MINI REVIEW

Principles of Continuous Risk Monitoring of Body Composition, Insulin Resistance, Endothelial Dysfunction and Nutrition to Improve General Health and Prevent Cardiovascular Disease and Cancer

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This paper presents a leap ahead innovation: a cloud based Cyber-Physical System, a mobile technology to integrate sensory data from various mobile devices of a user into individualized dynamic mathematical models of physiological processes, allowing for analysis and prediction by mathematical models combined with machine learning and maximizing control of physiological metrics by the user. This paper describes several bio-physical principles for realizing a Cyber-Physical System (CPS). A CPS allows for collection of a large amount of data for continuous risk monitoring and to support the creation of suitable metrics for dynamic behavioral interventions. The innovative concepts include using the following principles: 1. Holistic principle to connect different domains of physiological functioning which are directly and independently linked to morbidity and mortality like metabolic, cardiorespiratory, cardio-vegetative, oxygen delivering, endovascular and hemodynamic functioning; 2. Estimation of the parameters of the human energy metabolism using principles of "least action" or stationary action; 3. Estimation of daily changes of body composition and hydration status by using the "maximum information entropy" principle; 4. Using state space modeling where process models are connected to measurement models *via* the minimum variance Kalman filter/predictor realizing principles of Medical Cybernetics including optimal control theory; 5. Principle of individualized risk predictions realized by direct measurement and long-term observation of subclinical disease (screening) to allow early corrective action; 6. Utilizing principles of precision medicine and precision nutrition for primary prevention of cardiovascular disease and cancer.

The main innovation of this paper is to consider physiological state variables of modifiable risks over a lifetime and connect them to calculations of morbidity and mortality, offering a self-explaining context to raise self-awareness to reduce cardio metabolic risks, oxidative stress and endothelial dysfunction to prevent cardiovascular disease and cancer with appropriate behavior modification supported using CPS. In conclusion a CPS with machine learning using principles of optimal control theory supervised by physician can provide a truly individualized strategy for estimation, continuous monitoring, and prediction of physiological state variables for self-therapy, guided therapies, and mobile health interventions or cyber-therapy. CPS facilitated interventions allow for improving health, fitness, resilience and chance of survival of an acute illness.

Key Words: *Cardio metabolic health; Cardiorespiratory fitness; Cardio-vegetative stress monitoring; Endothelial dysfunction; Cardiovascular disease prevention; Cancer prevention; Machine learning; Modifiable risks; Continuous risk assessment and monitoring; Mobile health interventions; Cyber-therapy; Digital health*

INTRODUCTION

Moving away from traditional reductionism and embracing holistic approaches will certainly help fulfill the promise of Digital Health (DH) supported by tools of Medical Cybernetics (MC) and find workable solutions to tackle the ever growing health related challenges of humanity and introduce new approaches to prevent, manage and self-manage chronic non-communicative conditions such as cardiovascular disease and cancer in the 21st century.

Obesity or excess fat mass with associated insulin resistance is directly associated with shorter longevity and significantly increased risk of cardiovascular morbidity and mortality [1]. Furthermore, when a surrogate index of insulin resistance such as waist circumference is used to predict mortality, an elevated waistline was strongly predictive of an increased mortality rate among patients with cardiovascular disease [2], and it is an independent risk factor for cardiovascular disease (CVD) mortality [3, 4]. The significance of this is that an impaired mitochondrial lipid oxidation is a major anomaly in the chain of metabolic events leading to obesity and increase of insulin resistance [5]. High insulin resistance is associated with high respiratory quotient (RQ) reflecting lower fat burning than normal [6]. Similarly, there are strong connections between oxidative stress, endothelial dysfunction, endovascular inflammation and insulin resistance [7, 8]. Further, there is a causal relationship between insulin resistance and development of cancer [9]. It is recognized that the increased risk of cancer among insulin-resistant patients can be due to overproduction of reactive oxygen species (ROS) that can damage DNA contributing to mutagenesis and carcinogenesis [10]. An important example is that increased markers of ROS are independently linked to development of colorectal cancer [11]. Cancer patients with diabetes and insulin resistance are more likely to be sarcopenic, with higher incidence of malnourishment and compromised survival [12]. Importantly, lifestyle intervention with weight loss lowered incidence of obesity related cancers by 16% [13].

Recognizing that obesity, DM2, insulin resistance with associated endothelial dysfunction combined with poor nutrition poses an increased risk for development of CVD and cancer and the presence of these factors reduces survival chance is an important first step in forming a plan of interventions. Laboratory testing for insulin resistance, endothelial dysfunction and nutritional status can show early deviations from normal and could be used for screening. However, this one point in time screening is not likely to give enough persisting motivation for lifestyle change and continuous observation and monitoring is needed for risk factors of CVD and cancer. Current recommendations to prevent and treat obesity, DM2, insulin resistance, and CVD come from leading academic authors. One of the key points is to call for "a patient-centered approach that addresses patients' multimorbidities, needs, preferences, and barriers and includes diabetes education and lifestyle interventions as well as pharmacologic treatment..." However, a traditional recommendation for lifestyle change as

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in seems to be ineffectual in view of prevalence of obesity, insulin resistance and DM2. Specifically, the perceived needs to overcome barriers are: 1. Tools to gauge individual characteristics of the metabolism for a prescribed individualized lifestyle change to help set cardiovascular fitness goals, weight goals, track progress, and provide feedback to both patients and physicians during a weight-loss intervention 2. There is a need for healthy lifestyle interventions using mobile health and DH technology combined with a team to prevent and treat non-communicable diseases linked to insulin resistance and obesity. Clearly, there is a need also to facilitate efforts to reduce metabolic, cardiovascular and stress related risks with healthy lifestyle and to improve cardio metabolic and cardio-vegetative health and longevity with both self-management and guided therapy.

DISCUSSION

Prodigious scientist of mathematics and founder of cybernetics like Norbert Wiener and John von Neumann showed the direction how we can find workable solutions and build Cyber-Physical Systems utilizing principles of Medical Cybernetics to address increasing major public health issues which could be applicable in Primary Care, Corporate & Public Health, and Academic Research. The current paper lays out a pragmatic conceptual framework of how CPS could be put together for continuous risk assessment and for preventing morbidities like prediabetes, obesity, insulin resistance, DM2, CVD, cancer, and for supporting lifestyle changes and medical therapies. The here introduced principles of continuous risk monitoring of insulin resistance, endothelial dysfunction and nutrition could be the foundation on which future mobile health interventions and Digital Health related products can be built.

CPS is designed to support achieving general health including normal body composition, normal insulin resistance with age adequate endothelial functioning, and normal nutritional status along with exercise tolerance, normal autonomic functioning, and resilience against mental and physical harm. Achieving age adequate health goals becomes particularly important not just for DM2, CVD and cancer prevention but also to fight any acute illness. A particular example is given to us by the epidemic of Covid-19 which meets the pandemic of obesity/insulin resistance and people afflicted with metabolic conditions with associated high endothelial dysfunction levels have a reduced chance to survive. It is well documented now that obesity and associated insulin resistance worsen the outcome of Covid-19. The most important link is the state of metabolic inflammation that predisposes patients to an enhanced release of cytokines. Metabolic inflammation will also compromise the immune system, reducing the body's ability to tackle the infection, impairing the healing process, and prolonging the recovery. Improvements of sugar control and insulin resistance are key in the battle to reduce the proinflammatory state leading to morbidity and mortality. This event is further stressing the need for strategic planning to improve not just individual health but health at corporate, community and societal level. Currently NIH nutritional research initiative "precision nutrition" is calling for solutions that "advance understanding of the vitality of food in health". Stepping up to the challenges it appears that a CPS like product with its continuous monitoring and predicting risks and providing metrics associated with insulin resistance, endothelial dysfunction and nutrition could support NIH goals and primary care effort to improve the dismal statistics of prevalence of obesity and insulin resistance.

From primary health care point of view the innovation is that the current CPS can capture metrics of physiological functioning in 3 intertwined domains in the user's natural environment: metabolic, cardiorespiratory, and cardio-vegetative health. The metrics are centered on the common pathological pathway of obesity, insulin resistance, endothelial dysfunction, CVD and cancer. An all-encompassing risk assessment by CPS allows a quasi-real time monitoring for the user and the primary care giver. Analysis, prediction, and planning for change can be performed either at home or in the primary provider's office through a Metabolic Health Monitor (MHM) mobile and web app and display of results on the user's smartphone. As physical activity remains the main tool to fight insulin resistance and endothelial dysfunction an MHM like device with its metrics for physical activity along with metrics of metabolic, cardiorespiratory, and cardio-vegetative health could play a central role to guide user to personal best achievable results.

The 'leap ahead' innovation and significance of CPS is the continuing observation of important disease markers and allows for using this information for self- and guided management of modifiable risk factors with lifestyle and behavioral modification. The paradigm shift is here the extension of the current practice of using one point in time risk assessment with continuous individualized estimation of progress of various disease processes real time. ODI's idea is to use CPS, which collects highly impactful physiological data, compresses it into MC models, and determines and predicts the model parameters, which become the target for optimization of physiological functioning to reduce risk for morbidity/mortality. CPS provides metrics which are easily understandable, self-explaining, and completely describing processes increasing morbidity and mortality. Unique to our effort is the continuous observation of state variables in the users' natural environment raising self-awareness, enhancing motivation, and underscoring self-responsibility to reduce modifiable risks as much as possible. This could lead to reducing disease burden for the entire nation with implication for reducing societal costs to deal with them when they reach decompensated or catastrophic stage. The large volume of impactful data gathered together may find usage at different levels such as personal, community, corporate, and public health levels to fight non-communicative diseases in general.

CPS could be upgraded from support software to achieve fitness goals to an FDA approved and medically tested software to realize an Integrated Cyber-Physical System (ICPS). The medical software version could monitor progress of disease processes of metabolic (MF), cardiorespiratory (CR), cardio-vegetative (CV), oxygen delivering (OD), endovascular and hemodynamic (HD) functioning.

Cancer prevention strategy with constant monitoring for changes of insulin resistance by metrics of R-and Rw-ratio has been provided. It is envisioned that even the most vulnerable cancer patients with risk factors of obesity, sarcopenia, poor nutrition status, insulin resistance, DM2, and CVD could be supported with guided therapies by primary physician.

CPS and ICPS support the goals of "precision medicine" and "precision nutrition".

The individualized nature of precision medicine helps health care providers to have a holistic and functional understanding. An integrated approach considering among others environment, lifestyle, and heredity factors could be adopted. Information gained by CPS/ICPS lets providers more accurately predict which treatments will be most effective and safe, or possibly how to prevent the illness from starting in the first place.

CONCLUSION

In conclusion use of a CPS with machine learning using principles of optimal control theory with supervision by a physician can provide a truly individualized strategy for estimation, continuous monitoring, and prediction of physiological state variables for self-therapy, guided therapies, and cyber-therapy. CPS follows the principles of "precision medicine" and "precision nutrition".

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