthy eating plan and did not exercise regularly. HBA1c at consultation was 8.9%. He complained of both nocturnal and daytime hypoglycaemic episodes as low as 40s-50s occurring 2-3 times a week, requiring medical intervention. His complications are microvascular with risk for silent coronary ischemia. Peripheral autonomic neuropathy, background retinopathy, mild resolving episodes, classified as Type-2 Obesity per BMI. One of the major contributors for the observed diabetes complications, is the late diagnosis of diabetes conditions [26]. It has been quite well established, that full-blown diabetes occurs almost a decade after the prediabetes stage develops [29,30]. Now the researchers from Shinshu University in Japan, have tracked over 27,00 non-diabetic and diabetic adults, and found that increased fasting glucose, higher body mass index, and impaired insulin sensitivity, were detectable up to 10 years before the diagnosis of diabetes, as well as prediabetes. Results of these studies were reported, in this year’s European Association for the Study of Diabetes (EASD) Annual Meeting in Berlin, Germany.
Detecting clinical features, which could have been easily missed in Flow and shown, the capabilities of a well-integrated system, in report, we have used a novel diagnostic platform called TM. The severity of hyperglycemia can be better managed. In this case, various metabolic and cardiovascular risks associated with the cost effective noninvasive diagnostic platforms are available, then reduce or prevent, the vascular pathology or the development of regulatory guidelines or guidance statements. Many clinical trials recommend that normalizing blood glucose values or the HBA1c values alone, will not be sufficient in the optimal management of this complex chronic metabolic disease.

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