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Post-Exercise Changes of Beta Hydroxybutyrate as a Predictor of Weight Changes

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Summary

The aim was to find the differences in ketogenesis initiation in the early period after the exercise in obese patients and to find if these changes may predict the weight loss during the physical activity program. 96 females were enrolled. A clamped heart rate test (CHR) was performed to establish comparable exercise intensity. Blood samples for beta hydroxybutyrate (BOHB) assessment were collected prior, immediately after and 60 min after the test. Patients underwent a three month fitness program. Anthropometric measurements (fat mass and biochemical parameters) were measured. An energy intake was monitored and comparable in all subjects. A significant increase of BOHB was found in 60th minute after the test, when compared with initiation levels (BOHB1 vs. BOHB3; $p=0.03$). This increase correlates with % fat mass ($R=0.196$; $p=0.02$) and negatively with age ($R= -0.147$; $p=0.05$) and with weight reduction during the three-month program ($R= -0.299$; $p=0.03$). Serum BOHB increase after the single exercise may detect individuals with an ability to induce lipolysis in three-month program of physical activity for obese patients.

Key words

Obesity • Physical activity • Beta hydroxybutyrate • Fat mass • Weight reduction

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Introduction

The ability to predict weight and fat mass reduction is a major assumption for successful clinical weight loss programs. It is well known that effect of single exercise remains only for a certain period. This period is shorter particularly in patients with insulin resistance and diabetes that in non-diabetic population (Holloszy and Coyle 1984). The exercise may induce frequent epigenetic changes that may be associated with metabolic changes, including metabolism of BOHB (Pareja-Galeano *et al.* 2014). For successful weight reduction it is necessary to establish a negative energy balance. Only dietary restriction may result quite quickly in adaptation for low energy intake. Therefore weight loss slows down and the therapy from long-term period has been considered to be unsuccessful. For long-term successful therapy effect the physical activity with low or moderate intensity seems to be essential. Any physical activity stimulates utilization of carbohydrates and fats and fatty acids (Stranska *et al.* 2011). The lower physical activity intensity is the higher proportion of fatty acids has been utilized as a source of energy for muscle activity. Physical activity has many other benefits. Besides the positive effect on weight reduction it also affects many other metabolic processes. One of the most significant results is lowering of postprandial lipemia (Koutsari and Hardman 2001).

There are differences in ability to utilize fatty acids as an energy source in resting condition and during the exercise as well (Goodpaster *et al.* 2001). Physically

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more fit individuals have higher amounts of carnitine in their muscles. It facilitates fatty acids transfer through mitochondria membrane with their subsequent oxidation. Serum level of beta hydroxybutyrate (BOHB) was chosen as a marker of fatty acid utilization (Laffel 1999). We have a good experience using this marker for short-time period starvation tests: we have confirmed an individual increase of ketogenesis in patients with metabolic syndrome (Svacina *et al.* 1999, Haluzik *et al.* 2001). We placed a hypothesis whether there are potential differences in ketogenesis initiation during the physical activity in obese patients in the early period after the exercise and to find if these changes may predict the effect of intermediate lasting program of the physical activity. We wanted to find out whether any short-time exercise effect may be related to the effectiveness of long-time period exercise program evaluated by weight reduction in relationship to the short-time period BOHB changes.

Patients and Methods

96 patients from Obesity Center of the Third Internal medicine Clinic First Medical School in Prague was enrolled into the project with physical activity. Initial examination included anthropometric examination blood glucose, HbA_{1c}, insulin, C-peptide, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides (Table 1). Out of 96 patients enrolled into this project only 62 patients were evaluated and their data were used for statistical analysis (median age 46.5±10.9 years, initial BMI 35.2±6.16 kg/m^2, median % fat mass (FM) 36.11±7.16 %.). All of them reached at least 85 % compliance with physical activity and energy intake monitoring. These patients´ compliance to the project protocol reached at least 85 %. Detailed descriptive statistics can be found in Table 1. The reason for exclusion from this project was no compliance with physical activity protocol.

Table 1. Changes of anthropometric and metabolic parameters during 3 months reduction program (p-paired Wilcoxon-test).

Parameter	N	Month 0 ± SD	Month 3 ± SD	p value
Age (years)	62	46.5 ± 10.9		
Weight (kg)	62	100.73 ± 18.67	96.9 ± 18.6	0.001
BMI (kg/m^2)	62	35.2 ± 6.16	34.1 ± 6.21	0.001
Waist circumference (cm)	62	108.42 ± 14.88	104.62 ± 14.31	0.004
Fat mass (%)	62	36.11 ± 7.16	33.83 ± 7.23	0.001
VO_2max/kg (ml/kg/min)	62	25.05 ± 4.73	28.59 ±6.79	0.001
glucose (mmo/l)	62	5.14 ± 0.96	5.005 ± 0.731	n.s.
HBA_1c (%)	62	3.91 ± 0.65	3.88 ± 0.531	n.s.
C peptide (pmol/l)	62	0.98 ± 0.35	0.91 ± 0.39	0.04
Insulin – IRI (IU/l)	62	12.36 ± 7.4	12.08 ± 9.1	n.s.
Cholesterol (mmo/l)	62	5.11 ± 0.98	5.0 ± 0.99	n.s.
HDL cholesterol (mmo/l)	62	1.29 ± 0.33	1.34 ± 1.31	0.05
LDL cholesterol (mmo/l)	62	3.16 ± 0.75	3.04 ± 0.76	n.s.
Triglycerides (mmo/l)	62	1.425 ± 0.78	1.24 ± 0.64	0.004
CRP (mmo/l)	62	6.82 ± 7.32	4.71 ± 5.62	0.03

Month 0 ± SD – before three month program ± standard deviation. Month 3 ± SD – after three month program ± standard deviation.

In order to establish training exercise activity intensity a series of examination including spiroergometry and 30-min clamped heart rate test (CHR test) was performed. Spiroergometry examination was performed until subjective maximum was reached using VO_2peak measurement and maximal heart rate. After that a 30-min CHR test was performed at a 65 % level of maximal heart rate reserve. This test enables to establish a proper intensity of an exercise adjusted to the heart rate. A constant heart rate has been maintained by changing the intensity level of exercise. Based on the number and range of the changes of the exercise intensity an optimal heart rate for future training has been proposed. Blood samples for BOHB assessment were collected prior the test, immediately after the test and 60 min resting after the test termination. This test was followed by three month program managed by well experienced fitness coaches using heart rate monitoring sport-tester POLAR S810i with minimum of two training lessons under the supervision and at least one lesson at home. Weight loss at the end of the three-month program was evaluated in relationship to the BOHB changes in CHR test.

Several parameters were evaluated prior and after the three-month program (Table 1). Anthropometric measurements included % FM measured using bodystat. An energy intake was carefully monitored during the whole three-month program in order to rule out a significant energy restriction that might affect the results.

Statistics

SW Sigmastat version 3.5 was used for statistical evaluation. After testing of normality the values were compared using non-parametric paired Wilcoxon test (values prior and after the CHR test, values prior and after the program). Spearman´s correlation coefficients were calculated for serum BOHB changes and weight changes.

Results

BOHB serum level has not increased significantly from basal – BOHB1 0.131±0.177 vs. post 30-min test – BOHB2 0.124±0.149 (Table 2 and Fig. 1). But a significant increase was found in 60th minute after the CHR test termination – BOHB3 0.296±0.375 when compared with initiation levels (BOHB1 vs. BOHB3; p=0.03) (Table 4) and even when compared with the levels immediately after the CHR test termination (BOHB2 vs. BOHB3; p=0.02) (Table 3). This increase (BOHB1 vs. BOHB3) correlates negatively with age (R= −0.147; p=0.05 and % FM (R= −0.196; p=0.02) and with weight reduction during the 3-month program (R= −0.299; p=0.03) (Fig. 2). The whole group of patients was characterized by an expected increase of VO_2peak from 25.05±4.73 to 28.59±6.79 ml/kg/min (p=0.001). This finding has confirmed the high compliance rate with physical activity and with the study protocol. Weight reduction during the program correlates with BOHB increase 60 min after the CHR test (Fig. 2). Serum BOHB increase correlates with age and confirms lower ability to induce ketogenesis using exercise in older individuals. It is easier to induce ketogenesis in lower weight individuals with lower waist circumference, lower fat mass percentage and lower serum level of triglycerides.

Table 2. Beta hydroxybutyrate basal BOHB1 and its changes at the end of 30-min CHR test (BOHB2) and 60 min after recovery (BOHB3) (90 min from the beginning).

	N	START BOHB1	30 min BOHB2	90 min BOHB3
BOHB (mmol/l)	62	0.131±0.177	0.124±0.149	0.296±0.375

Table 3. Beta hydropxybutyrate differences between the end of the CHR test and 60 min recovery (non-parametric pair Wilcoxon´s test).

	n	Mean ± SD	p value
DIFBOHB1-2	62	0.00231± 0.078	n.s.
DIFBOHB1-3	62	0.16 ± 0.305	0,03
DIFBOHB 2-3	62	0.17 ± 0.294	0.02

Table 4. Correlation of the BOHB difference 0-90 min (BOHB1-3) and some parameters of metabolic syndrome (Spearman´s rank correlation).

	r	p value
Age (years)	-0.147	0.05
Weight (kg)	-0.21	0.01
Waist circumference (cm)	-0.206	0.01
Fat mass (%)	-0.196	0.02
Cholesterol (mmol/l)	-0.132	n.s.
Triglycerides (mmol/l)	-0.234	0.001
HDL-cholesterol (mmol/l)	0.23	n.s.

Discussion

It is well known that there are differences between the ability to utilize fat acids (so called fast and slow fat burners) (Goodpaster *et al.* 2001). It can be determined by predisposition of low physical fitness status. Among obese population there are differences in ability for ketogenesis induction by low energy diet

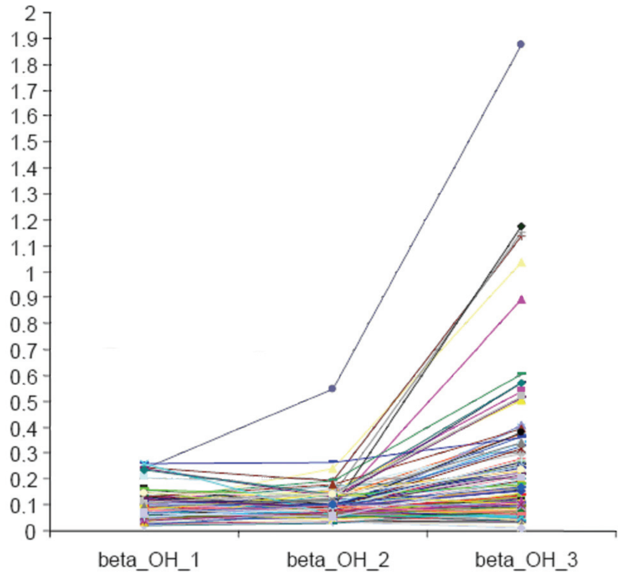

Fig. 1. BOHB changes between the end of the CHR test and 60 min recovery.

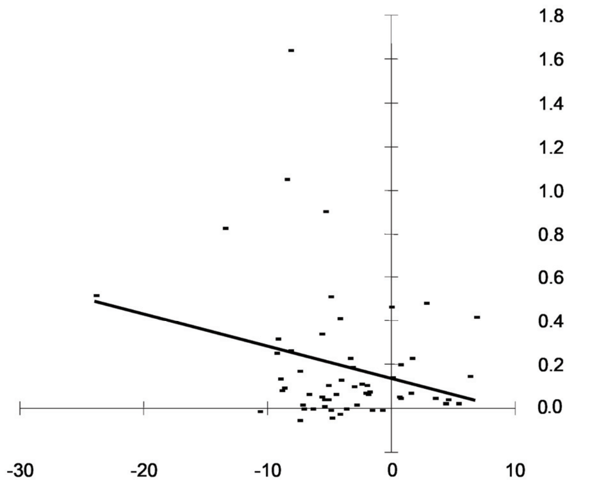

Fig. 2. Body weight changes in relationship to the BOHB3-1 serum level changes prior the test and at 90th minute of the test (Spearman´s correlation) (axis Y BOHB 3-1 in mmol/l, axis X weight change in kg).

(El Midaoui *et al.* 1996) and it seems that there are also differences in ketogenesis induction by effect of physical activity – during this activity and particularly after the activity. Exercise effect and increased energy output persists even several hours after the exercise termination. There are differences among lean individuals, patients with insulin resistance and diabetic patients (Storer *et al.* 2011). We have confirmed that BOHB serum levels increase may predict the effect of physical activity on the successful weight reduction. Physical activity prescription should be modified based on these results. Some studies confirm that exercise twice a day for shorter period is at least same effective as an exercise performed once day for a double time period (Snowling and Hopkins 2006). But it seems that for clinical use it is better to recommend an exercise with lower frequency. It provides a higher compliance of the patients. But if BOHB production decreases rapidly and does not increase accordingly within 60 min it is recommended to use low energy diet together with shorter exercise several times per day. Lower increase of ketogenesis in older patients is in accordance to our hypothesis confirming that there is a lower ability for weight reduction in older individuals. BOHB serum level increase negatively correlates with serum levels of triglycerides (R= −0.24; p=0.01), % FM (R= −0.196; p=0.02).

BOHB has not been currently every frequently used parameter. Point-of-care testing instruments for BOHB measurement are used for the early detection of diabetic ketoacidosis in pregnant females and in children. This parameter has not been currently used in obese population. Its measurement is very simple and useful: the individuals may differ in BOHB production and the production may be very simply monitored for example from breath (Storer *et al.* 2011, Samudrala *et al.* 2014).

The problems of BOHB have not been frequently studied in the experimental studies on the animals. But it was found that chronic increase of exercise may cause a better degradation of BOHB in the muscle mitochondria (El Midaoui *et al.* 1996). Recently fibroblast growth factor 21 has been considered as a significant indicator of lipolysis. But no relationship to ketogenesis was found in the experimental studies (Hotta *et al.* 2009).

Based on recent studies results ketogenic diets may result in moderate BOHB serum level increase and in higher weight reduction (Sumithran *et al.* 2013). Our data suggest that BOHB serum levels increase can be used as a predictive factor of weight reduction with physical activity. Sumithran suggests that elevated BOHB may also induce the weight reduction, therefore it could also be considered to be a pathogenetic factor inducing successful weight reduction.

Conclusion

BOHB serum levels increase within 60 min after the CHR test seems to be a useful predictive factor for weight reduction in obese patients for physical activity program. Its assessment may represent a beneficial parameter for optimal proposal of the physical activity programs for weight reduction in obese.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

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