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The respiratory quotient as a prognostic factor in weight-loss rebound

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OBJECTIVE: To investigate the possible metabolic factors predisposing to weight gain subsequent to the cessation of a rapid-weight-loss diet.
DESIGN: Prospective, longitudinal, intervention study of a 2 MJ diet daily for 28 d in a metabolic ward followed by a 12-month outpatient follow-up under a conventional, hypocaloric diet.
SUBJECTS: Thirty-five females and one male, all with morbid obesity defined by a body mass index $\geq 35\ kg/m^2$.
MEASUREMENTS: $\dot{V}O_2$ and $\dot{V}CO_2$ measured by 30 min indirect calorimetry to calculate resting energy expenditure and resting respiratory quotient at the beginning and end of very-low-calorie diet; body composition assessed by hydrostatic weighing on day 1; weight recorded on days 1 and 28 and at follow-up of 3, 6 and 12 months.
RESULTS: From among all the variables considered, the resting respiratory quotient measured on day 28, even adjusted for weight loss during hospitalisation, was the only one that correlated significantly with the weight changes recorded during follow-up.
CONCLUSION: Subjects who showed a respiratory quotient on day 28 in the lower range (< 0.72) were more able to maintain the weight-loss achieved with the very-low-calorie diet while those in the higher range (> 0.75) were less able to do so over the follow-up period. Thus, an appropriately measured respiratory quotient could prove useful in clinical practice as a prognostic marker of the long-term effectiveness of low- and very-low-calorie diets used to induce rapid weight loss.

Keywords: obesity; VLCD; body composition; resting energy expenditure; respiratory quotient.

Introduction

Prognostic factors for weight gain in the pre-morbid state, identified in longitudinal studies in populations prone to obesity, include a low metabolic rate, a high respiratory quotient (RQ) and an impaired insulin sensitivity.[1–6] However, cross-sectional studies indicate that patients with morbid obesity have higher metabolic rates, a lower RQ and a higher insulin resistance than lean controls, which may be due to an adaptation to a higher degree of adiposity.[7–12] The changes in these variables during weight reduction,[13–16] as well as in the weight-relapse period,[16–19] have been investigated but a consensus regarding weight-regain has yet to be reached.[16,17,20–22]

Very-low-calorie diets (VLCDs) are being used with increasing frequency as the treatment-of-choice for the seriously obese patient.[23] These diets have induced considerable weight reductions in short time-periods but the long-term maintenance of these achievements is questionable.[24] In the patho-physiology of obesity during VLCD treatment, factors such as metabolic rate and its components, body composition, hormonal status as well as fuel utilisation have been investigated.[25,26] However, the relationships between the biological characteristics of obese subjects and their ability to maintain the weight-loss achieved during the VLCD period have not been adequately addressed.

In a preliminary study of eight morbidly obese patients[27] we had observed that the fasting RQ measured on day 28 of a VLCD correlated with the individual's subsequent weight loss. The aim of the present study was to extend these findings to a larger patient group and for a longer period of follow-up, to identify those factors that could be prognostic of weight-regain subsequent to weight-loss on a VLCD regimen.

Methods

Subjects

The patients (35 females and one male) were recruited from among those attending the obesity clinic at the Hospital Sant Joan de Reus. Of these, 17 have been previously reported with respect to the energy adaptation, weight loss and RQ observations.[14,27] The subjects aged 37.2 ± 1.87 (range: 18–58 y) had morbid obesity (Body mass index (BMI) $\geq 35\ kg/m^2$) without diabetes mellitus, impaired glucose tolerance assessed by the oral glucose tolerance test,[28] bulimia nervosa,[29]

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and without primary or secondary metabolic disease. Four of the female patients were post-menopausal and the rest were menstruating regularly prior to and during hospitalisation. All were moderately sedentary and were not under any physical fitness training program. Table 1 summarises the physical characteristics of the study subjects. While attending the outpatient clinic all of them were prescribed a moderately hypocaloric, balanced diet (15% of energy as protein, 30% as fat and 55% as carbohydrate) as part of their weight-reduction program. Nevertheless, during the three monthly visits prior to recruitment into the study, no weight loss had been recorded and body weight had remained stable (±0.5 kg) which suggested an equilibrium in energy balance. The study protocol was approved by the Ethics Committee of the Hospital and each subject gave voluntary, fully-informed, written consent prior to participation in the study.

Study design

The subjects were checked-in in the afternoon of day 0 and hospitalised for 28 d during which they were prescribed a VLCD. On day 1 (before VLCD administration) and day 28, $\dot{V}O_2$ and $\dot{V}CO_2$ were measured under fasting conditions. Body composition by hydrostatic weighing was assessed on day 1 of hospitalisation. At the conclusion of the VLCD period, a balanced diet containing approximately the caloric equivalent of Resting Energy Expenditure (REE) assessed on day 28 was prescribed for sustained weight loss and the patients' weights were recorded at follow-up of 3, 6 and 12 months.

Weight-reduction diet

The liquid formula VLCD preparation (Modifast®, Wander SA, Bern, Switzerland) of 1915 kJ/d (458 Kcal/d) contained approximately 52 g protein, 46 g carbohydrate, 6.5 g fat (46 : 41:13 percent total energy, respectively) as well as electrolytes, trace elements and vitamins according to the Recommended Dietary Allowances.[30] Dietary compliance was assessed by measuring urinary ketone bodies three times a day The diet was provided in three iso-caloric aliquots (breakfast, lunch and dinner) on each of the 28 days of the study. Daily non-caloric fluid intake was > 2 L.

Pattern of physical activity

During hospitalisation, subjects followed a daily 60 min physical activity program consisting of walking on a treadmill and cycling on an ergometer. This moderate exercise was controlled with respect to duration and intensity by a physiotherapist. For the rest of the day the patients were allowed to continue with their sedentary activities such as reading or watching television. The physical activity program was stopped at least 48 h before the Energy Expenditure (EE) measurements performed on day 28 of VLCD.

Energy expenditure measurements

At 08.00 h after a 12 h overnight fast, $\dot{V}O_2$ and $\dot{V}CO_2$ were measured continuously for 60 min under basal conditions (at days 1 and 28 of hospitalisation) using open-circuit indirect calorimetry (Deltratrac®, Datex, Helsinki, Finland) which includes a differential paramagnetic O_2 sensor and an infrared CO_2 analyser. Exhaled air was collected using a canopy. REE was calculated from the last 30 min period of measurement using Weir's equation.[31] RQ is defined as the quotient of CO_2 production and O_2 consumption ($\dot{V}CO_2/\dot{V}O_2$).

From our previous studies it was noted that before each test, O_2 and CO_2 sensors needed to be calibrated using gas mixtures of precisely known O_2 and CO_2 concentrations. The precision of the RQ needed to be periodically assessed (approximately every two months) by the ethanol combustion test[32] as recommended by the manufacturers and when the RQ of ethanol did not correspond to the predicted value of 0.66 ± 0.02, the equipment needed to be overhauled, if necessary, by the manufacturers. Deltratrac flow was also assessed periodically by the combustion of 5 ml of ethanol and, if the resultant VCO_2 was not within the expected value of 3801 mL, the new flow was adjusted. The mean errors of RQ and flow determinations in our laboratory were $1 \pm 0.8\%$ ($n = 10$) and $1.71 \pm 1.5\%$ ($n = 4$) respectively. The within-individual mean standard deviation for day-to-day replicate measurements of REE in our laboratory, is 164 kJ which corresponds to a coefficient of variation of analysis of 2.3%.

Body Composition Measurements

Height was measured to the nearest 1 mm using a wall-mounted stadiometer (Holtain, Crosswell, Wales, UK). Weight was measured daily during hospitalisa-

Table 1 Physical characteristics of subjects on admission to hospital

	Mean ± s.e.m.	Minimum	Maximum
Age (y)	37.3 ± 1.9	18	58
Height (cm)	161.1 ± 0.9	147.8	177.7
Initial weight (kg)	114.6 ± 2.6	85.3	158.2
BMI (kg/m^2)	44.0 ± 1.0	35.0	61.8
Waist : Hip ratio	0.87 ± 0.001	0.75	0.99
Body fat (%)[1]	45.7 ± 0.9	25.9	60.7
FFM (kg)[1]	56.9 ± 1.4	43.5	79.1

[1]Assessed by hydrodensitometry analysis.
$n = 36$ (includes 17 subjects from Refs. 14 and 27).

tion before breakfast with the subjects lightly dressed and the weight of the clothes they had been wearing was subsequently subtracted. Body weights were recorded after discharge from hospital at 3, 6 and 12 months. Changes in body weight during the follow-up were expressed in kg. Whole body density was measured on day 1 using an hydrostatic weighing system as described previously.[14] Body fat was calculated from the equation of Siri,[33] assuming the density of fat to be 0.9 kg/L and the density of lean tissue to be 1.1 kg/L.

$$\%\mathrm{Fat} = [(4.95/\mathrm{d}) - 4.50] \times 100$$

A value for Fat-Free Mass (FFM) was obtained by subtracting fat mass from total body weight in air.

Moderately hypocaloric follow-up diet

After the VLCD period and just before discharge from hospital, the subjects were instructed by a dietitian to follow a balanced diet (15% of energy as protein, 30% as fat, and 55% as carbohydrate) based on food-item exchange. The energy content of the diet was equal to the individual's REE measured on day 28 so as to facilitate a sustained weight-loss.

Statistical analyses

All results are expressed as mean ± s.e.m. Paired data were analysed by the Student paired *t*-test. Regression analyses were performed for quantitative variables and regression coefficients (r) were derived. Statistical significance was set at $P < 0.05$.

A stepwise multiple regression analysis was performed to identify the factors affecting changes in body weight and resting energy expenditure during VLCD. Age, initial body weight, REE at day 1, respiratory quotient at days 1 (RQ_1) and 28 (RQ_{28}), BMI and FFM were entered as independent variables. These same factors were entered into the equations analysing the follow-up weight changes. Only the RQ_{28} correlated significantly with subsequent weight changes. The unexplained residual of the RQ in each individual was calculated by the general linear model procedure using the body weight change during VLCD as covariant. The adjusted respiratory quotient for each individual was calculated by adding the individuals residual respiratory quotient to the mean RQ of the whole group. *A posteriori* 3 groups were defined by tertile of RQ_{28} (Group A: $RQ_{28} < 0.72$, $n = 12$; Group B: RQ_{28} 0.72–0.75, $n = 12$ and Group C: $RQ_{28} > 0.75$, $n = 12$), and weight regain at follow-up of 3, 6 and 12 months was compared between groups by one-way analysis of variance (ANOVA).

Results

Body weight and resting energy expenditure during VLCD

A significant reduction in total body weight on the VLCD was observed in all subjects. Body weight was 114.6 ± 2.63 and 104.7 ± 2.48 kg on days 1 and 28 of hospitalisation ($P < 0.001$). In multiple linear regression analysis, initial REE and age together explained 49% of the observed variance in VLCD body weight changes ($P < 0.001$). As expected, the amount of body weight lost during VLCD correlated positively with initial REE ($r = 0.65$, $P < 0.001$) even when adjusted for FFM ($r = 0.55$; $P < 0.005$) and negatively with age ($r = -0.51$, $P = 0.001$). There was no relationship between body weight changes during VLCD and initial body weight, maximal lifetime weight, percentage body fat or FFM.

REE decreased significantly from 7933 ± 180 kJ/d (day 1) to 7043 ± 172 kJ/d (day 28) during rapid weight loss ($P < 0.001$). A significant reduction of REE was observed between days 1 and 28 ($P < 0.001$) when REE was adjusted for body weight. Initial REE was 140.4 ± 2.6 kJ/kg of FFM. No significant correlation was found between REE change and initial weight, body composition, maximal lifetime weight, initial REE nor RQ_1.

Determinants of resting respiratory quotient

RQ decreased significantly during hospitalisation (0.766 ± 0.005 at day 1 and 0.737 ± 0.005 at day 28; $P < 0.001$). Significant relationships were observed between resting RQ_1 and the initial weight ($r = -0.43$; $P = 0.009$), and BMI ($r = -0.37$; $P = 0.025$) and maximal lifetime weight ($r = -0.46$; $P = 0.005$).

Among all the body composition as well as the energy expenditure parameters measured at the beginning and at the end of the VLCD, only the changes in body-weight during the hospitalisation period correlated significantly with RQ_{28} ($r = -0.38$; $P = 0.02$). Since changes in body weight explained 14% of the observed variance in RQ_{28}, the RQ measured at the end of the VLCD was adjusted for this variable.

A significant relationship ($r = -0.37$; $P = 0.03$) was observed between maximal lifetime weight and the unadjusted resting RQ_{28}. This relationship ceased when RQ_{28} was adjusted for body weight changes during VLCD. No significant relationship was observed between body composition and energy expenditure parameters and the adjusted RQ_{28}.

Resting respiratory quotient as prognostic factor of weight-loss rebound

The follow-up weights were available in 36, 33 and 28 individuals at 3, 6 and 12 months, respectively. Significant relationships between unadjusted and adjusted RQ_{28} and weight evolution were observed. By simple correlation analysis, the unadjusted RQ_{28} correlated with the body weight changes (in kg) at 3 ($r = 0.51$; $P = 0.002$; slope = 65.0 ± 19.0), 6 ($r = 0.50$; $P = 0.003$; slope = 107.5 ± 33.7) and 12 months ($r = 0.44$; $P = 0.019$; slope = 139.6 ± 55.7) of follow-up (Figure 1).

No significant relationship was observed between body weight changes during follow-up and the fol-

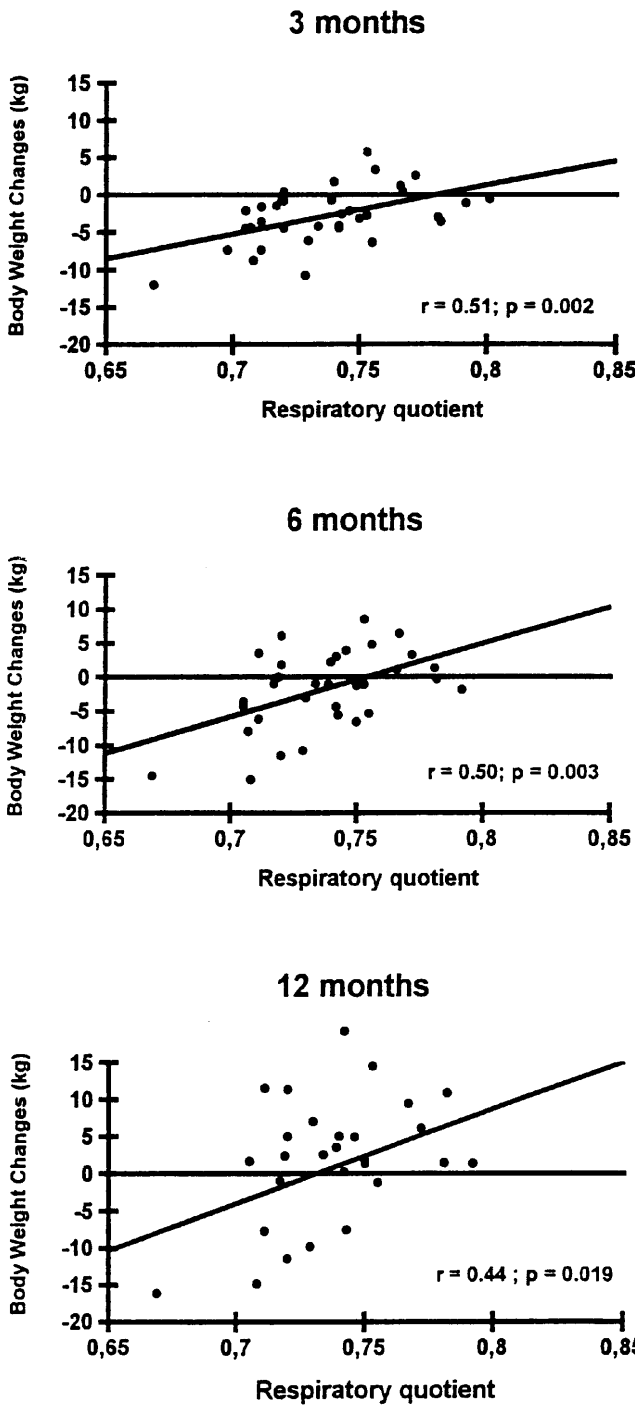

Figure 1 Correlation coefficients (r) between respiratory quotient and weight-change (kg) on follow-up. The figure represents the relationship observed between resting RQ measured on the day of discharge after 28 d of hospitalisation and weight changes noted at follow-up of 3, 6 and 12 months.

lowing variables: initial REE, RQ_1, initial weight, body composition, body-weight changes during VLCD, maximal lifetime weight, changes in REE and changes in RQ during hospitalisation. Using multiple linear regression, the RQ_{28}, even when adjusted for weight loss during VLCD, was an independent predictor of subsequent body weight changes ($r = 0.53$, $P = 0.001$; $r = 0.49$, $P = 0.004$; $r = 0.44$, $P = 0.002$ at 3, 6 and 12 months, respectively).

Figure 2 shows differences in body weight changes during the follow-up based on groups defined by tertiles of RQ_{28}. Significant differences between groups were observed at 3 months ($P = 0.014$), 6 months ($P = 0.008$) and 12 months ($P = 0.037$).

Discussion

That a reduced metabolic rate precedes the obese state and contributes to weight gain has been proposed following the findings of longitudinal studies conducted in Pima Indians[2] and in infants born to overweight mothers.[1] Mitigating against this would be the observation, in the present study, of no significant association between a low initial resting energy expenditure adjusted for age and body composition and weight-regain subsequent to weight-loss. An explanation of this could be that the original indicator (reduced metabolic rate) of probable weight gain is not apparent when the state of obesity is reached.[7]

In the present study, no relationship was observed between changes in REE over the 28 d period of energy restriction in relation to the subsequent weight-change in follow-up. It has been suggested, however, that obese patients on VLCD show an energy-metabolism adaptation during the diet by reducing the energy expended for life maintenance systems[14] and, in view of this adaptation, the medium- to long-term efficacy of VLCDs would be diminished. No confirmation of this adaptive mechanism could be drawn from the present study since measurements of FFM at day 28 were not available for the calculation of an adjusted REE. However, in the study of Weinsier *et al*[20] in which these measurements were available, no relationship between the diminution of the adjusted REE and subsequent weight-change was apparent.

From among all the variables considered, the RQ measured at the end of the VLCD was the only one that correlated significantly with weight changes during the follow-up. We had observed this phenomenon in a previous group of eight patients who were being investigated for their energy metabolism adaptability on re-feeding post-VLCD.[27] In order to verify this finding in a broader sample of study subjects, we included, in the present analyses, data on the subjects from references 14 and 27. The variance associated with this parameter was significantly reduced between the start and end of the controlled-diet period partly because after a 12 h fast and particularly following protracted conditions of severe and sustained energy restriction, dietary composition is no longer a contributory factor in the RQ.

Other variables identified as having an influence on RQ that may affect the interpretation of the present findings are insulin resistance,[4] the degree of adiposity[11] and energy-balance.[13] Although the degree of

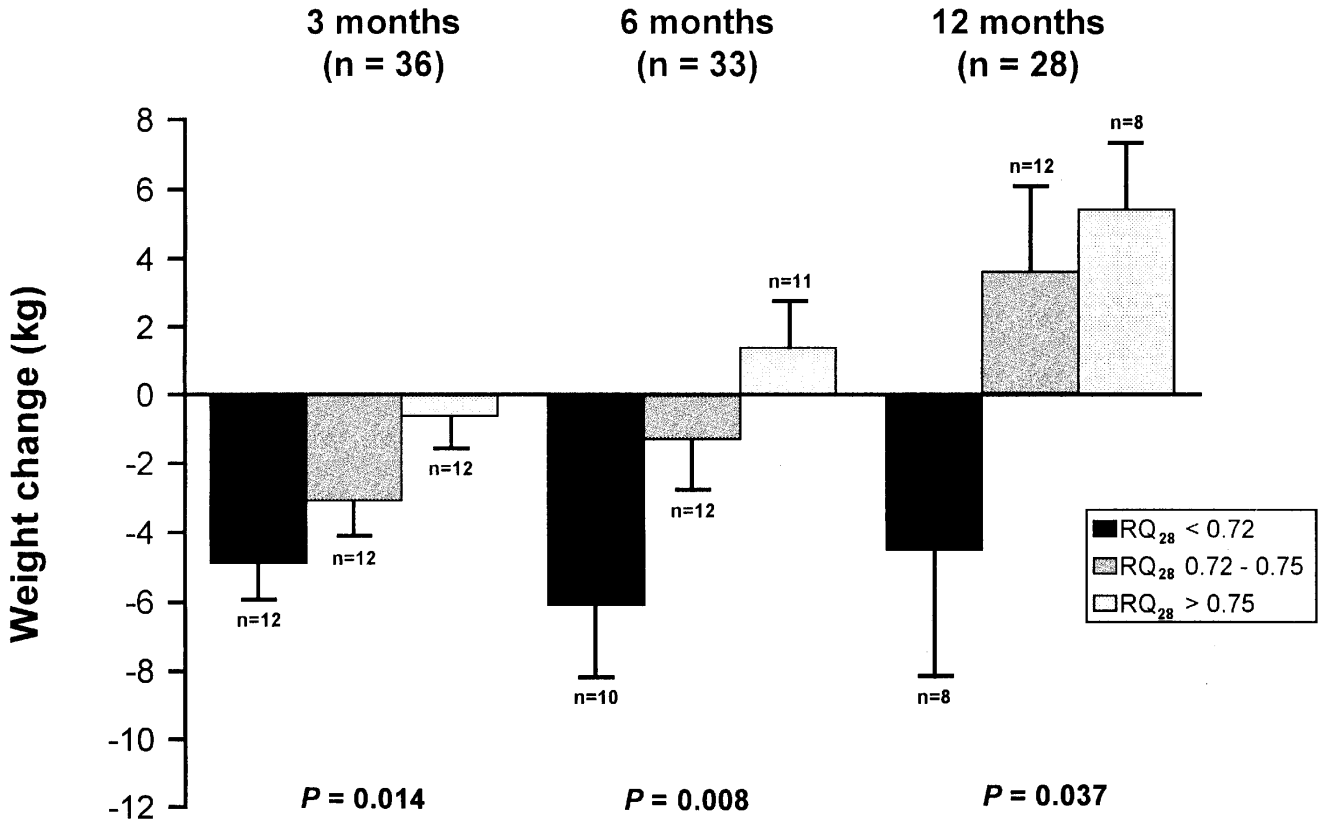

Figure 2 Weight changes (kg) at follow-up of 3, 6 and 12 months from the end of VLCD period. The subjects were defined on the tertile of respiratory quotient measured on day 28 of hospitalisation (RQ_{28}). Statistical comparisons between groups were by one-way analysis of variance (ANOVA). Bars represent the mean ± s.e.m.

insulin resistance was not quantified, none of the subjects studied had presented with an impaired glucose tolerance (as assessed under WHO recommendations).[28] Similarly, studies comparing obese individuals with control subjects indicate that the former have a lower RQ[11] as a result of an increased fat utilisation so as to favour weight stability. Although a previous expansion in fat stores appears to be a prerequisite for these differences in fuel utilisation to become apparent,[4] no experimental data are available to support a causal relationship between body fat mass and preferential fat oxidation.[16] In the present study, no correlation was found between body fat mass and RQ_{28} which could be because the subjects were a relatively homogeneous group of morbidly obese individuals and, as such, represent one extreme of the fat mass distribution curve. The range of fat mass in this group being limited, the contribution of the degree of adiposity to the variance in RQ would be obscured.

The third and probably the critical contributory factor, that of energy balance, needs to be considered. Energy balance is directly involved in fuel accessibility and, since all of the patients in the study had not been subjected to the same caloric restriction in relation to their individual energy needs during the VLCD period, RQ_{28} had been adjusted for weight-loss to preclude it being a confounding factor in the statistical analysis. At the time of the RQ_{28} measurement, after 28 d on VLCD and a 12 h fast, glycogen stores are not likely to supply a significant percentage of the energy requirement. Hence, the observed inter-individual variation in the adjusted RQ_{28} must be an expression of differences in the ratio of oxidation of protein to fat; subjects who showed an RQ_{28} in the lower range being able to access a greater percentage of energy from lipids under conditions of caloric restriction.

At the beginning of the study, the body weights of our patients were very close to their 'life-time maximal weight' and, having remained stable for the previous 3 months, would suggest that they had reached the point at which the fuel mix oxidation matches nutrient intake. The cost of this equilibrium, however, would be a supranormal expansion of body fat stores. As has been observed in post-obese women,[17] dietary intervention and weight loss cause a displacement from this steady-state towards a decrease in the percentage of fat-derived oxidation and, consequently, in the ability to adjust their macronutrient oxidation when on a high-fat diet. The result is an increased susceptibility to fat storage and weight gain when food availability is unrestricted.

Previous studies have reported a genetic heritability of RQ[4,34] which could be partially mediated by the degree of skeletal muscle activity of certain enzymes

involved in the β-oxidation of fatty acids. Cross-sectional studies demonstrated that the 24 h RQ correlated negatively with skeletal muscle lipoprotein lipase,[35] β-hydroxyacyl-CoA dehydrogenase, adenylokinase and creatine kinase activities.[36] Whether the preferential pattern of fuel utilisation by an individual is determined by skeletal muscle enzyme activity or by substrate availability is, as yet, unknown—although the size of body fat stores and insulin sensitivity/resistance are known to modulate circulating free fatty acid concentrations and are independent factors predicting percentage fat oxidation.[4,6] Also, physical exercise promotes lipid oxidation and physical training could have an effect on the lipolytic enzyme activities in skeletal muscle. However, the cause-effect sequence of the above observations have not been fully established and, similarly, the relative contributions of genetic and environmental factors to the process have not been quantified.

Hence, from the current body of knowledge, fasting RQ_{28} could partially explain the observed differences in body weight changes after VLCD through three possible mechanisms: (a) patients with higher lipolytic-enzyme activity could be better able to increase fat oxidation in response to a high-fat diet and, thus, limiting the amount of fat storage and weight gain; (b) an increased rate of carbohydrate/fat oxidation may cause a greater and/or faster post-prandial decrease in glycogen stores resulting in a suppression of satiety, an increase in appetite and an increase in food intake;[37] and (c) a higher RQ could reflect a deviation away from the steady-state in which the subject is able to maintain body weight and body composition; the amount of fat stores at which this steady-state is achieved, however, being considerably different between individuals. To verify these hypotheses, further investigations would need to be conducted with a larger number of subjects and to include 24 h RQ measurements to assess fuel utilisation in the course of a whole day so that the mechanisms involved in fasting as well as medium-term starvation RQ may be elucidated.

Conclusion

In summary, subjects with a higher resting RQ (> 0.75) at the end of the VLCD showed an increased risk of weight-loss rebound in the following year while those with a lower RQ (< 0.72) were able to maintain their weight-loss. Since resting RQ can be relatively easily and quickly determined, this parameter, when accurately measured, could be useful in routine clinical practice. For example, to identify those obese patients who would require closer monitoring and, possibly, additional therapeutic assistance to reinforce the long-term effectiveness of low- and very-low-calorie diets in the continued maintenance of weight-loss.

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