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# Metabolic Health Analysis and Forecasting with Mobile Computing

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## Abstract

The goal of this paper is to demonstrate feasibility of a concept of mobile computing to help users to reach and maintain metabolic health. For this purpose, we analyze data from 12 clinical studies with a total of 39 study arms from the international literature to show that insulin resistance measured by HOMA-IR could be followed and its changes could be predicted using our weight-fat mass-energy balance calculations taking advantage of the significant and strong correlation between changes of HOMA-IR and state variables of the energy metabolism like changes of weight, fat mass, R-ratio, Rw-ratio, and fat burning fraction of the energy production. We introduce here our extended weight-fat mass-energy balance calculation to assess de novo lipogenesis, adaptive thermogenesis, and the 24-hour nonprotein respiratory quotient. We show how we can analyze and predict individualized state variables of the metabolism, which serve as metrics for the quantification of the interrelationship between energy metabolism and insulin resistance facilitating management and self-management of insulin-resistance related conditions including obesity, fatty liver, prediabetes, metabolic syndrome, and type 2 diabetes. The feedback of individualized metrics using tools of the digital health era may amount to channeling focus also to patient-centered individualized care and to accelerating nutrition research.

**Keywords:** energy metabolism, insulin resistance, metabolic monitoring, mobile computing, 24-h nonprotein respiratory quotient, fat oxidation, carbohydrate oxidation, de novo lipogenesis, adaptive thermogenesis, obesity, fatty liver, prediabetes, metabolic syndrome, type 2 diabetes, cardiovascular morbidity, mortality, dynamic changes of behavior, lifestyle modification, patient-centered individualized care, digital health

## 1. Introduction

The purpose of this paper is to outline a new proposed direction of managing and self-managing metabolic health including insulin resistance in the era of mobile technology.

I am perhaps a rare breed of internist with previous training in biomedical cybernetics before entering medical school. My training and research experience in control engineering together with my experiences as a clinician in academic and nonacademic settings have inspired me to use mathematical modeling tools to

tackle the most sweeping health problem of our time which has reached now pandemic proportion all over the world, i.e., insulin resistance with its devastation in terms of rising cardiovascular disease (CVD), morbidity, and mortality. The reason for focusing on insulin resistance is the overwhelming evidence that insulin resistance syndrome has been proven to be an independent risk factor for CVD mortality, and effective, clinically usable indicators can be derived from readily measured variables [1].

Central to the mission of primary care is fighting the burden of noncommunicable chronic diseases including the most prominent one, CVD [2]. CVD is substantially higher in individuals with unhealthy lifestyle characteristics, including visceral obesity, prediabetes, diabetes, insulin resistance, metabolic syndrome, physical inactivity, poor diet, and cigarette smoking. One could ask the question, why is insulin resistance such an important issue and how could we address this problem more effectively? I see a four-pronged answer to this question:

1. There is a need for heightened awareness of the pathophysiological processes at play in CVD which is accelerated inflammation leading to atherosclerosis driven by insulin resistance. The higher level than normal of inflammatory markers and cytokines are triggered by complex cell physiology changes taking place initially in the visceral adipose tissue and likely related to the regulation of the deposition of the newly synthesized fat. A recently published research article [3] found new insight into the pathophysiological steps of how insulin resistance with or without obesity begets proinflammatory changes [4, 5] occurring, among others, at the arterial walls.
2. Measuring insulin resistance in clinical practice is a huge challenge. The gold standard is the “hyperinsulinemic euglycemic clamp,” which measures the amount of glucose necessary to compensate for an increased insulin level without causing hypoglycemia. Nowadays the test is rarely performed in clinical care. The frequently used clinical assessment is with the homeostatic model assessment of insulin resistance (HOMA-IR) which closely mirrors the glucose clamp technique [6]. This requires only point-of-care invasive measurement of fasting insulin and glucose level. There is a need for a continuous noninvasive measurement method which can provide the same information as HOMA-IR.
3. A lifelong heightened awareness is needed in our accelerated world which pulls us back to optimum decision-making by mindfulness regarding eating and exercising. We have biased perceptions regarding how much we eat [7], and we possess no bodily sensation regarding the size of the visceral fat (a prime source of insulin resistance) and its daily changes. The privacy of a personalized gage such as a smart watch or phone app is needed to gage changes of our metabolic health and fitness level [8].
4. For tracking insulin resistance noninvasively, there is a need to know the total fat balance [9–11] which includes also the daily de novo lipogenesis (DNL). Currently the standard way to measure DNL is the 24-h metabolic chamber [12, 13]. Mobile computing technology just may offer a key solution to this issue.

The tools needed to realize the new proposed approach are embedded into the science of cybernetics. Cybernetics is mostly concerned with exploring regulatory systems—their structures, constraints, and possibilities using mathematical modeling. Cyber-therapy is defined here as the combined use of individualized

mathematical-statistical modeling, prediction, planning for change, and gaining control and self-management of the metabolism with the option for guided therapy by feedback of information on components of the human energy metabolism of an individual. Our mathematical modeling techniques of the human energy metabolism [8–11] is a tool to observe the difficult-to-measure variables of the human energy metabolism, such as slowly occurring body composition changes including lean mass, protein mass, fat mass, extracellular and intracellular water mass, or practically impossible-to-measure variables like utilized macronutrient intake, oxidation rates, and the de novo lipogenesis. The overall goal of individualized cyber-therapy is to gain better control of the metabolism, i.e., reach and maintain optimum body composition and cardiometabolic fitness with minimized effort over the shortest possible time while staying well hydrated and maintaining optimal insulin sensitivity through self-management with mindfulness and/or guided therapy.

My recent paper to the same publisher [8] introduces a proposed cyber-physical system (CPS) as a framework to manage and self-manage metabolic health including insulin resistance. The essential elements of CPS comprise smart watch with appropriate sensors, smart phone, and bathroom scale with fat weight measuring capabilities. The various devices with their apps are connected through cloud computing. The main software component is a metabolic health monitoring app (MHM) performing data gathering and result display of metabolic trends [11]. MHM can make predictions regarding changes of the metabolic state variables (SVs) such as fat mass, lean body mass, insulin resistance changes by the  $R_w$ -ratio, 24-h nonprotein respiratory quotient, as well as the utilized macronutrient intake and oxidation rates. We developed mathematical models of the human energy metabolism allowing for estimation of the SVs [9–11] requiring serial fat weight and lean body mass measurements [9, 10]. We introduced our weight-fat weight-energy balance (WFE) calculations requiring only serial weight and fat weight measurements for basic calculations to estimate changes of insulin resistance [8]. In the same paper, we provided also evidence for feasibility of the CPS concept in healthy young men to track and predict insulin resistance.

Central to the goal of providing metrics for the quantification of insulin resistance is the recognition of its interrelationship with other easily and daily measurable state variables like weight and fat mass. In this regard we take advantage of the observation that there is a correlation between BMI/weight/body composition and insulin resistance measured, for example, with HOMA-IR [14, 15, 27]. We reported earlier that we found significant negative correlation between HOMA-IR and  $R$ -ratio or  $R_w$ -ratio [8, 10, 11, 15]. It has been also our research hypothesis that one could exploit the strong inverse correlation between HOMA-IR and the  $R$ -ratio or  $R_w$ -ratio and use this to measure indirectly changes of insulin resistance derived from serial weight and fat weight measurements [8].

The goal of this paper is to contribute to the developing field of mobile technologies and their use for health-related applications in three areas:

1. More evidence is provided for the connection between HOMA-IR and WFE calculations for clinical practice: here we show feasibility of our research hypothesis that insulin resistance changes by HOMA-IR can be predicted by using the WFE calculation framework in a wide variety of clinical scenarios involving insulin resistance changes and not just in young healthy men as it was already demonstrated in [8]. For this purpose, we use data from [16–27] to show further support for the idea that insulin resistance measured by HOMA-IR could be followed and its change could be predicted by WFE calculation.

2. We give here our theoretical considerations on how DNL and adaptive thermogenesis (AT) could be assessed with mobile technology during acute phase and at predicted steady-state equilibrium of the energy metabolism. AT becomes important when the energy metabolism goes from one steady state to another and the AT energy production or disappearance will oppose the direction of change [28]. We would like to introduce here our extended weight-fat weight-energy balance calculation allowing for DNL and AT calculations (WFE-DNL-AT) and pointing out its limitations.
3. I give here supportive results to the proposition of using WFE-DNL-AT calculations and show how insulin resistance changes with WFE-DNL-AT calculations compared with results of indirect calorimetry obtained by 24-h measurement in a metabolic chamber. For all of these purposes, I reanalyze the published trial data of the “Calorie for Calorie, Dietary Fat Restriction Results in More Body Fat Loss than Carbohydrate Restriction in People with Obesity” (CC trial) [29] using WFE-DNL-AT calculations.

All mathematical tools of WFE-DNL-AT calculation are summarized in Appendix.

## 2. Method of the correlation analysis between HOMA-IR and chosen state variables

This meta-analysis utilizes our dynamic energy balance equation (Eq. (1)) as it was introduced to the reader in [8]. This establishes a weight, fat weight, and energy balance calculation (WFE) based on the following mass and energy relationship:

$$Q_{Wk} \cdot \Delta W_k + Q_F \cdot \Delta F_k = (Q_{Wk} \cdot R w_k + Q_F) \cdot \Delta F_k = MEI_k - TEE_k = EB_k. \quad (1)$$

Essentially, the equation expresses the equivalent change of weight represented here as  $\Delta W_k = R w_k \cdot \Delta F_k$  and fat weight  $\Delta F_k$  in response to the energy balance  $EB_k$ , i.e., the difference of metabolized energy intake  $MEI_k$  and total energy expenditure  $TEE_k$  on a given day  $k$ . We listed in the glossary the meaning of each variable.

Eqs. (2)–(18) constitute the framework derived from Eq. (1) for the correlation analysis between the percentage change of HOMA-IR  $\Delta H\%$  and changes of state variables  $Rw$ -ratio  $\Delta R w$ , weight  $\Delta W$ , and fat burning fraction  $\Delta \chi$  over the course of a clinical trial. We used 39 study arms from 12 clinical trials with a variety of length of the studies performed ranging from 3 days to 365 days [16–27]. The correlation analysis was done in MATLAB. The outcome results of the trials are shown in **Table 1**. Here  $n$  is the number of days in the clinical trial, *subjects* means the number of participants,  $\Delta W_{n-0}$  designates the average weight change in kilograms during the trial period,  $\Delta F_{n-0}$  symbolizes the average fat weight change during the trial period in kilograms, and  $\Delta H_{n-0}$  stands for the average change of HOMA-IR with sugar in mg/dL and insulin in mU/L.

I calculate the average lean mass change  $\Delta L_{n-0}$  as the difference between average weight change and fat weight change as in Eq. (2):

$$\Delta L_{n-0} = \Delta W_{n-0} - \Delta F_{n-0}. \quad (2)$$

For current calculations we assume that the energy density value of lean mass change  $Q_{Lk}$  will remain stable, and it takes the value around  $Q_L \approx 1.8$  kcal/g which is



a value quoted in the literature [30], but its real value is unknown and uncertain. Likewise, the energy density parameter for weight change  $Q_{Wk}$  is calculated using the energy density value of lean mass change  $Q_L \approx 1.8$  kcal/g and using the energy relationship as in Eq. (3):

$$Q_{Wk} = Q_L \cdot \frac{\Delta L_k}{\Delta W_k}. \quad (3)$$

The  $\alpha w_k$  first-order term coefficient of the weight-fat logarithmic relationship is thought to be stable during the trial period under the stationarity assumption and therefore remains unindexed denoted as  $\alpha w$ . Its value is calculated from weight on the first day  $k=0$  and last day  $k=n$  of the study as in Eq. (4):

$$\alpha w = \frac{W_n - W_0}{\ln F_n - \ln F_0}. \quad (4)$$

The weight change and fat weight change on the first day and last day is calculated through several steps as in Eqs. (5)–(8):

Estimated daily energy balance for each day is the same  $EB_0$  as in Eq. (5):

$$EB_0 = Q_L \cdot \frac{(\Delta W_{n-0} - \Delta F_{n-0})}{n} + Q_F^* \cdot \frac{\Delta F_{n-0}}{n} \quad (5)$$

The first day's fat weight change  $\Delta F_1$  and  $F_1$  is calculated as in Eqs. (6) and (7):

$$\Delta F_1 = EB_0 \cdot \left( Q_W \cdot \frac{\alpha w}{F_0} + Q_F^* \right)^{-1} \quad (6)$$

$$F_1 = F_0 + \Delta F_1 \quad (7)$$

Here  $Q_F^*$  can take different values: for net fat loss  $Q_F^* \approx Q_F$ , it takes the value of 9.4 kcal/g; for net fat synthesis, the value is 9.4 + 2.38 kcal/g because synthesis cost of fat from glucose is added to the energy density of fat.

The last day's fat weight change  $\Delta F_{n-1}$  and  $F_{n-1}$  is calculated as in Eqs. (8) and (9).

$$\Delta F_{n-1} = EB_0 \cdot \left( Q_W \cdot \frac{\alpha w}{F_n} + Q_F^* \right)^{-1} \quad (8)$$

$$F_{n-1} = F_n - \Delta F_{n-1} \quad (9)$$

The first day's and last day's weight changes are calculated as in Eqs. (10) and (11):

$$\Delta W_1 = \alpha w \cdot (\ln F_1 - \ln F_0) \quad (10)$$

$$\Delta W_{n-1} = \alpha w \cdot (\ln F_n - \ln F_{n-1}) \quad (11)$$

The first day's and last day's Rw-ratio  $Rw_1$  and  $Rw_{n-1}$  is calculated as in Eqs. (12) and (13).

$$Rw_1 = \frac{\Delta W_1}{\Delta F_1} \quad (12)$$

$$Rw_{n-1} = \frac{\Delta W_{n-1}}{\Delta F_{n-1}} \quad (13)$$

Study	<i>n</i> days	Subjects	$\Delta W_{n-0}$	$\Delta F_{n-0}$	$\Delta H_{n-0}$
[16] Hypoenergetic	84	44	−7	−4.8	−0.12
[16] Hypoenergetic + walking	84	38	−8.8	−6.5	−0.56
[17] Low-carbohydrate	56	12	−7.4	−3.9	−1.3
[17] Low-fat	56	12	−6.5	−3.8	−0.6
[18] Healthy low-fat	365	305	−5.3	−3.7	−0.8
[18] Healthy low-carb	365	304	−6	−4.1	−0.7
[19] Hypo_LF/HC	5	10	−1.1	−1.2	−0.9
[19] Hypo_HF/LC	5	8	−1.5	−1.5	−0.9
[20] Whey protein 4 days	4	8	−5.4	−2.2	−1.8
[20] Sucrose 4 days	4	7	−4.3	−1.9	−1.1
[20] Whey protein 4 + 3 days	3	8	1.3	−0.6	0.6
[20] Sucrose 4 + 3 days	3	7	0.8	−0.9	0.4
[20] Whey protein 7 + 28 days	4	8	−0.5	−0.8	1.3
[20] Sucrose 7 + 28 days	4	7	−0.6	−1.3	0.8
[21] Low-glycemic 180	180	32	−4.5	−2.4	−0.5
[21] Low-fat 180	180	34	−3.75	−1.4	−0.2
[21] Low-glycemic 18-mo	360	32	1.75	0.8	0.4
[21] Low-fat 18-mo	360	34	2.25	0.3	0.2
[22] Women obese	77	17	−12.2	−9.5	−1.7
[22] Men obese	77	17	−17.6	−12.3	−1.8
[23] Women training 1	168	18	−2.7	−2.2	−0.1
[23] Women training 2	168	16	−2.3	−1.8	−0.2
[24] HC 2 day	2	11	−1.61	−0.20	−1.11
[24] LC 2 day	2	11	−2.64	−0.04	−1.69
[24] HC 77 day	77	11	−5.75	−4.17	−0.15
[24] LC 77 day	77	11	−5.09	−5.22	−0.15
[25] A_calorie Restriction	7	10	−3	−2.2	−0.61
[25] A_refeeding	7	10	3.1	1.4	0.82
[25] B_overfeeding	7	10	1.6	0.7	0.84
[25] B_calorie restriction	7	10	−3.4	−1.9	−1.08
[26] Women control M	365	87	−0.42	−0.11	−0.03
[26] Women control O	365	87	−1.34	−1.71	−0.12
[26] Women exercise M	365	117	−1.67	−3.08	−0.43
[26] Women exercise O	365	117	−2.67	−1.42	0.15
[26] Women diet M	365	118	−7.64	−11.15	−0.73
[26] Women diet O	365	118	−6.04	−5.25	−0.82
[26] Women diet+exercise M	365	116	−8.59	12.95	−0.75
[26] Women diet+exercise O	365	116	−9.58	−8.99	−0.88
[27] Correlation IS and WL	336	72	−10.8	−8.3	−14.2

**Table 1.**  
*Outcome results of 12 clinical trials with a total of 39 study arms.*

We calculate the absolute change of the  $Rw$ -ratio  $\Delta Rw$  over duration of the trial as in Eq. (14):

$$\Delta Rw = Rw_{n-1} - Rw_1 \quad (14)$$

We calculated the fat burning fraction using Eqs. (15) and (16):

$$\chi_1 = \frac{Q_{W1} \cdot Rw_1}{Q_{W1} \cdot Rw_1 + Q_F} \quad (15)$$

$$\chi_{n-1} = \frac{Q_{Wn-1} \cdot Rw_{n-1}}{Q_{Wn-1} \cdot Rw_{n-1} + Q_F} \quad (16)$$

We define the absolute change of fat oxidation fraction  $\Delta\chi$  as in Eq. (17):

$$\Delta\chi = \chi_{n-1} - \chi_1 \quad (17)$$

We calculated the percent change  $\Delta H\%$  of the HOMA-IR over the duration of the trial as in Eq. (18) where  $H_0$  is the average HOMA-IR value at baseline:

$$\Delta H\% = \frac{\Delta H_{n-0}}{0.01 * H_0} \quad (18)$$

### 3. Method of the analysis of the CC trial data with WFE-DNL-AT calculations

The detailed description of the WFE calculation with the capability of calculating DNL and adaptive thermogenesis/thermal loss (WFE-DNL-AT) is detailed in Appendix A. For demonstration purpose we apply this method to analyze the published result of the CC trial [29]. The CC trial [29] investigated 19 adults with obesity. The intervention was the selective dietary restriction of carbohydrate (RC) versus fat (RF) for 6 days following a 5-day baseline diet. Subjects received both the isocaloric baseline diets followed by either RC or RF diet in random sequence during two inpatient stays when they were confined to a metabolic ward for two 2-week periods each. The 24-h nonprotein respiratory quotient  $Rnp'_k$  was measured on day -4, 0, 1, 4, and 6 in a 24-h respiratory chamber. The baseline measurements were taken at day 0. The published data of the CC trial were sparse, and the results of laboratory measurements were published only for baseline and for the end point. I generated the needed daily weight  $W_k$  and fat weight  $F_k$  data using MATLAB's interpolation function 'pchip.' First, I calculated the daily  $Rw_k$ , fat burning fraction  $\chi_k$ , 24-hour nonprotein respiratory quotient  $Rnp_k$ , de novo lipogenesis  $DNL_k$ , and adaptive thermogenesis  $T_k$  without the a priori knowledge of the measured  $Rnp'_k$  on day 1, 4, and 6 using the uncorrected WFE-DNL-AT algorithm as in (A1, A2, A3, A6, A7). Second, I performed inverse calculations using the uncorrected WFE-DNL-AT model and the measured nonprotein respiratory quotient  $Rnp'_k$  on days 1, 4, and 6 as input to arrive at the indirectly measured de novo lipogenesis mDNL and adaptive thermogenesis mT denoted mDNLRC, mTRC for the RC arm and mDNLRF, mTRF for the RF arm of the CC trial. Finally, I analyzed how the fat intake fraction  $\varphi_k$  could be used to predict better the measured non-protein respiratory quotient  $Rnp'_k$  and to estimate mDNLRC, mTRC, mDNLRF, and mTRF and how to build a corrected WFE-DNL-AT, which includes (A4) for RF or (A5) for RC diet and could work without the a priori knowledge of the measured 24-h respiratory quotient  $Rnp'_k$ .



The steps of calculations followed the WFE algorithm as in [8], and for DNL and AT calculations, I used Eqs. (A1)–(A7). The unknown values for the adaptive thermogenesis coefficient  $c_{AT}$  and the unknown fraction of the metabolized carbohydrate intake for de novo lipogenesis  $c_{DNL}$  were assumed to be time independent for this analysis and their values were estimated with the assumption that at baseline the energy balance is zero and the energy system is at steady state. I used the same recursive minimization procedure as already explained in [8] to calculate  $\alpha w_k$ , the first-order term coefficient of the weight-fat logarithmic relationship, and the energy density for weight  $q_{Wk}$  and the Rw-ratio  $Rw_k$ .

4. Results of the correlation analysis between HOMA-IR and chosen state variables

The results of correlation analysis across 12 clinical trials with a total of 39 study arms are summarized in **Table 2**. The percent change  $\Delta H\%$  of the HOMA-IR over the duration of the trials was correlated with the absolute change  $\Delta Rw$  of the Rw-ratio, absolute weight change  $\Delta W$ , change of fat oxidation fraction  $\Delta \chi$ , and the absolute fat mass change  $\Delta F$ .

A sub-analysis was also performed with the results of correlation analysis of three clinical trials, [18, 26, 27], with inclusion of 11 study arms. The rationale for this sub-analysis was that all of them were long-term studies with duration of equal or longer than 336 days with satisfying the stationarity requirement for the analysis. The results of the sub-analysis are in **Table 3**.

	$\Delta H\%$	P value
$\Delta Rw$	−0.6745	0.0000024
$\Delta W$	0.6413	0.0000108
$\Delta \chi$	0.6218	0.0000238
$\Delta F$	0.4748	0.0022542

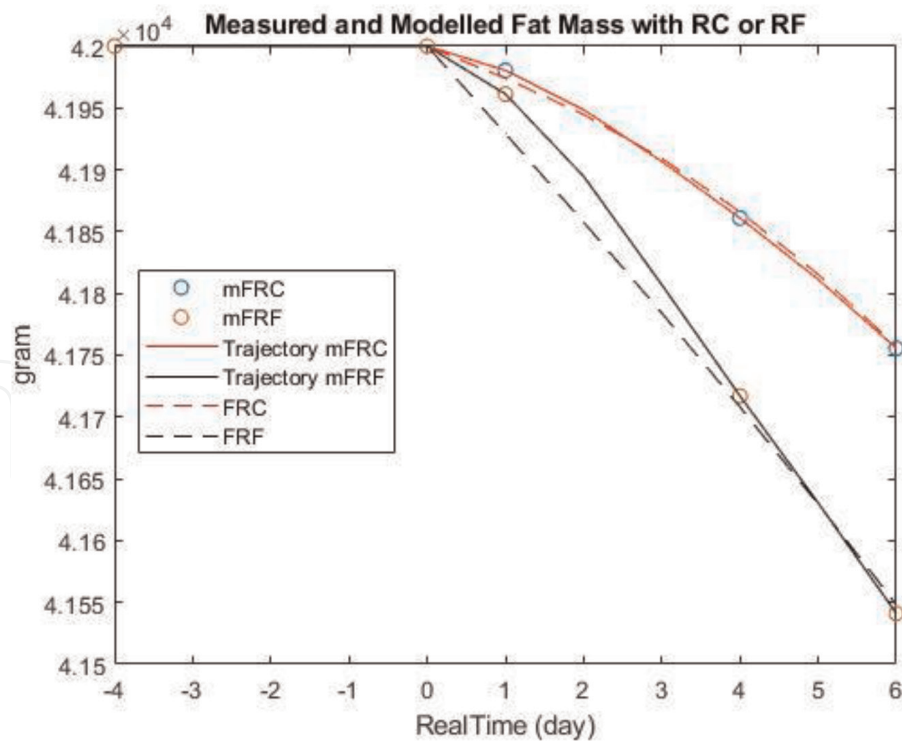
**Table 2.**  
Correlation results of 12 clinical trials with a total of 39 study arms.

	$\Delta H\%$	P value
$\Delta Rw$	−0.8481	0.0009699
$\Delta W$	0.8890	0.0002512
$\Delta \chi$	0.8206	0.0019656
$\Delta F$	0.7605	0.0065810

**Table 3.**  
Correlation results of three clinical trials: [18, 26, 27] with a total of 11 study arms.

5. Results of the analysis of the CC trial data with WFE-DNL-AT calculations

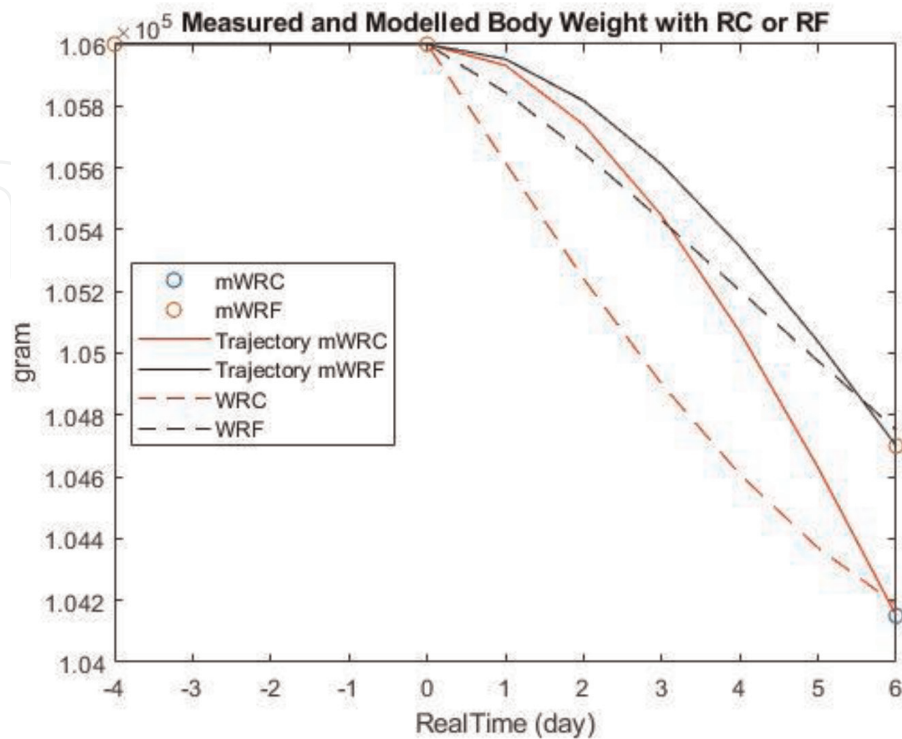
The results of the WFE-DNL-AT calculations using published data of the CC trial [29] are shown in **Figures 1–6**. In **Figure 1** the measurement points mFRC and mFRF and trajectories of the fat mass change in the RC and RF arm of the CC study are shown. The dashed lines FRC and FRF are the results of the WFE calculation.



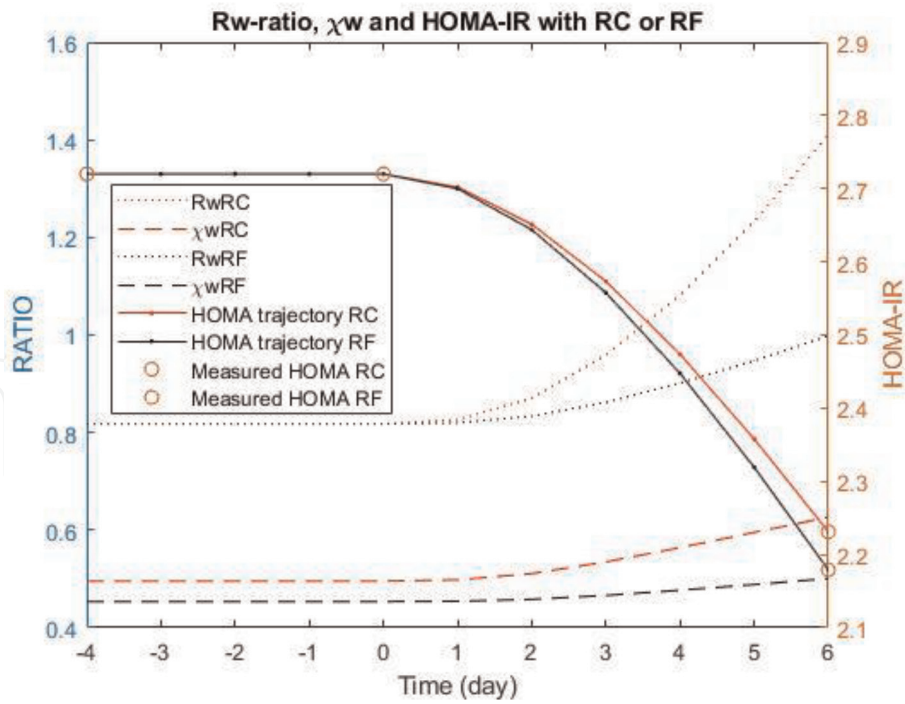
**Figure 1.**  
*Measured and model calculated loss of fat mass without apriori knowledge of measured  $Rnp'_k$*

In **Figure 2** the measurement points mWRC and mWRF and trajectories of body weight change in the RC and RF arm of the CC study are depicted. The dashed lines WRC and WRF are the results of the WFE calculation.

In **Figure 3** the measurement points and trajectories of HOMA-IR are shown in the RC and RF arm of the CC trial. The dashed lines are the model predicted calculations of the fat burning fraction  $\chi$  mRC and  $\chi$  mRF, and the dotted line represents the Rw-ratios RwRC and RwRF in the RC and RF arm of the CC study.

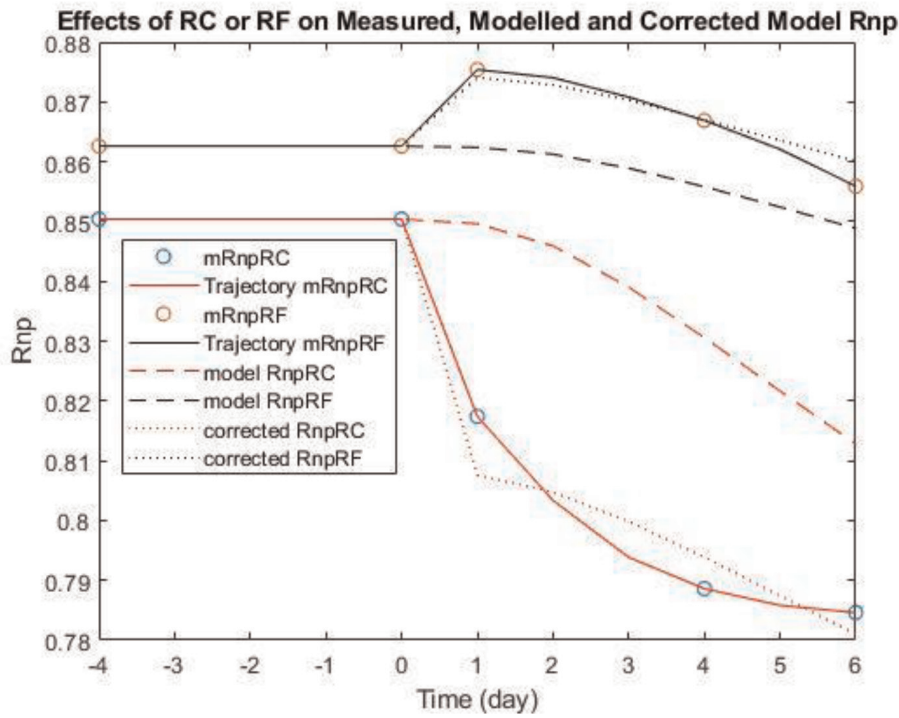


**Figure 2.**  
*Measured and model calculated weight loss without a priori knowledge of measured  $Rnp'_k$*

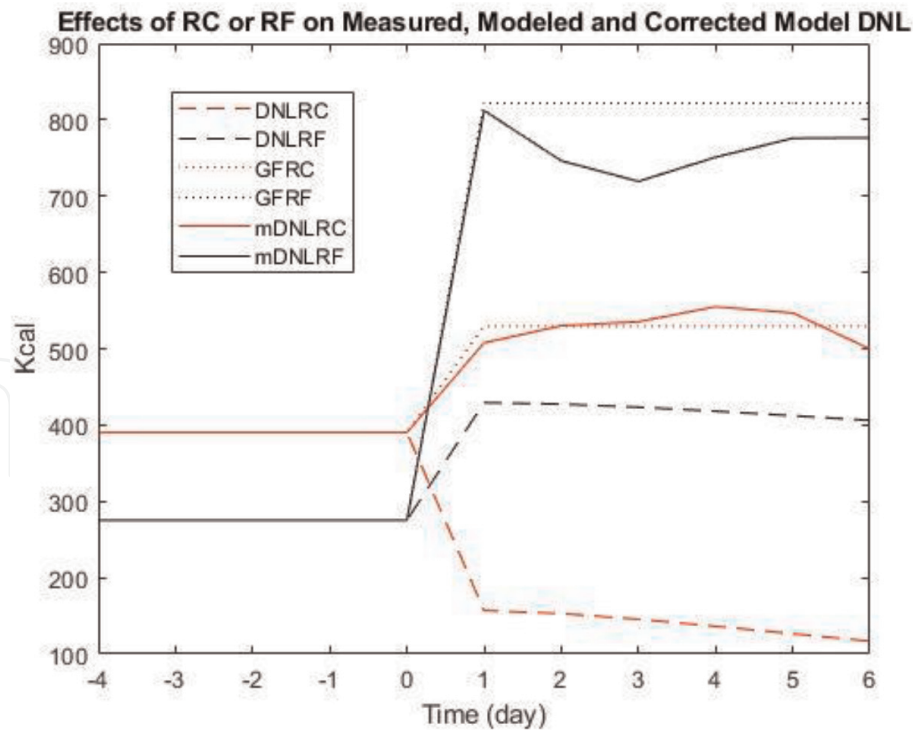


**Figure 3.** Model calculated  $Rw$ -ratio, fat burning fraction  $\chi_k$  without a priori knowledge of measured  $Rnp'_k$ .

The measurement points and trajectories of the measured nonprotein respiratory quotient  $Rnp'_k$  in the RC and RF arm of the CC study are depicted as mRnpRC and mRnpRF in **Figure 4**. The dashed lines are model predicted calculations of the nonprotein respiratory quotient  $Rnp'_k$  by the uncorrected WFE-DNL-AT model labeled as model RnpRC and model RnpRF. The dotted lines denoted as corrected RnpRC and corrected RnpRF are results calculated by the corrected WFE-DNL-AT model.

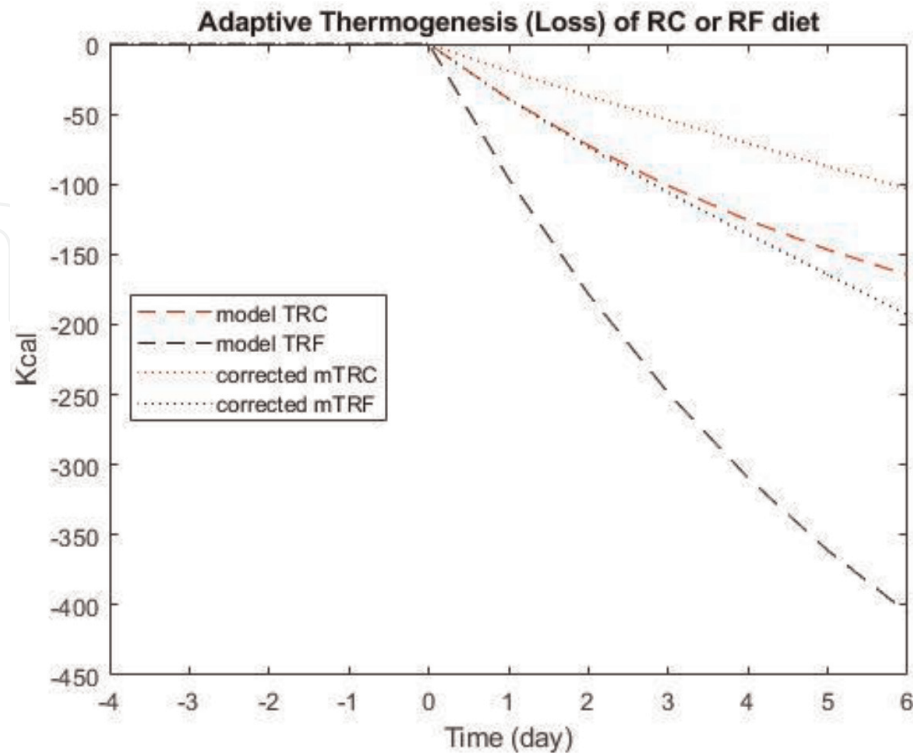


**Figure 4.** Measured nonprotein respiratory quotient  $Rnp'_k$ , uncorrected WFE-DNL-AT model predicted nonprotein respiratory quotient  $Rnp_k$ , and corrected WFE-DNL-AT model predicted nonprotein respiratory quotient  $Rnp_k$ .



**Figure 5.**  
The indirectly calculated DNL from measured nonprotein respiratory quotient  $Rnp'_k$ , DNL prediction by the uncorrected WFE-DNL-AT model, and predicted DNL by the corrected WFE-DNL-AT model calculation.

**Figure 5** is to demonstrate the results of DNL calculations using measured  $Rnp'_k$  on day 1, 4, and 6 using inverse calculations with the uncorrected WFE-DNL-AT model in the RC and RF arm of the CC study marked as mDNLRC, and mDNLRF. The uncorrected WFE-DNL-AT model predicted results are denoted as DNLRC and DNLRF marked with dashed lines. The dotted lines GFRC and GFRF are showing the results of the corrected WFE-DNL-AT model calculations for DNL.



**Figure 6.**  
The indirectly calculated adaptive thermogenesis using the uncorrected WFE-DNL-AT model and the corrected WFE-DNL-AT model calculation.



	RC diet		RF diet	
	$\Delta H\%$	P value	$\Delta H\%$	P value
Fat mass	0.9958845	0.9916711	1.0	0.9916711
Body weight	1.0	0.0000000	1.0	0.0000000
R-ratio	−0.9964298	0.0000000	−0.9973225	0.0000000
Rw-ratio	−0.9973225	0.0000000	−0.9979249	0.0000000

**Table 4.**  
*Correlation results in the CC [29] study.*

	RC diet		RF diet	
	Mean	Stand.dev.	Mean	Stand.dev.
Error fat mass	−0.2921	3.2736	−0.1098	5.4886
Error weight	185.7393	233.7933	55.4621	80.9364
Error lean mass	178.7499	217.0219	15.8333	26.239

**Table 5.**  
*Error of prediction results in grams in the CC [29] study.*

The adaptive thermogenesis/thermal loss calculation is in **Figure 6**. The dashed lines labeled with model TRC and model TRF are the results of the uncorrected WFE-DNL-AT model in the RC and RF arm of the CC study, respectively. The dotted lines labeled as corrected mTRC and corrected mTRF show the corrected WFE-DNL-AT results.

The correlation results between HOMA-IR and fat mass, body weight, R-ratio, and Rw-ratio are shown in **Table 4**. The errors of modeling fat mass, body weight, and lean mass in grams are shown in **Table 5**.

6. Discussion

The most important result of our meta-analysis across 12 clinical trials with a total of 39 study arms [16–27] is the high and significant correlation between changes of insulin resistance as measured with HOMA-IR and changes of Rw-ratio. The strength of this analysis is that the high correlation prevailed for all of the state variables examined regardless whether weight loss or weight gain was achieved during the trial and in the setting of a wide range of trial durations from 3 days to 365 days. As shown in **Table 2**, Rw-ratio ranked best regarding the level of correlation, followed by weight, fat weight, and fat burning fraction. Further, the high correlation is independent from dietary interventions such as isocaloric diet, over-feeding, or underfeeding or with or without exercise intervention. This result means also that the use of Rw-ratio as a surrogate marker for indirect measure of insulin resistance is justifiable for modeling changes of insulin resistance. The sub-analysis looked at studies lasting longer than 336 days. The correlation coefficients scored as in **Table 3** are even higher than in **Table 2** with all the studies included. This predictive strength of the Rw-ratio regarding insulin resistance change could be even stronger in situations when strict steady-state energy balance is present as expected with longer study duration. An important advantage of the simple WFE analysis with Eqs. (1)–(18) is that only serial measurement of weight and fat weight is used and no calorie counting was done. The prevailing daily energy balance can be simply calculated as in Eqs. (2)–(5). Likewise, R-ratio or Rw-ratio can be



obtained with simple arithmetic as in Eqs. (6)–(14), which can lead to the calculation of the fat burning fraction  $\chi_k$ . Using Elia and Livesey's formula [31], the fat burning rate  $\chi_k$  can be converted into the estimated 24-h nonprotein respiratory quotient  $Rnp_k$ . HOMA-IR change can be predicted by knowing that R-ratio and R<sub>w</sub>-ratio are strongly and inversely correlated. This means that their reciprocal values could be used to predict proportional change of HOMA-IR. The strong correlation is in accordance with earlier findings of Thompson and Slezak [27] who were the first to report correlation between measures of insulin sensitivity and weight loss. They showed that the McAuley formula, which contains reference to triglyceride, showed greater correlation with weight loss than HOMA-IR, which does not contain information on lipids, supporting the idea that the sugar, insulin, and lipid kinetics and energy dynamics could and should be measured and modeled together. Therefore, extending the WFE model with the capability of estimating DNL like in the WFE-DNL-AT model is of theoretical as well as of practical importance for clinical use.

One weakness of the current analysis is that no individual data are published and the published data represent lumped together averages of weight and fat weight measurements at the beginning and at the end of the study period. The lack of individual serial data of weight or fat weight does not allow to have an exact insight into the dynamic of the process of body composition change which could occur along a concave or convex monotone decreasing function. Therefore, it is important to have the individual data and build an individual model which could be used also, among others, for interpolation to find missing data points.

Also, measuring insulin resistance with HOMA-IR has its own weaknesses, and maybe the McAuley formula could hold promise to improve model predictions.

The strength of the WFE modeling scheme with Eqs. (1)–(18) is that it makes minimal assumptions requiring only weight and fat weight data and it works also well for prediction of changes of HOMA-IR even when only the baseline value and the last measured value are available. The practicality of this matter is that the already commercially available measuring devices such as bioimpedance body composition analyzers are available, although their accuracy could be questioned. However, as a countermeasure we suggest the use of the Kalman filter [10, 11, 32, 33] minimizing the variance of the measurements and maximizing consistency.

The main contribution to science of the CC trial is that it offers an important glimpse into the acute phase reaction of the body's adaptation to the energy deficit state of glucose vs. fat. Even though RC diet increased the measured net fat disappearance more than the RF diet, the RF diet was more effective in the overall fat weight loss. I interpret this result as the body's physiological adaptation to a new and negative energy balance by increasing the production of readily usable needed fuel such as triglyceride or extra  $DNL_k^A$  as a way to meet demand above and beyond the predicted new steady-state level of  $DNL_1^B$ . The increased demand comes from the sudden drop of energy intake and ensuing energy deficit accompanied by relatively undisturbed carbohydrate and fat fuel burning rates of the body. The suddenly needed extra energy for  $DNL_1^A$  comes from different sources in the RC vs. RF dietary interventions. In RC with drop of available glucose, the needed energies come from the fat pool. In the RF scenario, the body readily grabs the available glucose at hand coming from undisturbed carbohydrate energy intake. While equal calorie deficit is created under both RC and RF, the RF state would sink more calories into new fat synthesis, i.e.,  $DNL_k^A$ , as the fat synthesis from carbohydrate is an energy consuming process. This is because, according to Simonson [13], during lipogenesis each gram of lipid synthesized from glucose consumes  $q_{DNL} = 2.32$  kcal/g energy, and the process appears to be an energy "sink." In the RC diet, the needed extra triglyceride can be produced with simple lipolysis with no significant extra

energy consumption or energy “disappearance or sink.” Our modeling of this phenomenon with simple energy calculations for  $GFRF_k$  as in Eq. (A4) and for  $GFRC_k$  in Eq. (A5) is fully consistent with the measured result as demonstrated in **Figure 5**, where  $GFRF_k$  and  $GFRC_k$  and the measured DNL mDNLRC and mDNLRF are convincingly close to each other. The ratio of energy content of  $GFRF_k$  and  $GFRC_k$  reflects the difference of adaptation in RF vs. RC diet explainable now with Simonson’s postulate for lipid synthesis from glucose [13] and using the energy constant  $Q_{DNL} = 2.32$  kcal/g (see also Appendix A for more detail).

The strength of WFE-DNL-AT modeling is that the fat mass change predictions are accurate as in **Figure 1**, even under dietary interventions such as the RC or RF diet in the CC trial considered extreme. As fat mass measurement is a primary input data to our model calculations, its accuracy is essential to arrive at desired precision. Hall et al. [29] used DXA scan in the “CC” trial. Even with this very expensive tool, they felt that DXA still was inaccurate to determine fat mass in situations of dynamic weight change and shifting body fluids. Using commercially available bioimpedance scales for fat mass measurement with a one point in time, measurement certainly has much higher inaccuracy than DXA in determining the fat mass. However, currently most bioimpedance scales utilize the 50 kHz measuring frequency which gives quite suitable accuracy for extracellular water mass and intracellular water mass which resides mainly in lean mass, and the water content of the fat cell is negligible. In a way, the fat weight measurement by bioimpedance measurement is indirect: weight minus lean mass. This could be advantageous during weight loss when the fluids are shifting. Daily measurements with bioimpedance scale have the advantage that through obtaining a series of measurements, important secondary information related to weight, lean mass, and fat mass change can be obtained, and the variance of these measurements will allow for presentation of data in the  $\pm$  standard deviation form. In response to the need for practicality, accuracy, and transparency in bioimpedance measurements, our company, Ori Diagnostic Instruments, LLC, has invented a Body Composition and Hydration Status Analyzer in unison with a high-frequency dielectric property analyzer [32, 33] which can quantify the size of intracellular and extracellular water along with fat mass better than commercially available bioimpedance analyzers because it measures the dielectric properties of tissue also at high frequency which is more suitable for fat mass change measurements. We take advantage of serial measurements by providing a posteriori values to a Kalman filter where the a priori estimates are obtained from our self-adaptive model of the human energy metabolism [9]. The combination of process model and measurement model equations combined with Kalman filter realizes a classic state-space modeling scheme [9], keeping the variance of measurements at minimum and maximizing consistency.

Regarding the body weight prediction with WFE-DNL-AT, far more challenges could be raised. In **Figure 2**, it is shown how the measured and predicted weight deviates, especially at day 3. Here are a high number of influencing factors at work. Probably most importantly, the daily measured weight decreases could follow an exponentially declining concave function rather than a convex function such as the applied interpolation function “pchip” in MATLAB. Beyond this modeling error, the lack of modeling of the extracellular and intracellular water mass change along with modeling glycogen and protein store changes is an issue in the current form of WFE-DNL-AT. In this regard our company, Ori Diagnostic Instruments, LLC, has created a patented modeling solution which includes also modeling of the intracellular as well as extracellular fluid volume changes and predicts also protein store as well as glycogen store changes [32, 33]. All results appear in the scientific form  $\pm$  standard deviation, letting the user know about the accuracy and its change.

This demonstration study using CC trial data showed again the high level of correlation between HOMA-IR and R-ratio,  $R_w$ -ratio, weight, and fat mass as shown in **Table 4**. The modeling error of weight lean mass and fat mass was low as in **Table 5**. The calculated results for  $\chi_k$  depicted as dashed lines in **Figure 3** are nicely pointing to the measured HOMA-IR values, demonstrating the predictive power of the calculated burning rate regarding HOMA-IR change prediction. This is driving home the main point that indirect measurement and prediction of HOMA-IR is possible, and the WFE model predicts that the RF diet leads to more reduction of insulin resistance and concomitant fat reduction than RC as measured.

In terms of modeling and predicting correctly changes of  $R_{np}$ , the CC trial data were instrumental to improve our WFE-DNL-AT. It turns out that the truly measured  $R_{np}'_k$  can be reproduced accurately at known calorie imbalance either with RC or RF diet as demonstrated in **Figure 4**. In the case of RC diet, the drop of glucose supply leads to lipolysis as in the model of  $GFRC_k$  (see Appendix Eq. (A5)). During RF diet  $GFRF_k$ , energy will come mainly from available glucose and is easily quantifiable with our model (see Appendix Eq. (A4)). It has to be emphasized that the use of WFE-DNL-AT is possible only if the correct daily macronutrient energy of food is known.

This paper confirms for clinicians the long felt close relationship of insulin resistance to the energy metabolism, opening the theoretical opportunity to merge quantitative insulin sensitivity assessments such as the homeostasis model assessment [37] of glucose and insulin kinetics with quantitative modeling and measuring dynamics of the lipid metabolism including de novo lipogenesis, lipolysis, lipid deposition, and net lipid synthesis or net lipid loss along with lipid oxidation. Importantly, WFE-DNL-AT could be the first step to extend the homeostasis model assessment in this direction. The advantage of such modeling efforts is that the individual's entire lipid metabolism could be appropriately quantified for the clinician and connected to the processes of insulin and glucose kinetics. Further, the current modeling technique allows already for derivation of a person's individualized metrics of metabolic parameters with canonical representation [10], allowing for intra- and interindividual comparison of the parameters; observing daily changes and monitoring long-term changes of the energy metabolism with the help of a metabolic health monitoring app [11]; controlling the energy metabolism by possible implementation of a favorable adaptive control intervention with instantaneous feedback of metrics to the user to reach targeted results; and long-term analysis, cardiovascular risk assessment, and intervention planning by the healthcare team with observance of applicable clinical guidelines [2].

The ultimate outcome measure of any clinical intervention is mortality, including CVD and all-cause mortality. A CPS is empowered to calculate trends and trajectories of fat mass, which can also be translated into predicted changes of visceral fat and waist circumference. In addition to this, other important mortality predictors could be added, like heart rate variability, leading to improved prediction of all-cause mortality and sudden cardiac death [34, 35]. Measuring and tracking cardiovascular fitness in terms of exercise capacity and maximum oxygen uptake makes sense in view of the very strong inverse correlation between mortality and fitness [36] and direct correlation between insulin resistance syndrome and cardiovascular mortality [1]. Ultimately, in a fully developed CPS system, all essential metabolic variables and cardiovascular fitness measures could be tracked and used for prevention. An all-encompassing cardiovascular risk assessment by CPS could be achieved by adding traditional cardiovascular risk factors (i.e., blood pressure, smoking, age, gender, cholesterol, diagnosis of diabetes mellitus, among others), and these results would be at the fingertip of the user, who would be the owner of the data displayed on his/her smartphone. After proper consenting, secondary analysis of metabolic data could help not only clinical research but also insurance



companies to calculate costs and potentially reimburse the treatment/self-treatment and improvement of risk factors for CVD. A value-based health delivery system holds potential to incentivize participants to improve their lifestyle, especially if insurance companies would honor participants with a discount on the premiums for those who were successful to lower their cardiovascular risk.

One final point is worth mentioning regarding our Lagrangian equation as it appears in Eq. (A10). The seemingly useless-looking Lagrange multiplier terms such as  $\lambda_{aw_k}$ ,  $\lambda_{Q_{Wk}}$ ,  $\lambda_{c_{DNLk}}$ , and  $\lambda_{c_{ATk}}$  can provide important and coveted individual sensitivity values to the fixed valued constraints, i.e., sensitivity value of the energy metabolism to the parameters  $aw_k$ ,  $Q_{Wk}$ ,  $c_{DNLk}$ , and  $c_{ATk}$ . This can potentially reveal important individual sensitivity patterns to planned or executed interventions.

## 7. Conclusion

In this paper we presented the foundation of our mobile computing-based solutions to help better observe and control the energy metabolism. We see our approach as an appropriate response to the frustration of the public at large along with health professionals regarding perceived inadequateness of the current state of nutritional research [38] and at the same time give an answer to the call of academic authors for patient-centered individualized care [39]. Based on a rigorous examination of our methods here and in prior publications, we conclude that our mathematical modeling scheme along with the suggested computing tools is workable and appropriate to monitor, analyze, and predict individualized state variables of the metabolism, providing metrics for the quantification of the interrelationship between energy metabolism and insulin resistance which is strongly connected to obesity, fatty liver, prediabetes, metabolic syndrome, type 2 diabetes, cardiovascular morbidity, and mortality. Our mobile computing-based solutions have the potential of unlocking the vast potential of digital health. We achieved the goal of creating individualized metabolic metrics for use in mobile technology in the user's natural environment. We demonstrated that our Weight-Fat-Energy balance calculations are appropriate to predict changes of HOMA-IR. We found that the Weight-Fat-Energy balance calculations extended with the assessment of de novo lipogenesis and adaptive thermogenesis/loss predict the changes of the metabolic state variables such as  $R_w$ -ratio, weight, fat mass, and 24-h nonprotein respiratory quotient with very much acceptable accuracy. We found that the estimation of the de novo lipogenesis and adaptive thermogenesis calculations follow closely measurements that were done using a metabolic chamber for 5 days. It may just be possible to get 24-h respiratory quotient measurements in patients in their natural environment without using the metabolic chamber. We found that our analysis and predictions of the state variables of the metabolism remain valid not just at steady state but also during transitional phases. Incorporating Weight-Fat-Energy balance calculations with extended capability of de novo lipogenesis and adaptive thermogenesis assessment into mobile technologies and into a cyber-physical system [8] can provide appropriate real-time tools to monitor and optimally adjust modifiable risk factors of an individual's metabolism, allowing for planning and executing dynamic changes of behavior for optimization and control. All-encompassing cardiovascular disease risk scores can be created, tracked, modified with appropriate lifestyle changes, and used ultimately as outcome measures to improve health status. All these possibilities are applicable in resource-limited settings with minimal investment with implications for overall reduction of health costs and the potential to calculate sustainable reduction of premiums by insurers awarding compliance and efficacy in reaching and maintaining reasonable health status.

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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 on patent [32] and patent application [33], and the patent and patent application are owned by Ori Diagnostic Instruments, LLC.

Glossary

Measured variables

$F_k$	fat weight
$\Delta F_k$	fat mass change in 24 h
$W_k$	weight
$\Delta W_k$	body weight change in 24 h
$EB_k$	daily energy balance
$\Delta EB_k$	positively signed energy deficit
$EP_k$	energy production with substrate oxidation

Derived or estimated variables

$BMR_k$	basal metabolic rate
$c_{ATk}$	adaptive thermogenesis coefficient
$c_{DNLk}$	fraction coefficient of the metabolized carbohydrate intake used for lipid synthesis
$CI_k$	carbohydrate calorie intake
$DNL_k$	de novo lipogenesis
$DNL_k^A$	de novo lipogenesis in the acute phase of energy perturbation
$DNL_k^{ARC}$	de novo lipogenesis in the acute phase of energy perturbation with RC diet
$DNL_k^{ARF}$	de novo lipogenesis in the acute phase of energy perturbation with RF diet
$DNL_k^B$	de novo lipogenesis in the steady-state phase of energy perturbation
$GFRC_k$	glucose equivalent of energy for needed fat (DNL) energy with RC diet
$GFRF_k$	glucose equivalent of energy for needed fat (DNL) energy with RF diet
$L_k$	lean mass
$\Delta L_k$	lean mass change in 24 h
$mDNL_k$	calculated DNL using measured 24-h nonprotein respiratory quotient $Rnp'_k$
$MEI_k$	metabolically utilized energy intake
$mT_k$	calculated adaptive thermogenesis/thermal loss using measured 24-h nonprotein respiratory quotient $Rnp'_k$



$PAE_k$	physical activity energy expenditure via smart watch sensors
$T_k$	adaptive thermogenesis/thermal loss
$TEE_k$	total energy expenditure
$R_k$	R-ratio
$Rw_k$	Rw-ratio
$Rnp_k$	nonprotein respiratory quotient
$Rnp'_k$	measured nonprotein respiratory quotient
$\alpha w_k$	first-order term coefficient of the weight-fat logarithmic relationship
$\lambda_{ATk}$	Lagrange multiplier of the adaptive thermogenesis coefficient
$\lambda_{DNLk}$	Lagrange multiplier of the fraction coefficient of the metabolized carbohydrate intake used for lipid synthesis
$\lambda \alpha w_k$	Lagrange multiplier of the first-order term coefficient of the weight-fat logarithmic relationship
$\lambda Q_{Wk}$	Lagrange multiplier of the energy density for weight
$Q_C \approx 4.2 \text{ kcal/g}$	energy density for glucose
$Q_F \approx 9.4 \text{ kcal/g}$	energy density for fat (dioleoyl palmitoyl triglyceride)
$Q_F^* \approx Q_F = 9.4 \text{ kcal/g}$	in the case of net fat loss; for net fat synthesis, the value is $9.4 + 2.38 \text{ kcal/g}$ because synthesis cost of fat from glucose is added to the energy density of fat
$Q_{DNL} \approx 2.38 \text{ kcal/g}$	energy cost for synthesis of 1 g fat from glucose
$Q_L \approx 1.8 \text{ kcal/g}$	the energy density for lean mass
$Q_{Wk}$	energy density for weight
$\varphi_k$	fat intake fraction
$\chi_k$	fat burning fraction

## Appendix

The WFE calculation using Eq. (1) has been already introduced to the reader in [8]. WFE-DNL-AT is an extension of the WFE calculation to include de novo lipogenesis (DNL) and adaptive thermogenesis (AT). Here we are using similar annotation (see Glossary) as in [8] for the nonfat and fat balance as in Eqs. (A1) and (A2), respectively, which will include now DNL:

$$Q_{Wk} \cdot \Delta W_k = (1 - \varphi_k) \cdot MEI_k - DNL_k - (1 - \chi_k) \cdot TEE_k \quad (A1)$$

$$Q_F \cdot \Delta F_k = \varphi_k \cdot MEI_k + DNL_k - \chi_k \cdot TEE_k \quad (A2)$$

WFE calculations can provide ways to determine  $Q_{Wk}$ ,  $Rw_0$ , and  $\chi_k$  without calorie counting. In order to calculate  $DNL_k$ , the measurement of the total energy expenditure  $TEE_k$  and the metabolized energy intake and along with it the fat intake fraction  $\varphi_k$  are needed. In addition, knowledge of the utilized carbohydrate intake  $CI_k$  is a prerequisite as our modeling proposition for DNL follows on one hand the modeling proposition of Hall [35], and on the other hand, it follows the common clinical observation that with increasing insulin sensitivity, less DNL is generated and vice versa with decreasing insulin sensitivity (increasing insulin resistance),

more DNL is generated. We use here our earlier observation that the R-ratio or the  $Rw$ -ratio is inversely correlated with HOMA-IR and mimics a measure for insulin sensitivity [8, 10, 11]. Hence the proposed model for steady-state level of DNL at baseline at day  $k = 0$  is in Eq. (A3):

$$DNL_0^B = \frac{c_{DNL0} \cdot CI_0}{Q_{W0} \cdot Rw_0 + Q_F} \quad (A3)$$

Here  $c_{DNL0}$  means the fraction of the metabolized carbohydrate intake which is used for de novo lipogenesis, and its value needs to be determined. At steady state all variables must be stable over time with little or no change. The new steady state is symbolized as  $DNL_j^B$  where index  $j = 1$  enumerates the steady states in sequence. Between two steady states, the DNL calculation will have acute phase component. For fasting experiments, we show here our modeling of the acute phase component. In acute phase of fasting, the production of DNL must cover the needed fat (mainly triglycerides) for the relatively unchanged fat burning rate of the body cells. The important principle for understanding the metabolic pathways is the fact that glucose is the prime ingredient for DNL production and fat cannot be directly converted to sugar. However, lipolysis can provide the needed free fatty acid and glycerol if glucose is not readily available. We found evidence by studying results of the CC study that the acute phase  $DNL_k^A$  is determined primarily by the sudden rise of the positively signed energy deficit  $\Delta EB_k$ . The energy source to cover  $DNL_k^A$  is different in RF diet versus RC diet.

In case of RF diet where the required energy  $\Delta EB_k$  comes from undisturbed glucose supply, the glucose is oxidized to fat during lipid synthesis to meet the demand for  $DNL_k^{ARF}$ . This is a process which would increase Rnp above 1 [31] if the ongoing fat oxidation is ignored. However, with the ongoing fat oxidation, the 24-h Rnp will not rise above 1, but it would show an increasing trend toward 1 as demonstrated in **Figure 4**. The glucose equivalent energy for needed fat energy is denoted here as  $GFRC_k$  in kcal, and a simple formula in Eq. (A4) expresses at least at the beginning of the adaptation of the quantitative relationships:

$$DNL_k^{ARF} = GFRC_k = \Delta EB_k \quad (A4)$$

During the RC diet, the acute phase  $DNL_k^{ARC}$  is thought to come mainly from the fat pool through lipolysis. I modeled this in a way which clearly shows how the initial adaptation to RC diet would proportionally compare with the RF diet. This formula is in Eq. (A5):

$$DNL_k^{ARC} = GFRC_k = \frac{Q_C}{Q_C + Q_{DNL}} \cdot \Delta EB_k \quad (A5)$$

Here  $GFRC_k$  stands for the glucose equivalent energy in kcal to meet the fat energy demand. The factor  $Q_C/(Q_C + Q_{DNL})$  is to express that only a fraction of  $\Delta EB_k$  is needed coming from fat pool with RC diet compared with glucose energy source with RF diet. The modelling equation in Eq. (A5) of the RC diet differs from Eq. (A4) of the RF diet because the Simonson's rule [13] does not apply in the RC scenario, but it will very much apply to RF scenario where lipogenesis occurs from glucose, and each gram of lipid synthesized from glucose consumes  $Q_{DNL} = 2.32$  kcal/g energy. The graph of **Figure 5** shows well that the theoretical models in Eq. (A4) and (A5) run very close to the measured values.

Here we give our modeling of the adaptive thermogenesis which occurs with energy imbalance with metabolic changes to oppose the body composition change. In practical terms with negative energy balance, the adaptive thermogenesis  $T_k$

diminishes the total energy expenditure; vice versa with weight gain, the adaptive thermogenesis  $T_k$  adds the total energy expenditure leading to lesser weight increase than expected by simple calorie counting. For modeling this phenomenon, we chose to use Hall's equation for adaptive thermogenesis [35] as in Eq. (A6):

$$c_{ATk} \cdot T_k = \frac{1}{\tau} \cdot \frac{MEI_{j=0} - MEI_{j=1}}{MEI_0} - c_{ATk} \cdot \frac{T_{k-1}}{\tau} + c_{ATk-1} \cdot T_{k-1} \quad (A6)$$

Here,  $c_{AT}$  means adaptive thermogenesis coefficient, a parameter which must be estimated. The value for the time constant is assumed to be  $\tau = 7$  according to Hall [35]. If uncertainty exist, then parameter estimation is needed also for  $\tau$ .  $MEI_{j=0}$  means metabolized energy intake at baseline steady state, and  $MEI_{j=1}$  is the energy intake at the end of the adaptation period when the next steady state has been reached.

The total adaptive thermogenesis sums up over time from  $i = 0$  until final day  $i = k$  as in Eq. (A7), assuming a quasi-stable  $c_{ATk}$  over the examined time period:

$$T_k(c_{ATk}) = \sum_{i=0}^k \left( \frac{1}{c_{ATk} \cdot \tau} \cdot \frac{MEI_{j=0} - MEI_{j=1}}{MEI_0} - \frac{T_{i-1}}{\tau} + T_{k-1} \right) \quad (A7)$$

For days with transition from one steady state to another, the total energy expenditure  $TEE_k$  is replaced by the sum of energy production  $EP_k$  and the adaptive thermogenesis/sink  $T_k$  as in Eq. (A8):

$$TEE_k = EP_k + T_k \quad (A8)$$

The daily energy production can be determined from Eq. (A9):

$$EP_k = PAE_k + BMR_k \quad (A9)$$

For theoretical purpose, we want to update here our proposed thermodynamic Lagrangian functional presented already in [8] to determine the unknown parameters  $\alpha w_k$  and  $q_{Wk}$  for WFE calculations. In doing so, we utilize the principles of indirect calorimetry and the principle of "least action or stationary action" [8].

The extended model WFE-DNL-AT is empowered to calculate DNL as well as AT. For this purpose the determination of the following unknown parameters are needed,  $\alpha w_k$ ,  $q_{Wk}$ ,  $c_{DNLk}$ , and  $c_{ATk}$ , by using known values of  $W_k$ ,  $F_k$ ,  $EP_k$ ,  $MEI_k$ ,  $CI_k$ , and  $\varphi_k$ . The new form of the thermodynamic Lagrangian functional contains now implicitly  $DNL_k$  as a function of  $c_{DNLk}$ ,  $CI_k$ ,  $q_{Wk}$ , and  $Rw_k$  and the adaptive thermogenesis/thermal loss  $T_k$  as a function of the parameter  $c_{ATk}$  as shown in Eq. (A10):

$$\begin{aligned} \mathcal{L} = & \sum_{k=0}^n \left[ (q_{Wk} \cdot Rw_k + q_F) \cdot \Delta F_k + MEI_k - PAE_k - BMR_k - T_k(c_{ATk}) \right]^2 \\ & + \lambda \alpha w_k \cdot \left[ \Delta W_k - \alpha w_k \cdot \frac{\Delta F_k}{F_k} \right]^2 \\ & + \lambda q_{Wk} \cdot [q_{Wk} \cdot \Delta W_k - MEI_k + EP_k + T_k(c_{ATk}) - q_F \cdot \Delta F_k]^2 \\ & + \lambda c_{DNLk} \cdot \left[ \varphi_k - \frac{q_{Wk} \cdot Rw_k}{q_{Wk} \cdot Rw_k + q_F} - \frac{c_{DNLk} \cdot CI_k}{TEE_k \cdot (q_{Wk} \cdot Rw_k + q_F)} \right]^2 \\ & + \lambda c_{ATk} \cdot [TEE_k - EP_k - T_k(c_{ATk})]^2 \end{aligned} \quad (A10)$$

Note that  $TEE_k$  can be calculated from the energy balance equation which is the sum of Eqs. (A1) and (A2).

The Lagrangian functional  $\mathcal{L}$  contains all energy forms entering and exiting the human body along with the subsidiary conditions for the unknown parameters  $\alpha w_k$ ,  $Q_{Wk}$ ,  $c_{DNLk}$ , and  $c_{ATk}$  from beginning day  $k = 0$  to end  $k = n$  of observation. The equations with the constraints for the unknown parameters  $\alpha w_k$ ,  $Q_{Wk}$ ,  $c_{ATk}$ , and  $c_{DNLk}$  add up to zero, and they are entered with their time-dependent Lagrange multipliers and  $\lambda \alpha w_k$ ,  $\lambda Q_{Wk}$ ,  $\lambda c_{DNLk}$ , and  $\lambda c_{ATk}$  as in Eq. (A10). A minimization procedure will give the estimations for the unknowns  $\alpha w_k$ ,  $Q_{Wk}$ ,  $c_{DNLk}$ , and  $c_{ATk}$ .


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