Chapter

Cyber-Physical System for Management and Self-Management of Cardiometabolic Health

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Abstract

We want to demonstrate the feasibility of the concept of a cyber-physical system (CPS) by showing good correlation of insulin resistance by HOMA-IR with changes of state variables (SVs) such as R-ratio, Rw-ratio, calculated 24 h nonprotein respiratory quotient, and fat-burning fraction from serial measurements of weight and fat mass. We utilize principles of indirect calorimetry. We calculate SVs from published data of an energy perturbation study. We perform correlation analysis between changes of insulin resistance measured with HOMA-IR and selected SVs. The result of this correlation analysis confirms a highly significant correlation between HOMA-IR and the selected SVs. The implication of these results is that CPS is a suitable concept to indirectly measure and predict the otherwise very-difficult- or impossible-to-measure slow changes of SVs and capture them for the first time noninvasively. Serial fat and weight measurements and energy calculations can help unmask changes of insulin resistance in response to user's diet and exercise habits, creating the necessary environment to measure metabolic flexibility. Further, CPS has the potential to estimate cardiorespiratory fitness by indirectly estimating maximum oxygen uptake from measuring heart rate reserve, heart rate variability, and pulse oximetry changes with exercise.

Keywords: energy metabolism, metabolic profile, insulin resistance, metabolic monitoring, cardiometabolic health, self-management

1. Introduction

This book chapter introduces to practicing physicians the framework of our cyber-physical system (CPS) for management and self-management of cardiometabolic health. The hypothesis here is that cardiometabolic functions relevant to cardiovascular disease (CVD) mortality including insulin resistance can be tracked and predicted from measuring physical activity, heart rate, and pulse oximetry by a smart watch and from serial weight and fat weight measurements obtained from a bioimpedance fat scale. CPS serves the need for individualized precision methods to gauge cardiometabolic health with metrics/trajectories and predict slow changes of cardiometabolic health in health as well as in disease. There is a need to provide this information as a feedback to patients and their care team to

facilitate prevention and treatment of chronic noncommunicable disease, improve rehabilitation after acute cardiovascular illness, and facilitate needed behavior change for cardiometabolic risk reduction to improve cardiovascular as well as all-cause mortality. Computer-generated feedback may provide a framework for automation and self-improvement to meet daily goals of therapeutic efforts.

Based on our research in systems biology, a cyber-physical system (CPS) can be construed for noninvasively tracking, drawing trajectories, and indirectly measuring daily changes and predict the otherwise very-difficult- or impossible-to-measure slow changes of the daily *s*tate *v*ariables (SVs) of the metabolism and capture them for the first time noninvasively in freely moving humans in their natural environment outside of a metabolic laboratory setting.

Components of CPS are (A) a management software tool (MST); (B) a metabolic health monitor (MHM) app; (C) software on MHM capturing biometric signals from sensors of heart rate, physical activity, and pulse oximetry from a smart watch; and (D) software on MHM capturing biometric signals related to body composition and hydration status from Ori Diagnostic Instruments' (ODI) patented apparatus for impedance spectroscopy. MHM is running ODI's proprietary self-adaptive individualized stochastic mathematical model of the human energy metabolism (SAM-HEM) [1–3] via cloud computing. Based on our published simulation studies, SAM-HEM is a suitable concept to capture daily changes of the following SVs: weight; fat mass; lean mass; protein mass; intracellular water mass; extracellular water mass; utilized macronutrient intake and substrate oxidation of carbohydrate, fat, protein; and the R-ratio (ratio of the daily lean mass change velocity divided by the daily fat mass change velocity) which could be used as a surrogate marker for insulin resistance. SAM-HEM is a self-learning algorithm with daily updates using the minimal variance Kalman filter/predictor to arrive at the best metabolic model fitting to the available measured data. The trajectories of SVs are displayed on MHM and MST with errors of calculations allowing for analysis of past events, tracking current metabolic events real time, predicting metabolic changes in the future, and supporting self-management as well as guided therapies. We envision also that the same smart watch can provide sufficient information to track cardiorespiratory fitness by estimated maximum oxygen uptake. Our innovation is to merge the assessment of metabolic fitness/flexibility measurements with the assessment of cardiorespiratory fitness and realize CPS to improve cardiometabolic health.

The challenges ahead are the following: The prevalence of obesity and type 2 diabetes (T2D) is ranked the highest in the USA and Mexico in the American continent [4]. The proportion of the population with abnormal glucose tolerance is 52.4% for the USA (14.4% T2D, 38% prediabetes) [5] and 33.5% for Mexico (14.1% T2D, 19.1% prediabetes) [6].

Central to our mission in primary care is to fight the burden of noncommunicable chronic diseases including the most prominent one, cardiovascular disease (CVD). CVD is substantially higher in individuals with unhealthy lifestyle characteristics, including obesity, prediabetes, diabetes, insulin resistance, metabolic syndrome, physical inactivity, poor diet, and cigarette smoking [7]. In forging the battle against these problems, I see the following paramount problems:

1. There is a certain degree of fatigue toward "dieting," "weight loss," and hearing the word "obese." According to a recent survey [8], many sufferers of obesity wanted to become "healthy" so they could be "fit" and "strong" and expressed the wish for general health.

2. The problem with targeting weight loss only is that it does not distinguish between the loss of adipose and lean tissues. Further, it intuitively contradicts

the notion of the obesity paradox, i.e., increased BMI is associated with increased survival and reduced mortality among patients with cardiovascular risk [9]. A mortality study in adults showed that normal weight at the time of incident diabetes had higher mortality than adults who are overweight or obese [9, 10]. This apparent obesity paradox is best explained by insulin resistance which is the primary underlying factor in cardiovascular disease. Fat mass itself and insulin sensitivity (reciprocal of insulin resistance) may be the decisive link between mortality and weight status [10]. Moreover, a more recent study [11] confirms what most clinicians have felt for a long time that obesity or excess fat mass with associated insulin resistance is directly associated with shorter longevity and significantly increased risk of cardiovascular morbidity and mortality [11]. 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 [12], and it is an independent risk factor for CVD mortality [13].

3. Clearly, there is a need for healthy lifestyle interventions using self-management along with support team approach to prevent and treat noncommunicable diseases linked to overweight and obesity [14] to achieve cardiorespiratory fitness along with metabolic health with lowest possible insulin resistance. Effective programs and technology tools together are needed to support behavior change approaches toward healthy lifestyle. Recently, behavior change strategies have emphasized the need for feedback loops for self-directed behavior modification [15]. However, there is a paucity of personalized, time-adjusted, dynamic interventions supporting feedback control for health behavior interventions [16]. There is a needed tool to observe the slow changes of cardiovascular fitness and metabolic health metrics closely as a feedback of information for patient and primary care provider to facilitate self-directed behavior change [3] as well as for guided therapy by the healthy lifestyle team. The hurdles to develop such behavior change models with dynamic feedback loops and corresponding supportive technology tools are (A) the lack of gold standard measures for important behavior constructs, (B) tools allowing for planning and executing dynamic changes of behavior, (C) a dynamic behavior change model using self-directed behavioral change strategies, and (D) outcome measures for optimization [3, 16].

Given the pandemic of overweight and obesity involving 1.9 billion people worldwide according to the World Health Organization, new and fresh ideas and approaches are needed. One of the goals of the current article is to introduce to researchers and clinicians a widely applicable toolset which could unleash the potential of the modern Digital Era and tackle the extraordinary burden of insulin resistance, obesity, prediabetes, metabolic syndrome, and type 2 diabetes on humanity. In this article, inspirations were taken from thoughts and works of giant and prodigious scientists of the twentieth century, the unbelievably huge potential of smartphone technologies, combined with the tremendous power of human networking through the Internet. With the current novel framework, we strive to use the minimum set of assumptions about the process and measurement.

Eugene Wigner (1902–1995) stated that there is a "miracle of the appropriateness of the language of mathematics for the formulation of the laws of physics" ... which may appear to us with "unreasonable efficiency." The inspiration here is, why not use mathematical tools for the formulation of the applicable laws to the human energy metabolism such as the first and second laws of the thermodynamics

when considering, for example, the fat balance, i.e., fat in minus fat out? Though indirect calorimetry already makes reference to these laws, the indirect calorimetry technology use is intricately connected to respiratory gas exchange measurements which are difficult to do with the daily routine of life. However, mathematical models can be created with input variables with easier realization in daily life such as weight and fat weight measurement with bioimpedance fat scale. Further, appropriately built mathematical models can provide indirect measurements of difficult-to-measure variables of the human energy metabolism like fat versus carbohydrate oxidation rate or changes of insulin resistance [1–3] and provide a solution to gain a special quantified insight into the fat and the entire energy metabolism. Currently, the computational model of the human energy metabolism (CM-HEM) [17] and its improved version [18] is considered the most complete. CM-HEM uses the three compartmental partitioning of the entire energy flow, centered around the major macronutrient energy stores: glycogen G, fat F, and protein P. Hall was able to test his model and found satisfactory agreement between the model predictions and the measured group averaged data from the Minnesota Study [17], as well as 50 other studies [18]. Although CM-HEM behaves appropriately for different groups of subjects, it is presently unclear whether individual subject responses can be predicted [19], and CM-HEM may be limited in its ability to provide precise information on an individual basis [19]. Further, CM-HEM uses food intake as an input rather than an output variable, and it would be particularly interesting to determine utilized food intake from body composition changes [19]. CM-HEM is neither linear nor recursive nor individualized to a particular subject, and therefore, it is not suited to performing recursive parameter identification of the human energy metabolism, nor is it able to perform inverse calculation of utilized energy intake. Further, insulin resistance is not considered in CM-HEM when in fact insulin resistance plays a crucial role influencing fat and carbohydrate oxidation rates and the entire dynamic of body composition change [1–3]. Obviously, individualized models are needed which can be tied to easily measurable input variables such as weight and fat weight and provide insight into the fat and nonfat energy balance and change of insulin resistance.

A second insightful guidance to our approach comes from John von Neumann (1903–1957) for the fight against insulin resistance. During his time, he foresaw already that "science, as well as technology, will in the near and in the farther future increasingly turn to problems of structure, organization, information, and control." This raises the question, why not use Neumann's self-organization and system theory ideas to control and prevent insulin resistance and obesity? In this regard using certain universal principles for energy calculation, such as the principle of "least action/ stationary action," for example, in Lagrangian and Hamiltonian mechanics, can be instrumental in setting up suitable control equations or functionals, such as the Hamilton-Jacobi-Bellman equation in control theory for dynamic optimized control [20]. This Hamilton-Jacobi-Bellman equation can allow for dynamic optimization of the energy system to achieve the desired state in the shortest possible time with minimized efforts.

The third inspirational insight comes from Rudolf E. Kálmán (1930–2016) and his invention of the "Kalman filter." This is briefly a statistical tool with tremendously widely used successful applications to control a vast array of consumer, health, commercial, and defense products. According to Grewal [21], the Kalman Filter is possibly the greatest discovery in the twentieth century and made the moon landing among others possible. This raises the question, why not use the Kalman filter to estimate and predict fat mass change? A potential application of Kalman's minimum variance estimator and predictor could be twofold: (1) Updating the a priori estimation equations for the measurement variables (weight, fat weight) with

a posteriori results and (2) providing a posteriori estimation for the process variables such as lean mass L, glycogen mass G, fat mass F, protein P, intracellular water mass ICW, and extracellular water mass ECW. This will realize a dynamic state-space modeling connecting the measured variables with the process variables, never losing the measured reality and keeping full statistical knowledge about confidence intervals and other statistical properties of results. The beauty of the Kalman estimators is that they operate also as a predictor when no updated measurements are provided.

Central to the development of the noninvasive metrics for the human energy metabolism is to have a novel metric for insulin resistance from energy flow point of view through the body. Insulin resistance is related to ectopic fat accumulation and reduced capacity of fat oxidation and inflexibility in regulating fat oxidation combined with the increased propensity of glucose oxidation and glucose-induced suppression of fat oxidation [22]. Experimental weight perturbation showed concordant changes of the glucose vs. fat oxidation fraction in skeletal muscle [23]. The correlation between BMI/weight/body composition and insulin resistance measured, for example, with Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), is well documented in the medical literature [24, 25]. It is increasingly recognized also that there is a dynamic correlation between changes of weight, fat weight, and insulin sensitivity/resistance changes. Building on the above observations and reviewing energy perturbation studies from the international literature, we observed also a high level of correlation between weight, fat weight, and HOMA-IR [26]. We found also that our newly defined R-ratio and Rw-ratio showed highly significant correlation with HOMA-IR, and we proposed these measures as metrics for insulin resistance [2, 3, 26]. We recognized that monitoring R-ratio and Rw-ratio may give an important tool for monitoring changes of insulin resistance; we developed CPS for this purpose. We have provided the derivation of our formulas used in CPS in the Appendix. The lists of measured and derived variables in CPS are listed in the glossary.

The essential input parameters, weight W_k and fat weight F_k, are captured by the software on MHM from a "bathroom scale" performing measurements of body composition (weight, fat weight) and hydration status (intracellular and extracellular water mass) developed by Ori Diagnostic Instruments (ODI), which is a patented apparatus for impedance spectroscopy [27, 28]. Without calorie counting and just using the required input ΔW_k, ΔF_k, and EB_k, the fat and nonfat energy balance can be estimated along with the weight-related alpha $\hat{\alpha w}_k$, the energy density parameter for weight change $\hat{\varrho_{W}}_k$, the weight-related Rw-ratio Rw_k, the lean mass-related alpha $\hat{\alpha}_k$, the energy density parameter for lean mass change $\hat{\varrho_{L}}_k$, the lean mass-related R-ratio R_k, the nonprotein respiratory quotient Rnp_k, and the fat-burning fraction χ_k as in Eqs. (1)–(19).

With additional measurement of physical activity (PAE) energy expenditure via smart watch sensors and using the measured or calculated value of the basal metabolic rate BMR_k (by either using Harris-Benedict formula or by actual measurement of BMR_k with indirect calorimetry), the total energy expenditure can be obtained as in Eq. (20).

If steady-state equilibrium in the metabolism can be assumed and the total energy expenditure is known, then it is possible to calculate food fraction φ_k, total metabolized energy intake MEI_k, fat intake FI_k, and fat oxidation FO_k in addition to $\hat{\alpha w}_k$, $\hat{\alpha}_k$, $\hat{\varrho_{W}}_k$, $\hat{\varrho_{L}}_k$, R_k, Rw_k, Rnp_k, and χ_k.

If equilibrium state is uncertain, then we would recommend additional macronutrient calorie counting on designated calibration days (maybe every 2 weeks). This could improve accuracy and would allow deeper insight into the dynamics of SVs of the metabolism.

One of the goals of this chapter is to demonstrate the feasibility of the concept of CPS for its main function which is to predict changes of insulin resistance and fat oxidation from serial measurements of weight and fat mass. Unfortunately, there is a paucity of published data with longitudinal observations and serial measurements of the measurable components of the energy metabolism including measuring markers of insulin resistance. A complete data set to study the insulin resistance and weight-fat weight relationship would require the following data: serial measurements of macronutrient energy intake (EI), total energy expenditure (TEE) and serial fat mass (F), and lean body mass (L) or weight (W) measurements. Very few trial data are published only with serial measurements of markers of insulin sensitivity or resistance. Nevertheless, we were able to identify a study suitable for our aim, which is to demonstrate the feasibility of our concept of CPS to track and predict SVs and markers of insulin resistance. Here we use published data from the study entitled "Effects of brief perturbation in energy balance on indices of glucose homeostasis in healthy lean men (EBPE) [29]."

2. Method

For all calculations I used MATLAB. To demonstrate the main functions of our CPS, we use here the published data of EBPE [29]. In this study 10 healthy men participated in two cycles of controlled 7-day periods of caloric restriction (CR) and refeeding (RF) in protocol A and overfeeding (OF) and caloric restriction (CR) in protocol B at ±60% energy requirement. Insulin resistance was assessed by HOMA-IR on the basis of measured serum insulin and glucose levels in the study participants. The mandatory input data to CPS is weight, fat weight, and daily energy balance values EB_k. The daily weights were directly scanned in from the published graphs [29]. The fat weight data points were available only at baseline and at the end of CR, RF, and OF cycles. I used MATLAB's Piecewise Cubic Hermite Interpolating Polynomial to connect these fat data points in order to have daily fat mass estimates (see **Figure 1a** and **b**). I calculated the energy balance EB_k from the difference of the metabolically utilized energy intake minus total energy expenditure.

I estimated weight-related alpha $\hat{\alpha w}_k$, energy density parameter for weight $\hat{\varrho}_{Wk}$, Rw-ratio Rw_k, and fat-burning fraction χ_k from ΔW_k, ΔF_k, and EB_k utilizing the methods described in Eqs. (1)–(19).

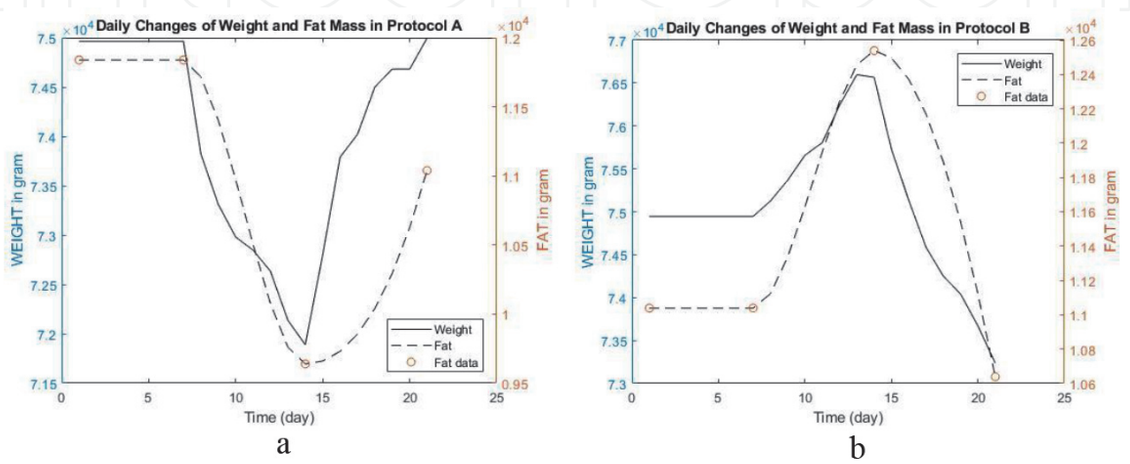

Figure 1.
(a) Daily weight and fat weight in protocol A. (b) Daily weight and fat weight in protocol B.

For calculation of correlations between HOMA-IR and weight, fat weight, R-ratio, Rw-ratio, fat-burning fraction χ_k, and nonprotein respiratory quotient Rnp_k, I used MATLAB's corrcoef function.

For demonstration purposes, I plugged the mandatory input variables ΔW_k, ΔF_k, *and* EB_k as well as the known ingested macronutrient calories CI_k, FI_k, and PI_k into SAM-HEM algorithm with Kalman filter [1–3]. As a measure of goodness of fit of the metabolic model SAM-HEM, I calculated the predicted mean value and standard deviation of the modeling error, i.e., model-predicted value minus the known trajectory of weight, fat weight, and lean mass.

3. Results

The input weight and fat weight data are shown in **Figure 1a** for Protocol A and in **Figure 1b** for Protocol B. The measured data points for fat mass are connected with MATLAB's Piecewise Cubic Hermite Interpolating Polynomial. The results of Rw-ratio Rw_k and fat-burning fractionation χ_k for Protocols A and B are in **Figure 2a** and **b**, respectively. The measured data points for HOMA-IR are connected with MATLAB's Piecewise Cubic Hermite Interpolating Polynomial.

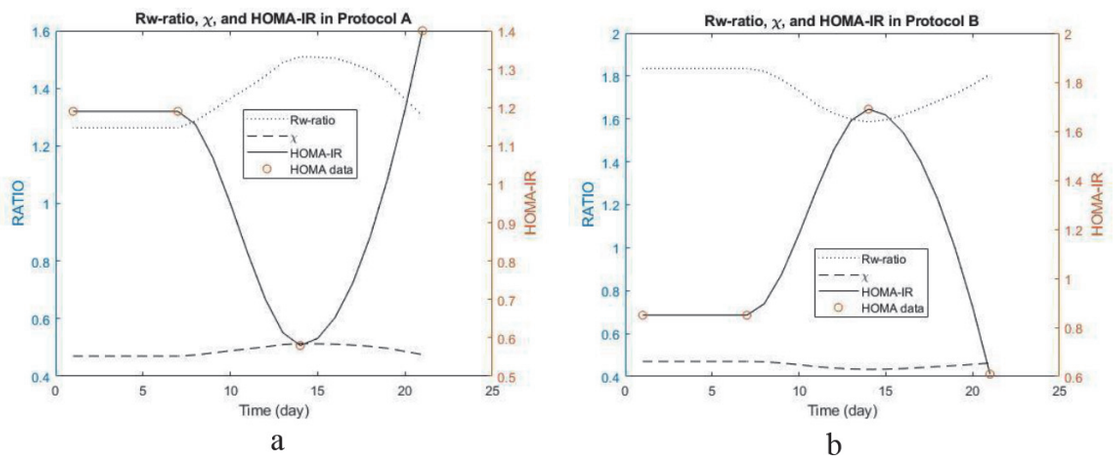

Figure 2.
(a) Daily changes of Rw-ratio, χ_k, and Homa-IR in protocol A. (b) Daily changes of Rw-ratio, χ_k, and Homa-IR in protocol B.

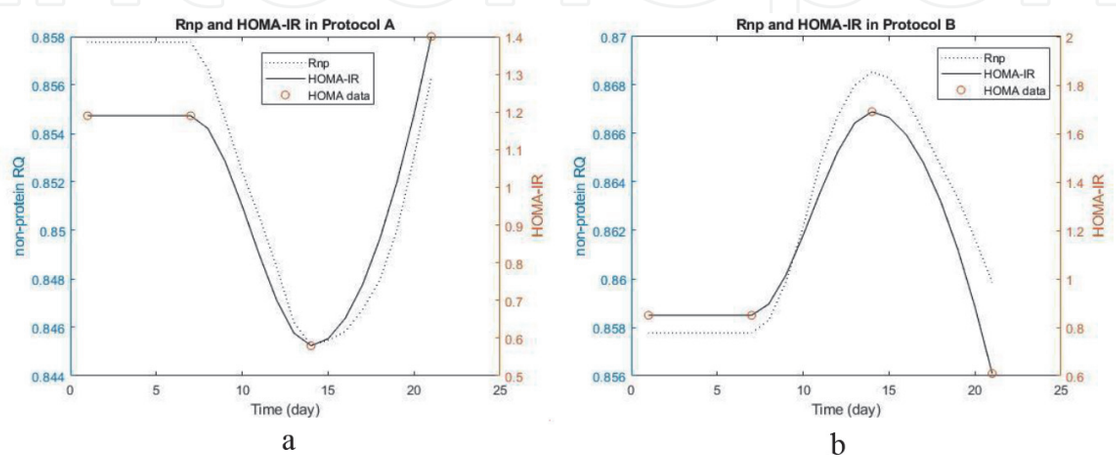

Figure 3.
(a) Daily changes of Rnp and Homa-IR in protocol A. (b) Daily changes of Rnp and Homa-IR in protocol B.

In **Figure 3a** and **b**, the changes of the nonprotein respiratory quotient can be seen for Protocol A and for Protocol B. **Figure 4a** for Protocol A and **Figure 4b** for Protocol B show the results of utilized macronutrient intakes carbohydrate CI and fat FI, as well the macronutrient oxidations for carbohydrate CarbOx and fat FatOx.

The correlation coefficients between HOMA-IR and W_k, F_k, R_k, Rw_k, Rnp_k, and χ_k along with their P value are shown in **Table 1**.

The results of goodness of fit of the SAM-HEM metabolic model to the known trajectory of weight, fat weight, and lean mass are shown in **Table 2**.

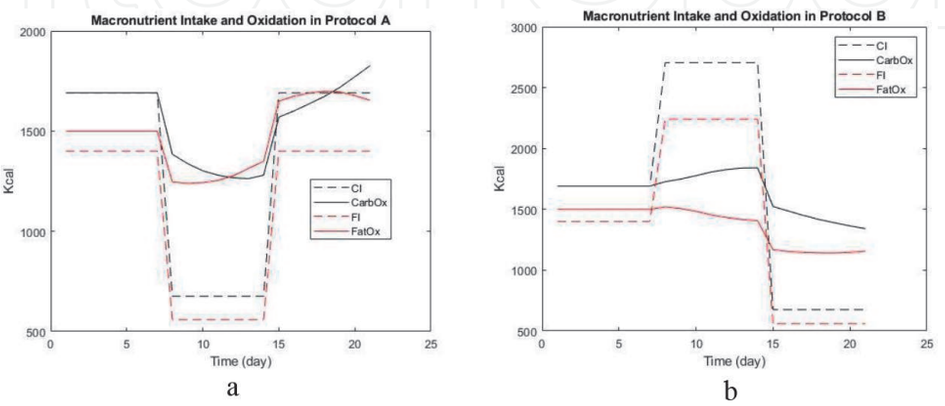

Figure 4.
(a) Daily metabolized carbohydrate and fat intake and oxidation in protocol A. (b) Daily metabolized carbohydrate and fat intake and oxidation in protocol B.

	Protocol A		Protocol B	
	HOMA-IR	**P value**	**HOMA-IR**	**P value**
W_k	0.828219114701	0.000003557891	0.6464400352912	0.00154355168
F_k	0.873415795383	0.000000235522	0.9999138255551	0.00000000000
R_k	−0.77770999896	0.000033325699	−0.971975709210	0.00000000000
Rw_k	−0.92129422123	0.000000003126	−0.967645037740	0.00000000000
Rnp_k	0.935321042397	0.000000000000	0.9529177800117	0.00000000000
χ_k	−0.9354436104	0.000000000000	−0.952802142972	0.00000000000

Table 1.
Correlation coefficients between HOMA-IR and W_k, F_k, R_k, Rw_k, Rnp_k, and χ_k.

	Protocol A		Protocol B	
	Mean deviation in grams	**Standard deviation**	**Mean deviation in grams**	**Standard deviation**
W_k	220.1045	893.8795	−289.2232	512.9418
F_k	−11.8265	122.9743	−13.3447	94.0426
L_k	21.8630	90.8594	−35.0486	40.6444

Table 2.
Goodness of fit of the SAM-HEM metabolic model to W_k, F_k, and L_k data.

4. Discussion

Insulin resistance is a pathogenic factor for type 2 diabetes. Insulin resistance has a deleterious impact on glucose and lipid metabolism, blood pressure, coagulation abnormality, inflammation, oxidative stress, and endothelial dysfunction. Population studies suggest that insulin resistance is an important target to reduce CVD risk [30]. A significant proportion of apparently healthy subjects are insulin resistant. About 30–40% of subjects are afflicted with insulin resistance in affluent countries, and the total number is over 1 billion worldwide [30]. HOMA-IR-estimated insulin resistance is associated with subsequent symptomatic CVD in the general population independent of all classic and several nontraditional risk factors [30]. The main result of EPBE [29] is that it clearly demonstrates the profound effect of energy perturbation on changes of insulin resistance. Insulin resistance remained slightly impaired at the end of Protocol A (CR followed by RF) as opposed to the end of Protocol B (OF followed by CR) where the insulin resistance created by OF was normalized by CR. As it is discussed by the authors of [29], the benefit of calorie restriction in terms of improvement of insulin sensitivity is firmly established in the medical literature in various disorders like binge eating with bulimia, weight cycling, obesity, and type II diabetes. In the EPBE study, euglycemic clamp measurements were performed parallel to the HOMA-IR. Observing these in parallel, an overarching picture emerges that the sugar and insulin dynamics are strongly connected to quantifiable dynamics of body composition and the fat metabolism as well as the carbohydrate- vs. fat-burning energy utilization.

Our feasibility demonstration for the main features of CPS is focused on assessing changes of insulin resistance. Using trial data from EBPE [29], we correlated HOMA-IR as a surrogate marker for insulin resistance with our surrogate markers such as R-ratio, Rw-ratio, 24 h nonprotein respiratory quotient, and fat-burning fraction. We found high correlation across the examined metabolic variables W_k, F_k, R_k, Rw_k, Rnp_k, and χ_k with HOMA-IR along with highly significant P value for each examined variable.

The implication is that these results show strong evidence for the feasibility for our concept to a have a noninvasive long-term monitoring tool for insulin resistance for users in their natural environment. Displaying W_k, F_k, R_k, Rw_k, Rnp_k, and χ_k on MHM and MST via our CPS can provide the needed tool to users and their providers to observe and use adaptive control strategies to improve the otherwise undetectable and invisible phenomena caused by insulin resistance and reach metabolic health.

A new method for metabolic research has been introduced here to extend the principles of indirect calorimetry to a broader application which considers serial measurements of changes of body composition and hydration status with no gas exchange measurements and is still able to estimate 24 h nonprotein respiratory quotient. For this purpose, a Lagrangian functional L was set up to establish the quantitative relationships between changes of fat mass, weight, and energy balance. Without calorie counting and just using the required input weight change ΔW_k, fat mass change ΔF_k, and energy balance EB_k, the fat and nonfat energy balance can be estimated along with important semi-stable energy parameters of the metabolism including the weight-related alpha $\hat{\alpha w}_k$, the energy density parameter for weight change $\hat{\varrho_{W}}_k$, the weight-related Rw-ratio Rw_k, the lean mass-related alpha $\hat{\alpha}_k$, the energy density parameter for lean mass change $\hat{\varrho_{L}}_k$, the lean mass-related R-ratio R_k, the nonprotein respiratory quotient Rnp_k, and the fat-burning fraction χ_k. Finding proof for the quantitative relationship between insulin resistance and Rw_k, R_k, Rnp_k, and χ_k was difficult due to lack of previous studies [24] with the

needed measurements and due to non-availability of individual data of participants of potentially qualified metabolic studies. Thompson and Slezak [25] showed first that weight and fat loss are correlated well with markers of insulin resistance/sensitivity. Kelley et al. [22] was able to show that in vivo insulin sensitivity was related to a higher in vitro capacity for fat oxidation of skeletal muscle samples. The same author found also that the strongest predictor of improved insulin sensitivity was associated with enhanced fasting rates of fat oxidation. In this context "metabolic flexibility" in the skeletal muscles is discussed in the literature [24, 31]. One definition of metabolic flexibility is the ability to switch from fat to carbohydrate oxidation during insulin-stimulated glucose disposal. Another definition of metabolic flexibility is the capacity for the organism to adept fuel oxidation to fuel availability [31]. The opposite of metabolic flexibility is metabolic inflexibility which is an important feature of insulin resistance. In the state of insulin resistance, the fuel switching is impaired, and there is an impaired capacity to upregulate muscle lipid oxidation. Metabolic inflexibility and state of insulin resistance manifest as decreased fasting rates of fat oxidation and the lack of further suppression of fat oxidation during heightened level of insulin action postprandially [32]. A defining characteristic of metabolic inflexibility is when after a fat-rich diet, an impaired drop of overnight fasting RQ (impaired fat oxidation) can be observed. Further, insulin-resistant subjects manifest less lipid oxidation during fasting condition and greater lipid oxidation during insulin-stimulated conditions relative to non-insulin-resistant subjects. The failure to augment lipid oxidation during fasting conditions likely is a key mechanism leading to lipid accumulation within skeletal muscle [32]. Supporting evidence for impaired lipolysis, diminished fat oxidation, and metabolic inflexibility was confirmed recently in obese girls with polycystic ovary syndrome and increased insulin resistance [33].

The main likely mechanism of metabolic inflexibility is that the impaired capacity to upregulate muscle lipid oxidation in the face of high lipid supply may lead to increased muscle fat accumulation and insulin resistance [31]. Many studies have shown when people are in energy balance, the 24 h food fraction φ_k, fat-burning fraction χ_k, and nonprotein respiratory quotient Rnp_k match each other [31]. With the current technology, metabolic flexibility can be studied in a metabolic chamber by measuring RQ. The testing modalities include overnight sleep study with RQ measurement or measuring RQ in response to high-carbohydrate diet or in response to high-fat diet [31]. The overnight study can show that the subject with metabolic inflexibility would burn less fat during fasting state than the individual with normal metabolism. At least 2 days of waiting is needed for seeing a clear difference in response between flexible and inflexible individuals when dietary changes are performed because adaptive mechanisms of the body prevail initially. The person with metabolic inflexibility would burn less sugar compared with a person with metabolic flexibility in response to high-carbohydrate diet. Conversely, the fat burning is better in the normal metabolism than the impaired flexibility in response to the high-fat diet. After 6–7 days, an equilibrium sets in again, and the final RQs become indistinguishable between sufferer of inflexibility and healthy, and the 24 h food fraction φ_k and fat-burning fraction χ_k settle close to the same value [31]. In summary, it is tempting to speculate that a CPS equipped with the capability to monitor nonprotein respiratory quotient Rnp_k could detect flexibility vs. inflexibility in response to dietary challenges of the user in his or her natural environment.

It is important to point out that the energy perturbation study EPBE /34/ was done in healthy men with no confounding metabolic abnormalities. Nevertheless, the correlation analysis reveals the profound connection between insulin resistance change (as measured by HOMA-IR) and energy metabolism with manifestations of

substrate utilization and fat-burning capability. This becomes significant when we want to measure metabolic flexibility and create a metric for metabolic health in general. As insulin resistance (and HOMA-IR) is connected to mortality, so is metabolic inflexibility which could be now measured outside of a metabolic laboratory. In earlier publications of ours, we found evidence for close correlation already between HOMA-IR and R-ratio in a wide variety of clinical conditions including obesity, postmenopausal state, metabolic syndrome, and prediabetes /2, 3, 24/. Data from EPBE /34/ prove now that the connection between insulin resistance and R-ratio or metabolic flexibility/inflexibility exists across human physiology and pathophysiology in health or disease. Actually, EPBE /34/ helped defining the quantifiable meaning of "metabolic health," and we have now practically usable metrics for it explaining also the title of this chapter.

It is important to consider why visceral obesity and the associated increased waist circumference are a good predictor for CVD mortality [33]. The visceral fat leads to high concentration of fatty acids which contributes to impaired liver metabolism and fatty liver. The visceral adipose tissue has been shown to be loaded with macrophages which contribute to the pro-inflammatory profile of visceral obesity which would drive endothelial dysfunction and contributes to mortality. The visceral obesity-induced lipo-toxicity eventually leads to ectopic fat depositions not just in the liver but also the heart, kidney, and also skeletal muscle [34]. For management of visceral obesity, prediabetes, metabolic syndrome, and type 2 diabetes, it is important to know that physically very active persons afflicted with these conditions experience 50% reduction of CVD risk burden [33]. Further, physical activity induces a selective mobilization of visceral adipose tissue and ectopic fat even in the absence of weight loss. Consequently, our "leap ahead" innovation to unify metabolic function assessment with cardiopulmonary fitness assessment may provide an important tool to fight for less insulin resistance and higher cardiorespiratory fitness. CPS has the promise to become a comprehensive cardiometabolic function assessment tool in freely moving individuals requiring only wearing a smart watch and using a specialized stand-up scale (high accuracy bioimpedance analyzer) for serial measurement of fat mass and weight.

Increased insulin resistance states in obesity, prediabetes, metabolic syndrome, and type 2 diabetes represent a high-risk state for CVD. Restoration of impaired insulin resistance and its manifestation of impaired glucose tolerance can significantly reduce the risk of future diabetes in prediabetics and decrease the estimated CVD risk [34]. The diabetes prevention program (DPP) [35, 36] showed a clear reduction in diabetes incidence in participants assigned to the lifestyle interventions or metformin. Actually, lifestyle intervention was about twice as effective as metformin for prevention of diabetes and was the only intervention associated with regression to normal glucose regulation. Seeing the overwhelming evidence of importance of lifestyle change, we propose to utilize a CPS-like approach as outlined in introduction to help this process. CPS can be used to observe SVs such as weight, lean body mass, fat mass, R-ratio, Rw-ratio, calculated 24 h nonprotein respiratory quotient, and fat-burning fraction from serial measurements of weight, fat mass, and daily energy balance estimates EB_k. EB_k can be obtained either as per Eq. (5) with no calorie counting requirement or for enhanced accuracy with calorie counting and measurements of the physical activity energy expenditure and following Eq. (20). As a workable answer to behavioral changes mentioned in the introduction, we propose using SVs for "(A) gold standard measure" for metabolic functioning and as "(D) outcome measures for optimization" as a foreseen requisite to make breakthroughs in the fight against obesity and insulin resistance [3, 15, 16]. The predictive power of SAM-HEM can draw trajectories of SVs and allow for trend

analysis and prediction and serve as "(B) ...tools allowing for planning and executing dynamic changes of behavior," as desired by behavior scientists [15, 16]. The desire for a (C) dynamic behavior change model development using self-directed behavioral change strategies can arrive with further development of CPS using control equations like the Hamilton-Jacobi-Bellman equation for dynamic optimized control [20] and with further technologies of artificial intelligence.

The main contribution of this chapter to medicine and life science is that it lays out a framework using CPS to observe and monitor long-term SVs of the metabolism including markers of insulin resistance. The CPS approach may point to new and promising directions to find workable solutions to challenges of unhealthy metabolic conditions such as insulin resistance, obesity, prediabetes, metabolic syndrome, and type 2 diabetes.

5. Conclusion

We provided important supportive evidence for feasibility for our concept of CPS for indirectly measuring and predicting the otherwise very-difficult- or impossible-to-measure slow changes of SVs and capture them for the first time noninvasively in freely moving humans in their natural environment outside of a metabolic laboratory setting. Serial fat and weight measurements and energy calculations can help unmask changes of insulin resistance in response to user's diet and exercise habits, providing tools to measure metabolic flexibility which can be used as a surrogate marker for metabolic health. Further, CPS has the potential to estimate cardiorespiratory fitness by indirectly estimating maximum oxygen uptake from measuring heart rate reserve, heart rate variability, and pulse oximetry changes with exercise. CPS is a tool to observe the two major risk factors of CVD at the same time: metabolic health and cardiorespiratory fitness, and therefore the new term cardiometabolic health is justifiable and introduced here to emphasize the two interlinked physiological functions impacting mortality significantly. CPS can enable managed and self-improvement of cardiometabolic health. CPS armed with further technologies of control engineering and artificial intelligence can unleash the potential of digital health to help manage conditions essential to primary care and to the public at large.

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Conflict of interest

The author declares that there is no conflict of interest regarding the publication of this paper. No specific funding was provided for this research. This research was performed as part of the author's employment with Ori Diagnostic Instruments, LLC. The author is the inventor of patent [27] and patent application [28], and the patent and patent application are owned by Ori Diagnostic Instruments, LLC.

Glossary

Measured variables	
F_k	fat weight
ΔF_k	fat mass change in 24 h
W_k	weight
ΔW_k	body weight change in 24 h
EB_k	daily energy balance
Derived or estimated variables	
BMR_k	basal metabolic rate
CI_k	carbohydrate calorie intake
CO_k	oxidized carbohydrate calories
ECW_k	extracellular water mass
FI_k	fat intake
FO_k	oxidized fat calories
ICW_k	intracellular water mass
L_k	lean mass
ΔL_k	lean mass change in 24 h
MEI_k	metabolically utilized energy intake
PAE_k	physical activity energy expenditure via smart watch sensors
TEE_k	total energy expenditure
R_k	R-ratio
Rw_k	Rw-ratio
Rnp_k	nonprotein respiratory quotient
α_k	first-order term coefficient of the lean body—fat logarithmic relationship Tylor series expansion
$\hat{\alpha}_k$	estimation of α_k
αw_k	first-order term coefficient of the weight—fat logarithmic relationship Tylor series expansion
$\hat{\alpha w}_k$	estimation of αw_k
$\varrho_F \approx 9.4$ Kcal/g	energy density for fat
$\varrho_L \approx 1.8$ Kcal/g	the energy density for lean mass
$\hat{\varrho_{L}}_k$	estimation of ϱ_L
ϱ_{Wk}	energy density for weight
$\hat{\varrho_{W}}_k$	estimation of ϱ_{Wk}
φ_k	fat intake fraction
χ_k	fat-burning fraction

A. Appendix

The following mathematical descriptions use elementary mathematics and a minimum set of assumptions, similar to the landmark article of [37]. These equations could be regarded as an extension of the work of [37], with my main points being that the fat-burning fraction can be calculated from serial fat and weight changes, producing the same result as 24 h indirect calorimetry. Importantly, the equations allow the clinician to determine the nonprotein respiratory quotient with serial weight and fat weight measurement, avoiding the necessity for gas exchange analysis. An important advantage of this mathematical method is that it can be used anywhere outside of a metabolic laboratory.

The R-ratio for modeling of the insulin resistance is defined in our analysis as the ratio of lean body mass change velocity ΔL_k (lean mass change in 24 h) and fat mass change velocity ΔF_k (fat mass change in 24 h) of day k as in Eq. (1).

$$R_k = \frac{\Delta L_k}{\Delta F_k}. \tag{1}$$

Likewise, Rw-ratio can be defined as the ratio of weight change velocity ΔW_k (body weight change in 24 h) and fat mass change velocity ΔF_k (fat mass change in 24 h) of day k as in Eq. (2).

$$Rw_k = \frac{\Delta W_k}{\Delta F_k}. \tag{2}$$

We proposed the Rw-ratio for modeling of the insulin resistance as it is easier to measure change of weight than lean mass [26].

The total energy balance for the day k can be expressed as in Eq. (3):

$$\varrho_{Wk} \cdot \Delta W_k + \varrho_F \cdot \Delta F_k = MEI_k - TEE_k. \tag{3}$$

The same energy balance as in (3) can be expressed also using Rw-ratio or Rw_k as in Eq. (4):

$$\left(\varrho_{Wk} \cdot Rw_k + \varrho_F\right) \cdot \Delta F_k = MEI_k - TEE_k = EB_k. \tag{4}$$

According to (3) and (4), the total energy balance (metabolically utilized energy intake MEI_k minus total energy expenditure TEE_k) is connected to changes of weight ΔW_k and body fat mass change ΔF_k at the end of day k where the energy distribution is governed by the energy density parameter for weight ϱ_{Wk} and fat ϱ_F. In the case of positive energy balance, ΔL_k, ΔW_k, and ΔF_k will have a positive sign, otherwise negative. ϱ_F is the daily energy density of the fat mass change which is estimated to be $\varrho_F \approx 9.4$ Kcal/g. Rw_k and ϱ_{Wk} need to be estimated as direct measurement is not possible. The main idea and proposition here are to estimate Rw_k from serial weight and fat weight measurement. ϱ_{Wk} is estimated here from serial measurement of weight and energy balance EB_k. Accordingly, the input to our models is going to be known measured values of daily weight W_k and fat weight F_k. The daily energy balance EB_k is indirectly measured or calculated. If no calorie counting and total energy expenditure measurements are done, then the option exists to use (5):

$$EB_k \approx (\varrho_L \cdot R_k + \varrho_F) \cdot \Delta F_k. \tag{5}$$

Here the energy density value of lean mass change ϱ_L is used, which is assumed to be around $\varrho_L \approx 1.8$ Kcal/g and is a semi-stable value [19]. Now the estimation of R_k and Rw_k is needed. Here we exploit the observation that there is a logarithmic relationship between lean mass and fat mass according to Forbes [38]:

$$L_k = \alpha_k \cdot \ln(F_k). \tag{6}$$

The same assumption can be used for weight and fat weight interrelationship:

$$W_k = \alpha w_k \cdot \ln(F_k). \tag{7}$$

Now the daily lean mass change ΔL_k can be connected to the daily fat change ΔF_k using the first-order term coefficient in the Taylor series expansion. It is

noteworthy that this calculation avoids the division by zero for cases when there is no change of fat mass.

$$R_k = \frac{\Delta L_k}{\Delta F_k} \approx \frac{\alpha_k}{F_k}. \tag{8}$$

Here alpha α_k is the first-order term coefficient in the Taylor series expansion of the lean body-fat logarithmic functional relationship. For the value of $\alpha = 10.4$ is used [38] if mass is measured in kilograms. Though intuitively it is felt that this may not be the case for everybody every time, the stability assumption for α over prolonged time is made by multiple authors [19, 38, 39]. Obviously, finding the individual applicable value of α_k is desired [19].

Now, the daily weight change ΔW_k can be connected to the daily fat change ΔF_k using the first-order term coefficient in the Taylor series expansion similar to Eq. (8).

$$Rw_k = \frac{\Delta W_k}{\Delta F_k} \approx \frac{\alpha w_k}{F_k}. \tag{9}$$

Obviously, finding the individual applicable value of the semi-stable daily lean mass change-related alpha α_k, weight-related alpha αw_k, and ϱ_{Wk} is needed. For this purpose we want to take advantage of the principle of "least action" or "stationary action," which is assumed to hold true at steady state of an energy system. The same principle is widely used in Lagrangian or Hamiltonian mechanical systems. We want to extend this variational principle to the thermodynamic system of the human energy metabolism. Briefly stated, the time integral of a thermodynamic energy functional (Lagrangian functional) of the observed energy system under stationary assumption will assume a minimum value. The justification for our approach is that the first and second laws of thermodynamics (Hess's law) are fully applicable for indirect calorimetry as well as thermic energy calculations [37, 40]. The use of the principle of "least action/stationary action" will predict that the energy metabolism works with the minimum consumption of fuel and would not waste energy unnecessarily. Here we introduce our thermodynamic Lagrangian functional where the time integral is replaced by summation of energies for each day from day $k = 1$ to day $k = N$:

$$\begin{aligned} L = \sum_{k=0}^{k=N} & \left[\left(\varrho_{Wk} \cdot Rw_k + \varrho_F\right) \cdot \Delta F_k\right]^2 + \lambda\alpha w_k \cdot \left[\Delta W_k - \alpha w_k \cdot (\ln F_k - \ln F_{k-1})\right] \\ & + \lambda\varrho_{Wk} \cdot \left[EB_k - \varrho_{Wk} \cdot \Delta W_k - \varrho_F \cdot \Delta F_k\right]. \end{aligned} \tag{10}$$

The minimum solution of L is sought for very slow changing semi-stable αw_k and ϱ_{Wk} for known ΔF_k, ΔW_k, and EB_k. This solution could be obtained with numerical methods to minimize the Lagrangian functional L. The Lagrange multipliers $\lambda\alpha w_k$ and $\lambda\varrho_{Wk}$ are non-zero variables and are part of the minimization procedure, and they multiply the constraints for conservation of mass and energy, respectively. Metabolic studies suggest that a new steady state of equilibrium ensues in 5–6 days [31] after a change of input variables occurs and equilibrium is reached. The parameters αw_k and ϱ_{Wk} can be considered stable. The Lagrangian functional L may also contain the parameter α_k in a similar fashion to αw_k if needed. Instead of using head-on numerical minimization methods to find the semi-stable parameters αw_k and ϱ_{Wk}, I prefer using the recursive least square method (RLS) of the general form $y_k = \hat{z} \cdot x_k$ where the time-dependent variables y_k and x_k are known and estimate for parameter $\hat{z}$ is sought. RLS has the advantage that the

estimate of $\hat{z}_{k-1}$ at time $k-1$ can be updated at the arrival of the new measured variables y_k and x_k. This method allows us to estimate $\hat{\alpha w}_k$ when ΔW_k, ΔF_k, and F_k are available. Similarly, $\hat{\varrho_{W}}_k$ can be estimated when a new set of ΔW_k, ΔF_k, and EB_k are available.

Once all parameters of the energy balance Eq. (4) are known, the nonfat energy balance and fat energy balance can be calculated as in Eqs. (11) and (12), respectively:

$$\varrho_{Wk} \cdot \Delta W_k = (1-\varphi_k) \cdot MEI_k - (1-\chi_k) \cdot TEE_k, \tag{11}$$

$$\varrho_F \cdot \Delta F_k = \varphi_k \cdot MEI_k - \chi_k \cdot TEE_k. \tag{12}$$

Here φ_k designates fat intake fraction as defined in Eq. (13), and χ_k denotes the fat-burning fraction as in Eq. (14).

$$\varphi_k = \frac{FI_k}{MEI_k}, \tag{13}$$

and

$$\chi_k = \frac{FO_k}{TEE_k}. \tag{14}$$

In Eq. (13), FI_k represents fat intake, and in Eq. (14), FO_k stands for oxidized fat calories of day k.

We made an important observation in [2, 3, 26] that the R-ratio R_k strongly and negatively correlates with HOMA-IR. Building on this observation and using Rw-ratio Rw_k, we introduce here a possible modeling of the connection between insulin resistance and substrate fractionation. At assumed steady state, the fat-burning fraction χ_k approximates food fraction φ_k according to [31], and they become quasi equal. Under this condition the nonfat and fat energy balance can be written in a simplified form as in Eqs. (15) and (16):

$$\varrho_{Wk} \cdot \Delta W_k = \frac{\varrho_F}{\varrho_{Wk} \cdot Rw_k + \varrho_F} \cdot (MEI_k - TEE_k), \tag{15}$$

$$\varrho_F \cdot \Delta F_k = \frac{\varrho_{Wk} \cdot Rw_k}{\varrho_{Wk} \cdot Rw_k + \varrho_F} \cdot (MEI_k - TEE_k). \tag{16}$$

Accordingly, the carbohydrate burning fraction $1-\chi_k$ and the fat-burning fraction χ_k can be written as in Eqs. (17) and (18):

$$1-\chi_k = \frac{\varrho_F}{\varrho_{Wk} \cdot Rw_k + \varrho_F} = \frac{CO_k}{CO_k + FO_k}, \tag{17}$$

$$\chi_k = \frac{\varrho_{Wk} \cdot Rw_k}{\varrho_{Wk} \cdot Rw_k + \varrho_F} = \frac{FO_k}{CO_k + FO_k}. \tag{18}$$

Important properties of Eqs. (15) and (16) are that they add up to the total energy balance equation as in Eq. (3). It can be seen in this pair of equations that with decreasing insulin resistance, i.e., decreasing HOMA-IR and concomitantly increasing Rw-ratio Rw_k, the fat-burning fraction χ_k increases, and the carbohydrate burning fraction $1-\chi_k$ would decrease. Similarly, with increasing insulin resistance, i.e., increasing HOMA-IR and concomitantly decreasing Rw-ratio Rw_k, the fat-burning fraction χ_k decreases, and carbohydrate burning fraction $1-\chi_k$ would increase as demonstrated in **Figure 2a** and **b**.

Further, according to Elia and Livesey [37] during nonprotein energy production, the nonprotein respiratory quotient Rnp_k can be calculated from the fat-burning fraction χ_k using stoichiometry under the assumption that mainly dioleylpalmityltriglyceride and glucose are used as fuels for oxidation as in Eq. (19) adopted from Elia [37].

$$Rnp_k = \frac{a - \chi_k \cdot a + \chi_k \cdot b \cdot c}{a - \chi_k \cdot a + \chi_k \cdot b}. \tag{19}$$

The constant values in [37] are $a = 19.502$, $b = 21.120$, and $c = 0.7097$.

All calculations from Eqs. (1)–(19) use the same assumption as Elia and Livesey [37] for their formulas, which remain in keeping and coincide with traditional indirect calorimetry calculation as introduced by Lusk [37].

The somewhat arbitrary looking choice of definitions Eqs. (17) and (18) can be justified with our experience that increasing insulin resistance would lead to more sugar burning and less fat burning. Further it allows for the calculated burning fraction χ_k in Eq. (18) to be used as an input variable to calculate the nonprotein respiratory quotient Rnp_k as in Eq. (19). The result of this choice is also that an increasing (or decreasing) burning fraction χ_k would translate into a decreasing (or increasing) nonprotein respiratory quotient Rnp_k as demonstrated in **Figure 2a** and **b** and **3a** and **b**.

We calculate the total energy expenditure as in Eq. (20):

$$TEE_k = PAE_k + BMR_k. \tag{20}$$

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