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Increased postabsorptive and exercise-induced whole-body glucose production in patients with chronic obstructive pulmonary disease

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ABSTRACT

Skeletal muscle biopsy studies have consistently shown a decreased oxidative phenotype in patients with moderate to severe chronic obstructive pulmonary disease (COPD). Limited information is available regarding potential adaptations or abnormalities in anaerobic metabolism and glucose homeostasis. Whole-body glucose production was assessed at rest and during exercise in COPD patients with moderate disease severity (forced expiratory volume in 1 second, 52% ± 3%), prestratified into normal-weight (n = 7; body mass index [BMI], 27.5 ± 0.9 $kg{\cdot}m^{-2}$) and underweight subjects (n = 6; BMI, 20.6 ± 0.7 $kg{\cdot}m^{-2}$), and in 8 healthy controls matched for age and BMI with the normal-weight COPD group. Glucose tolerance was normal in all subjects. Rate of appearance (R_a) of glucose at rest and during submaximal cycling exercise was measured in postabsorptive state by infusion of stable isotope tracer [6,6-$^2H_2$]glucose. Resting glucose R_a was significantly enhanced in underweight COPD patients compared with controls (16.7 ± 0.3 vs 15.1 ± 0.4 $\mu mol{\cdot}kg$ fat-free $mass^{-1}{\cdot}min^{-1}$, $P < .05$) and was inversely related to fat-free mass ($r = -0.75$, $P < .01$). Furthermore, the exercise-induced increase in glucose R_a was enhanced in COPD patients (81.9% ± 3.4% vs 72.1% ± 2.0%, $P = .05$), resulting in elevated end-of-exercise glucose output. Differences were most pronounced in underweight patients, who were also characterized by enhanced plasma catecholamine levels and decreased insulin concentrations (all, $P < .05$). In normal-weight patients, there was evidence for decreased insulin sensitivity assessed by homeostatic modeling technique. Whole-body glucose production is increased in underweight COPD patients with normal glucose tolerance. It is hypothesized that lowered body weight in COPD has unique effects on glucose uptake despite reduced skeletal muscle oxidative capacity, relative hypoxemia, and sympathetic activation.

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Author contributions: FMEF designed and conducted the study, collected the data, performed the statistical analyses, and wrote the manuscript. HPS helped with the protocol and reviewed the results and preliminary versions of the manuscript. EPAR helped in the study conduction. The laboratory of MTA performed the sample analyses. EFMW was involved as promotor of the thesis of FMEF and reviewed the manuscript. AMWJS was the study supervisor and was involved in study design, discussion of results, and manuscript preparation.

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1. Introduction

Deficiencies in metabolic pathways involved in muscle substrate utilization and energy homeostasis have been consistently reported in skeletal muscle biopsies of patients with chronic obstructive pulmonary disease (COPD) [1]. Reduced skeletal muscle fat oxidative capacity, abnormal mitochondrial function being most pronounced in underweight patients [2], and greater dependence on anaerobic metabolism have been shown [3]. Potential implications for whole-body substrate metabolism and especially glucose homeostasis are yet unknown. Theoretically, COPD patients are at risk for disturbances in intermediary glucose metabolism because hypoxemia [4], loss of lean body mass [5], neurohumoral activation [6], a proinflammatory state [7], and respiratory medication are known to influence glucose metabolism in vivo. Clinical implications of altered glucose homeostasis, that is, insulin sensitivity, are among others the well-established increased cardiovascular risk in COPD [8].

In this study, glucose metabolism, measured by whole-body glucose production and plasma levels of hormones involved in glucose homeostasis, was assessed in COPD patients and healthy age-matched controls. Because disturbances in intermediary metabolism might contribute to changes in body composition in COPD (ie, ratio of fat vs fat-free mass [FFM]) and body composition itself is a determinant of glucose output, potential alterations in glucose metabolism were studied in both normal-weight as well as underweight COPD patients. Submaximal bicycle exercise was used as a stimulus to endogenous glucose production to augment potential small disturbances at rest.

2. Methods

2.1. Study population

Patients were recruited at the outpatient department for respiratory disease of Maastricht University Medical Centre+, whereas the control group was recruited from an advertisement in a local newspaper. All subjects were men. Patients fulfilled the criteria for COPD according to American Thoracic Society guidelines [9]. An oral glucose challenge was performed in 16 COPD patients and 9 controls. Three patients and 1 control subject dropped out of the study because of abnormal values, as defined below. For subgroup analysis, the COPD group was divided into a group of 7 patients with a body mass index (BMI) comparable to the control group and a group of patients with similar degree of airflow obstruction but a significantly lower BMI. None of the patients exhibited *chronic respiratory insufficiency*, defined as P_aO_2 less than 7.3 kPa, or received supplemental oxygen therapy. Because the primary aim of the study was to investigate altered glucose metabolism as primary defect, subjects with a history of diabetes mellitus type 1 or 2, thyroid, or other endocrine disorders; recent weight loss; malignancies; clinically apparent heart failure; renal, hepatic, or other gastrointestinal disease; or recent surgery were excluded. Furthermore, none of the subjects used oral glucocorticosteroids as maintenance treatment or had respiratory tract infection or exacerbation within a 4-week period before the study. There were no differences in the use of pulmonary medications between COPD subgroups (see the *online* supplement for details). Written informed consent was obtained from all subjects, and the study was approved by the medical ethical committee of Maastricht University Medical Centre+.

2.2. Study design

The study was performed at the outpatient metabolic ward on 2 separate occasions. During the first visit, medical history was checked; and physical examination was performed by a physician. In addition, weight and body composition were measured and lung function and incremental exercise tests were carried out. Furthermore, to exclude subjects with abnormal glucose tolerance or diabetes mellitus, an oral glucose challenge was performed. See the *online* supplement for details on these measurements and for some basic principles of stable isotope tracer methodology. Eligible subjects subsequently participated in the glucose stable isotope tracer protocol, as described below.

2.3. Glucose stable isotope tracer protocol

After an overnight fast, subjects reported at the laboratory at 7:30 AM and were studied at rest in the supine position. A Teflon catheter was inserted into a forearm vein for isotope infusion, and a second catheter for sampling of arterialized venous blood was placed retrograde in a dorsal hand vein of the contralateral arm and maintained at 60°C in a thermoregulated box. At 8:00 AM, after taking a blood sample for background enrichment of plasma glucose, subjects were administered a single intravenous dose of [6,6-$^2H_2$]glucose (17.6 μmol·kg body weight [BW]$^{-1}$, >99% enriched; Cambridge Isotopes, Andover, MA) to prime the glucose pool. Thereafter (t = 0), a continuous infusion of [6,6-$^2H_2$]glucose (0.22 μmol·kg BW^{-1}·min^{-1}) dissolved in 0.9% saline was started via a calibrated pump (IVAC 560, San Diego, CA). Blood samples were taken at t = 110 and 120 minutes. The exact infusion rate in each experiment was determined by measuring the glucose concentration and enrichment in the infusate. At t = 120 minutes, COPD patients started to exercise on a cycle ergometer at 50% of peak workload (W_{max}) for 20 minutes, whereas controls exercised at an identical absolute workload (30 W = 50% of mean W_{max} in COPD patients) for the same duration. Blood samples were drawn at t = 125, 130, 135, and 140 minutes. The protocol continued with 1-hour recovery period, during which blood samples were taken at t = 155, 170, 185, and 200 minutes. Thereafter, controls performed a second 20-minute exercise test at 50% of their individual W_{max} to study potential alterations in glucose kinetics at identical relative submaximal workload. Blood samples were taken at t = 205, 210, 215, and 220 minutes during exercise and at t = 235, 250, 265, and 280 minutes during a second recovery period of 1 hour. Plasma levels of glucoregulatory hormones were determined at t = 110, 140, 200, 220, and

280 minutes. To minimize changes in substrate isotopic enrichment, infusion rate of glucose tracer was doubled (0.44 μmol·kg BW^{-1}·min^{-1}) during submaximal exercise [10]. During the study, subjects were allowed to drink water only.

2.4. Sample collection and analysis

During the glucose challenge, venous blood samples were collected in sodium fluoride–containing tubes and immediately placed on ice. Within 15 minutes, blood glucose was analyzed by the glucose oxidase method with a YSI 2300 STAT Plus analyzer (YSI, Yellow Springs, OH).

Blood samples (5 mL) for [6,6-$^2H_2$]glucose enrichment and glucose and glycerol concentrations were collected on heparin, immediately put on ice, and centrifuged at 4000 rpm at +4°C for 10 minutes. For determination of insulin and cortisol, 3 mL of arterialized venous blood was put into a coagulation tube, which was centrifuged for 10 minutes at 3000 rpm at room temperature. Serum was separated and centrifuged again for 5 minutes at 3000 rpm. An iced EDTA- and Trasylol-containing tube was used to collect blood for the measurements of glucagon. After mixing, plasma was separated from cells by centrifugation at 4000 rpm for 10 minutes at +4°C. Samples for catecholamines were collected in iced EDTA tubes, centrifuged at 4000 rpm for 10 minutes at +4°C, and stored in a glutathione-containing tube. All aliquots of plasma and serum were frozen immediately in liquid nitrogen, stored –80°C, and transported on dry ice before assay.

Plasma insulin concentrations were determined by a chemiluminescent immunometric assay and plasma cortisol concentrations were measured by a chemiluminescent immunoassay, both on an Immulite 2000 system (Diagnostic Products, Los Angeles, CA). Glucagon was determined by radioimmunoassay (125-I Glucagon RIA; LINCO Research, St Charles, MO). Serum free fatty acids (FFA) were measured by an enzymatic colorimetric method (NEFA C kit; Wako Chemicals, Neuss, Germany). Catecholamines were determined by an in-house reversed-phase high-performance liquid chromatography method with fluorescence detection.

2.5. Gas chromatography–mass spectrometry

[6,6-$^2H_2$]glucose enrichment and glucose and glycerol concentration were measured as described earlier [11,12]. Briefly, plasma samples were deproteinized with methanol. The aldonitrile pentaacetate derivative of glucose was injected into a gas chromatograph/mass spectrometer system (model 6890 gas chromatograph coupled to a model 5973 mass selective detector, equipped with an electron impact ionization mode; Hewlett-Packard, Palo Alto, CA). Separation was achieved on a J&W DB17 column (30 m × 0.25 mm; *df*, 0.25 μm; Agilent Technologies Nederland, Amstelveen, the Netherlands). Glucose concentrations were determined by gas chromatography using xylose as an internal standard. Glucose was monitored at mass-to-charge ratio 187, 188, and 189. The enrichment of [6,6-$^2H_2$]glucose was determined by dividing the peak area of mass-to-charge ratio 189 by the peak area of mass-to-charge ratio 187 and correcting for natural enrichments.

2.6. Calculations

The rate of appearance (R_a) of glucose at rest was calculated by dividing the infusion rate of [6,6-$^2H_2$]glucose by the resulting enrichment of plasma aldonitrile pentaacetate glucose. Glucose R_a is composed of endogenous glucose production and exogenous tracer infusion. During submaximal exercise, glucose R_a was calculated using the single-pool non–steady-state Steele equation, adapted for stable isotope methodology as described elsewhere [13]:

$$R_a = (F - V_d[(C_2 + C_1)/2][(E_2 - E_1)(t_2 - t_1)])/((E_2 + E_1)/2),$$

where F is the infusion rate (in micromoles per kilogram FFM per minute); V_d is the distribution volume of glucose; C_1 and C_2 are glucose concentrations at times 1 (t_1) and 2 (t_2), respectively; and E_1 and E_2 are the glucose enrichments at t_1 and t_2, respectively. Because of the short duration of submaximal exercise, the volume of distribution of glucose was assumed to be 100 mL kg BW^{-1} (personal communication with Prof Dr Robert R Wolfe [13]).

Insulin sensitivity was assessed using the homeostatic modeling technique (HOMA) [14] based on fasting plasma glucose and insulin levels.

2.7. Statistics

Results are expressed as mean ± standard error of the mean (SEM). Statistical analysis on baseline differences between COPD patients and controls was performed using an unpaired Student *t* test. One-way analysis of variance was used to determine differences in R_a of glucose, substrate and hormone concentrations, and functional parameters between patients with a reduced BMI, patients with a normal BMI, and controls. Least significant difference multiple comparison test was used as post hoc test. Pearson correlation analysis was performed to investigate linear relationship between variables of glucose metabolism, glucoregulatory hormones, body composition, lung function, and exercise performance. All P values < .05 were considered statistically significant.

3. Results

Thirteen male COPD patients and 8 male healthy volunteers with normal glucose tolerance participated (Table 1). Fat-free mass was significantly reduced in COPD patients compared with controls, whereas fat mass was comparable. Patients were characterized by moderate airflow obstruction, moderately reduced diffusing capacity, and normoxemia at rest. Exercise capacity was significantly reduced in COPD vs controls, whereas peripheral oxygen saturation at rest was comparable and no significant exercise-induced desaturation occurred in any of the groups (data not shown). Underweight COPD patients were characterized by reduced FFM and fat mass in comparison to normal-weight patients and increased residual volumes, but the severity of airflow limitation and arterial blood gases were comparable. Furthermore, exercise capacity was equally impaired in both COPD groups.

Table 1 – Baseline characteristics of the study groups (mean ± SEM)

	Controls (n = 8)	COPD all (n = 13)	COPD normal BMI (n = 7)	COPD reduced BMI (n = 6)
Age, y	65 ± 2	67 ± 3	64 ± 4	70 ± 4
Body composition				
Height, cm	175.1 ± 2.3	170.7 ± 1.4	172.9 ± 1.9	168.1 ± 1.5 *
Weight, kg	83.9 ± 5.1	71.3 ± 4.0	82.5 ± 3.5	58.2 ± 2.1 ‡,‖
BMI, kg·m^{-2}	27.3 ± 1.4	24.3 ± 1.1	27.5 ± 0.9	20.6 ± 0.7 ‡,¶
FFM, kg	61.8 ± 2.5	51.1 ± 2.1 †	56.1 ± 2.4	45.3 ± 1.5 ‡,‖
FFMI, kg·m^{-2}	20.1 ± 0.7	17.5 ± 0.6 *	18.8 ± 0.8	16.0 ± 0.4 ‡,§
FM, kg	22.1 ± 3.0	20.2 ± 2.5	26.4 ± 2.9	12.9 ± 0.8 *,‖
FMI, kg m^{-2}	7.1 ± 0.9	6.8 ± 0.8	8.8 ± 0.9	4.6 ± 0.3 *,‖
Lung function				
FEV_1, % predicted	103 ± 4	52 ± 3 ‡	53 ± 5 ‡	51 ± 5 ‡
DL_{CO}, % predicted	113 ± 6	62 ± 4 ‡	62 ± 7 ‡	62 ± 4 ‡
RV, % predicted	111 ± 8	150 ± 11 *	124 ± 10	180 ± 12 ‡,‖
P_aO_2, kPa	–	8.5 ± 7.4	8.5 ± 7.4	8.5 ± 7.8
P_aCO_2, kPa	–	5.1 ± 0.2	5.1 ± 0.2	5.1 ± 0.1
Functional capacity				
Peak work rate, W	220 ± 23	74 ± 7 ‡	83 ± 11 ‡	65 ± 6 ‡
$V'O_{2max}$, mL·min^{-1}	2522 ± 167	1266 ± 86 ‡	1409 ± 133 ‡	1099 ± 55 ‡
Glucose challenge				
Glucose t_0 (mmol·L^{-1})	5.8 ± 0.2	5.7 ± 0.3	5.9 ± 0.5	5.4 ± 0.3
Glucose t_2 (mmol·L^{-1})	4.8 ± 0.6	6.4 ± 1.0	7.1 ± 1.7	5.6 ± 0.5

Fat-free mass assessed by bioelectrical impedance analysis. FFMI indicates fat-free mass index; FM, fat mass; FMI, fat mass index; FEV_1, forced expiratory volume in 1 second; DL_{CO}, diffusing capacity for carbon monoxide; RV, residual volume; P_aO_2, arterial oxygen tension; P_aCO_2, arterial carbon dioxide tension; $V'O_{2max}$, maximal oxygen consumption; t_0, fasting plasma concentration; t_2, plasma concentration 2 hours after oral glucose load.

Significance of differences between COPD patients and controls is indicated as follows:

* $P < .05$.

† $P < .01$.

‡ $P < .001$.

Significant differences between COPD patients matched for BMI and patients with a reduced BMI are shown as follows:

§ $P < .05$.

‖ $P < .01$.

¶ $P < .001$.

Glucose R_a at rest was significantly increased in COPD patients compared with controls (16.6 ± 0.4 vs 15.1 ± 0.4 μmol·kg FFM^{-1}·min^{-1}, $P < .05$). Only in patients was glucose R_a inversely related to FFM ($r = –0.75$, $P < .01$). Resting glucose R_a of underweight COPD patients (16.7 ± 0.3 μmol·kg FFM^{-1}·min^{-1}) was significantly enhanced compared with controls (15.1 ± 0.4 μmol·kg FFM^{-1}·min^{-1}, $P < .05$), whereas glucose R_a at rest of normal-weight patients (16.1 ± 0.6 μmol·kg FFM^{-1}·min^{-1}, not significant) was not increased (Fig. 1A).

Doubling of the [6,6-$^2H_2$]glucose infusion rate at the start of exercise prevented a decline in tracer-to-tracee ratio (TTR) in both COPD patients as well as controls (Fig. 1B). In fact, postexercise TTR was significantly increased compared with resting TTR for both groups (COPD: $16.52 \cdot 10^{-2} \pm 0.042 \cdot 10^{-2}$ to $18.31 \cdot 10^{-2} \pm 0.048 \cdot 10^{-2}$, $P < .001$; controls: $14.85 \cdot 10^{-2} \pm 0.080 \cdot 10^{-2}$ to $17.58 \cdot 10^{-2} \pm 0.094 \cdot 10^{-2}$, $P < .001$).

There was a physiological increase in glucose R_a during submaximal exercise in both COPD patients as well as controls (P values for paired samples < .001), but the proportional increase in glucose R_a during submaximal exercise at identical workload was enhanced in COPD patients compared with controls (+81.9% ± 3.4% vs +72.1% ± 2.0%, $P = .05$). The relative increase in glucose production was related to norepinephrine concentrations in COPD ($r = 0.61$, $P < .05$). In addition, the proportional increase in glucose R_a was significantly enhanced in COPD patients with a reduced BMI (+ 90.4% ± 5.3%) compared with normal-BMI patients (+ 74.7% ± 2.2%, $P < .01$). Consequently, glucose R_a was significantly elevated in patients compared with controls during submaximal exercise at both identical absolute and relative workloads and during the following recovery periods. End-of-exercise glucose R_a of underweight patients (31.6 ± 0.8 μmol·kg FFM^{-1}·min^{-1}) was significantly enhanced in comparison to controls after submaximal exercise at both identical absolute (25.8 ± 0.6 μmol·kg FFM^{-1}·min^{-1}, $P < .001$) as well as identical relative workload (24.1 ± 0.7 μmol·kg FFM^{-1}·min^{-1}, $P < .001$) (Fig. 1A). Furthermore, normal-BMI patients showed significantly elevated glucose R_a (28.0 ± 1.0 μmol·kg FFM^{-1}·min^{-1}) after submaximal exercise in comparison to controls.

Fasting plasma levels of glucose, insulin, glucagon, cortisol, FFA, and glycerol were comparable in COPD patients and controls, whereas concentrations of epinephrine and norepinephrine tended to be increased in COPD patients ($P = .05$ and $P = .07$, respectively) (Table 2). Plasma levels of glucose remained constant during submaximal exercise and recovery in comparison to fasting levels and were comparable in both groups (Fig. 1C). As expected, end-of-exercise glucagon and catecholamine concentrations were significantly enhanced in COPD patients and controls in comparison to baseline values, whereas insulin levels were significantly suppressed.

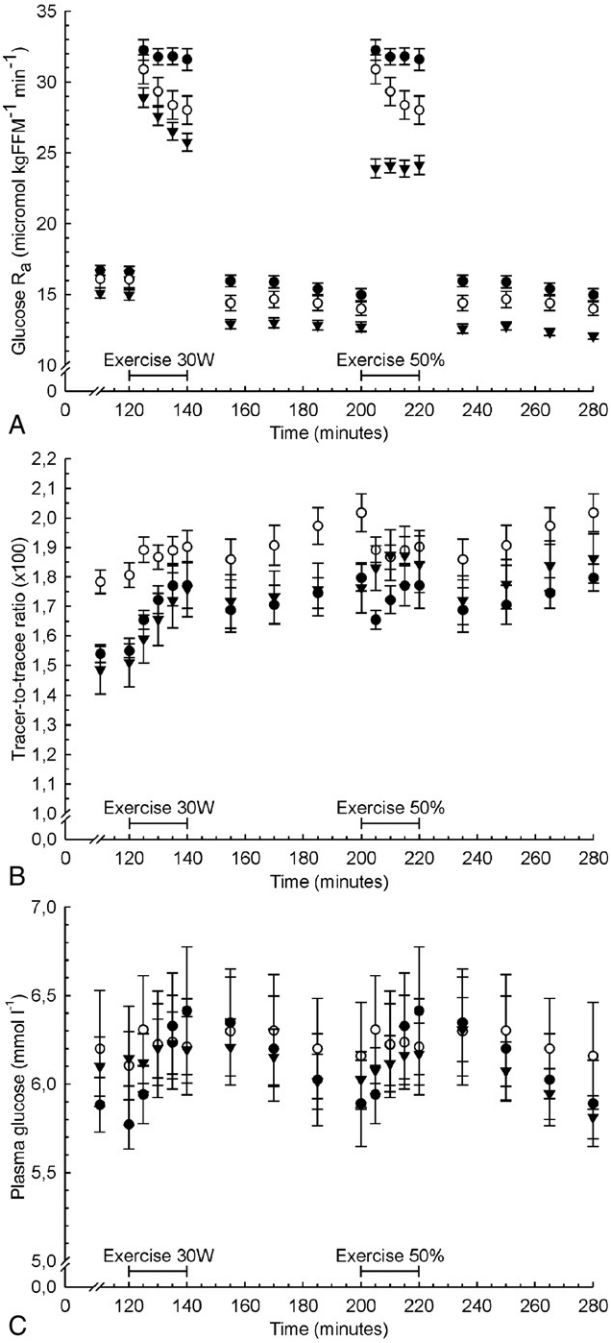

Fig. 1 – Glucose metabolism in COPD and controls. COPD patients with a reduced BMI are represented by closed circles. Values of COPD patients with a normal BMI are shown as open circles, and control values are depicted by closed triangles. A, Rate of appearance of glucose at rest, during exercise at 30 W (= 50% of peak workload of COPD patients), exercise at 50% of individual peak workloads, and recovery (mean ± SEM). Glucose R_a was significantly increased during the entire protocol in COPD patients with a reduced BMI, in comparison to controls. During exercise, glucose R_a of normal-BMI patients was also significantly enhanced compared with controls. B, Tracer-to-tracee ratios for the 3 groups (mean ± SEM). C, Plasma glucose levels in the study groups (mean ± SEM).

As shown in Table 2, low-BMI patients were characterized by reduced plasma insulin concentrations and elevated catecholamine levels in comparison to patients with a normal BMI and controls. Normal-BMI patients showed increased insulin levels compared with controls. Plasma concentrations of glucose, glucagon, cortisol, FFA, and glycerol were comparable in all groups.

The HOMA score was comparable in COPD patients and controls (Table 2), but was significantly reduced in patients with a reduced BMI in comparison to normal-weight patients and controls, indicating increased insulin sensitivity, as plasma glucose concentrations were comparable (Fig. 2). In normal-weight patients, HOMA score tended to be increased in comparison to controls, indicating reduced insulin sensitivity in this patient group. The HOMA score was significantly related to BMI ($r = 0.57$, $P < .05$) and fat mass index ($r = 0.74$, $P < .01$) (Fig. 3) in bivariate regression analysis.

4. Discussion

The results of this first study on glucose kinetics in COPD can be summarized as follows. Postabsorptive whole-body glucose production is enhanced in COPD patients with moderate disease severity compared with healthy subjects when expressed per kilogram FFM. This increased glucose turnover is present in the resting state and is amplified during exercise. Alterations in glucose production are predominantly present in underweight patients, although submaximal exercise revealed enhanced intermediary glucose metabolism in normal-weight COPD patients as well. Finally, there is indirect evidence for insulin resistance in normal-weight COPD patients and increased insulin sensitivity in underweight patients with COPD.

4.1. *Glucose production in COPD*

There are several possible pathophysiological explanations for the increased glucose production in COPD. Acute and chronic hypoxemia, which may be chronically present in end-stage COPD or intermittently during exercise in less severe COPD, causes an increment in glucose production in healthy subjects [5]. Although chronic respiratory failure was an exclusion factor in the present study and exercise-related oxygen desaturation did not occur, resting arterial oxygen tension of the COPD patients was below reference values for healthy subjects.

Furthermore, decreased skeletal muscle oxidative capacity may result in enhanced endogenous glucose production in COPD. The observation of an increased glucose production in combination with normoglycemia implicates an increased glucose tissue uptake. After uptake, glucose can either be stored as glycogen, lactate, or fat or be oxidized. Jakobsson et al [4] reported reduced resting glycogen concentrations in quadriceps muscle of normal-weight COPD patients with chronic respiratory failure. Others [15,16] described similar muscle glycogen content in COPD patients and controls, although resting lactate and pyruvate concentrations [15] were enhanced. If oxygen delivery is adequate, muscle pyruvate and lactate increase when the rate of pyruvate

Table 2 – Postabsorptive resting and end-of-exercise plasma substrate and hormone concentrations (mean ± SEM)

	Controls (n = 8)	COPD all (n = 13)	COPD normal BMI (n = 7)	COPD reduced BMI (n = 6)
Resting state				
Glucose (mmol·L^{-1})	5.79 ± 0.19	5.65 ± 0.29	5.90 ± 0.48	5.37 ± 0.26
Insulin (pmol·L^{-1})	49 ± 8	51 ± 10	76 ± 12 *	22 ± 6 ‖
HOMA score	13.4 ± 2.5	14.3 ± 3.2	21.5 ± 4.1 †	5.8 ± 1.5 ‖,‡
Glucagon (pmol·L^{-1})	63 ± 6	68 ± 4	71 ± 7	65 ± 5
Cortisol (nmol·L^{-1})	292 ± 31	306 ± 28	303 ± 36	310 ± 49
FFA (mmol·L^{-1})	1.12 ± 0.14	1.04 ± 0.08	1.08 ± 0.13	0.99 ± 0.11
Glycerol (mmol·L^{-1})	83.3 ± 6.5	90.6 ± 7.1	85.0 ± 9.5	97.1 ± 11.1
Epinephrine (nmol·L^{-1})	0.42 ± 0.07	0.74 ± 0.14	0.52 ± 0.12	1.01 ± 0.24 *,§
Norepinephrine (nmol·L^{-1})	0.42 ± 0.10	1.02 ± 0.24	0.85 ± 0.21	1.22 ± 0.46 *
End of exercise				
Glucose (mmol·L^{-1})	6.19 ± 0.19	6.30 ± 0.21	6.21 ± 0.27	6.41 ± 0.36
Insulin (pmol·L^{-1})	51 ± 8	55 ± 10	66 ± 13	19 ± 3 *,‖
Glucagon (pmol·L^{-1})	62 ± 7	71 ± 6	79 ± 10	64 ± 4
Cortisol (nmol·L^{-1})	285 ± 23	394 ± 30	386 ± 37	404 ± 52 *
FFA (mmol·L^{-1})	1.75 ± 0.24	1.44 ± 0.13	1.45 ± 0.15	1.42 ± 0.25
Glycerol (mmol·L^{-1})	223.1 ± 36.5	217.6 ± 30.4	207.7 ± 40.5	229.1 ± 49.7
Epinephrine (nmol·L^{-1})	0.79 ± 0.16	3.28 ± 1.23	3.68 ± 2.40	2.88 ± 1.00
Norepinephrine (nmol·L^{-1})	1.32 ± 0.18	2.30 ± 0.45	2.41 ± 0.51	2.18 ± 0.86

Significance of differences between patients and controls is indicated as follows:
* $P < .05$.
† $P = .06$.
‡ $P = .09$.
Significant differences between COPD patients with normal BMI and patients with a reduced BMI are shown as follows:
§ $P < .05$.
‖ $P < .01$.

production by glycolysis exceeds the oxidative capacity of the tricarboxylic acid pathway. Indeed, COPD patients are characterized by an impaired skeletal muscle oxidative capacity; and this is associated with disturbed lactic acid kinetics [17]. Furthermore, an increased proportion of type 2 muscle fibers, with a reduced oxidative enzyme activity, is observed in COPD [18], indicating a shift toward a glycolytic energy production in these patients. Increased glucose turnover in COPD patients might very well be an adaptation to an increased dependence on glucose for energy provision. In the present study, no muscle biopsies were taken; so this hypothesis cannot be proven. However, the fact that enhanced glucose production was accompanied by a reduced fat mass and the finding of nonelevated muscle glycogen content by others [15,16] support this hypothesis of increased muscle glucose use for

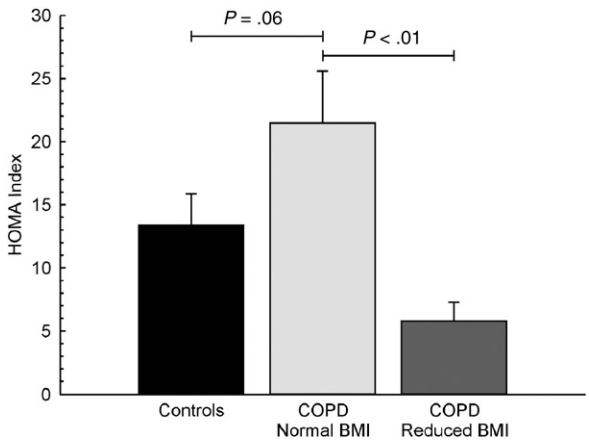

Fig. 2 – Homeostasis model assessment index for insulin sensitivity in subgroups of COPD patients with normal and reduced BMI and controls. Insulin sensitivity was significantly reduced in COPD patients with normal BMI in comparison to patients with reduced BMI. Furthermore, there was a strong tendency toward decreased insulin sensitivity in normal-weight COPD patients in comparison to controls matched for BMI.

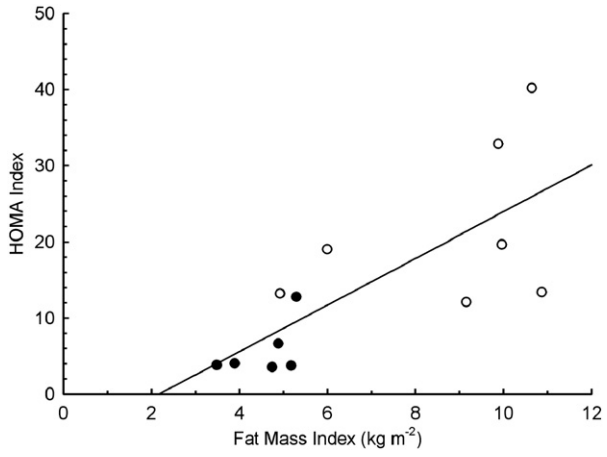

Fig. 3 – Bivariate correlation between fat mass index and HOMA index for insulin sensitivity in COPD patients. Chronic obstructive pulmonary disease patients with reduced BMI are depicted by closed circles, whereas open circles represent normal-weight COPD patients. A significant positive correlation was observed ($r = 0.74$, $P < .01$).

adenosine triphosphate production at the cost of increased glucose storage. A recent study suggested that COPD patients may benefit from restoration of the reduced mitochondrial (oxidative) capacity by pharmacologic intervention [19].

Neurohumoral activation, reflected by elevated catecholamines, is consistently found in COPD and may contribute to systemic manifestations of the disease [6]. Catecholamines increase glucose production by stimulating glycogenolysis and gluconeogenesis, and elevated levels of these were indeed observed in this study. However, no linear relationship between catecholamine levels and resting glucose production was found, possibly because of the small group size.

The systemic use of corticosteroids in COPD may lead to hyperglycemia by increasing hepatic glucose production and inhibiting glucose uptake and utilization by peripheral tissues. In addition, β-adrenoceptor agonists are able to induce hyperglycemia. Because none of the patients in the study used oral glucocorticosteroids and daily inhalations of β_2-adrenoceptor agonists were suspended until after the study and equally distributed between patient groups, a role for medication in the observed results is unlikely.

4.2. *Glucose production and body composition in COPD*

Basal and exercise-induced glucose output of underweight patients was slightly increased in comparison to normal-weight patients and was evidently elevated compared with healthy subjects. Although glucose production was inversely related to FFM, differences in body composition between COPD subgroups cannot explain these results. Studies in healthy nondiabetic individuals showed that lean body mass was a *positive* predictor of postabsorptive endogenous glucose output, irrespective of BW [5,20]. Thus, disease-specific factors related to cachexia, such as more pronounced hypoxemia, reduced oxidative capacity, or skeletal muscle fiber type redistribution, may account for the predominant disturbance of glucose output in the underweight patients. Moreover, preferential atrophy of type IIx glycolytic muscle fibers in COPD might affect the relationship between whole-body glucose production and FFM [21]. Furthermore, increased levels of catecholamines in underweight patients probably contribute because catecholamines are considered the primary drive behind stimulation of exercise-induced glucose production in healthy subjects [22] and a positive correlation between norepinephrine levels and exercise-induced change in glucose production was observed in this study.

4.3. *Insulin sensitivity*

The HOMA index was comparable in COPD patients and controls. However, insulin sensitivity was significantly decreased in normal-weight COPD patients compared with underweight patients; and HOMA score was related to BMI and fat mass. In comparison to controls, insulin sensitivity of normal-weight patients tended to be decreased, whereas there was a trend toward increased insulin sensitivity in underweight COPD patients. This observation is in accordance with a study by Koehler et al [23], who reported reduced insulin sensitivity, measured by HOMA score, in a large group of normal-weight patients compared with underweight COPD patients. Potential mechanisms underlying decreased insulin sensitivity in these patients include BW [24], the presence of low-grade systemic inflammation [24], and hypoxemia [25].

Regarding the observed duality in insulin sensitivity in underweight and normal-weight COPD patients, it is important to notice that being underweight is also associated with increased insulin sensitivity in healthy subjects [26]; so this is not a unique feature in COPD. However, it is remarkable that insulin sensitivity was increased in underweight patients characterized by elevated levels of circulating catecholamines because it is known that epinephrine induces hyperglycemia and peripheral insulin resistance in vivo [27].

Before drawing conclusions on the issue of insulin resistance in (subgroups of) COPD patients, a study using the "criterion standard" method to measure insulin sensitivity, that is, the hyperinsulinemic euglycemic glucose clamp procedure, is needed. Until then, the contribution of insulin resistance to increased cardiovascular mortality in COPD [8] remains speculative.

4.4. *Clinical implications*

In contrast to underweight COPD patients, who showed clear disturbances in resting glucose production that warrant further investigation, resting endogenous glucose production of normal-weight COPD patients was comparable to controls. However, a short period of exercise revealed an enhanced glucose turnover in this group. This observation is relevant to daily living conditions in these patients. Early lactic acidosis is a common finding in COPD [28], indicating increased metabolic stress during relatively low-intensity exercise. The metabolic demands of specific physical activities are usually quantified in *metabolic equivalents*, defined as the ratio of work to resting metabolic rate. The calculated energy cost of the submaximal bicycle exercise in the present study is approximately 3 metabolic equivalents, which is comparable to home activities such as sweeping, downstairs and implied walking, walking the dog, and carrying small children in healthy subjects [29]. Performance of these or more intense activities of daily living by both underweight as well as normal-weight COPD patients might thus result in temporary enhancements in glucose turnover. The clinical implications of these daily bursts of metabolic stress and especially the effects on energy balance, body composition, and cardiovascular risk are unknown and are the subject of future investigations.

5. Conclusions

Postabsorptive resting and exercise-induced whole-body glucose production is increased in clinically stable patients with COPD Global Initiative for Chronic Obstructive Lung Disease stage II to III. Enhanced glucose output is observed in both underweight as well as normal-weight patients, but predominantly in the first group. Epiphenomena of COPD such as reduced skeletal muscle oxidative capacity, relative hypoxemia, and sympathetic activation may contribute to this observation. Additional research is warranted to further clarify the relationships between whole-body substrate metabolism, muscle energy supply, and body composition

and the clinical implications of the present findings. Nevertheless, this study provides a strong rationale to investigate the value of nutritional and pharmacologic interventions targeting intermediary glucose metabolism in moderate COPD.

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.metabol.2010.09.004.

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