Opuntia Ficus-Indica Ingestion Stimulates Peripheral Disposal of Oral Glucose Before and After Exercise in Healthy Men

Karen Van Proeyen, Monique Ramaekers, Ivo Pischel, and Peter Hespel

The purpose of this study was to investigate the effect of Opuntia ficus-indica (OFI) cladode and fruit-skin extract on blood glucose and plasma insulin increments due to high-dose carbohydrate ingestion, before and after exercise. Healthy, physically active men (n = 6; 21.0 ± 1.6 years, 78.1 ± 6.0 kg) participated in a double-blind placebo-controlled crossover study involving 2 experimental sessions. In each session, the subjects successively underwent an oral glucose tolerance test at rest (OGTTR), a 30-min cycling bout at ~75% VO_{2\text{max}} and another OGTTR after exercise (OGTT_{EX}). They received capsules containing either 1,000 mg OFI or placebo (PL) 30 min before and immediately after the OGTTR. Blood samples were collected before (t_0) and at 30-min intervals after ingestion of 75 g glucose for determination of blood glucose and serum insulin. In OGTTR, an additional 75-g oral glucose bolus was administered at t_60. In OGTTR, OFI administration reduced the area under the glucose curve (AUC_{GLUC}) by 26%, mainly due to lower blood glucose levels at t_30 and t_60 (p < .05). Furthermore, a higher serum insulin concentration was noted after OFI intake at baseline and at t_30 (p < .05).

In OGTTEX, blood glucose at t_60 was ~10% lower in OFI than in PL, which resulted in a decreased AUC_{GLUC} (~37%, p < .05). However, insulin values and AUC_{INS} were not different between OFI and PL. In conclusion, the current study shows that OFI extract can increase plasma insulin and thereby facilitate the clearance of an oral glucose load from the circulation at rest and after endurance exercise in healthy men.

Keywords: nutritional supplements, postexercise recovery, insulinogenic, blood glucose clearance

High-intensity exercise typically leads to a depletion of body carbohydrate stores, primarily muscle glycogen (Bergstrom & Hultman, 1966; Romijn et al., 1993). Hence, high-dose oral carbohydrate intake during early recovery is pivotal to stimulate muscle glycogen resynthesis postexercise (Burke, Hawley, Wong, & Jeukendrup, 2011; Ivy, Lee, Brozinick, & Reed, 1988). Therefore, typical sports recovery drinks include a high-carbohydrate dose, composed of rapidly absorbable sugars such as maltodextrin and dextrose. The increased plasma insulin level due to high-dose glucose ingestion plays a pivotal role in enhancing muscle glucose uptake and glycogen synthesis. Insulin-receptor stimulation causes phosphorylation of three key tyrosine molecules on the insulin receptor, which activates Akt by phosphorylation. This signal eventually translates into stimulation of muscle-glucose transport by translocation of GLUT4 to the sarcolemma. In addition, activation of Akt inactivates glycogen synthase kinase 3, which promotes glycogen synthesis by stimulation of the glycogen-synthase enzyme (Jensen & Richter, 2012; Jensen, Ustad, Olnes, & Ai, 2011; Richter, Derave, & Wojtaszewski, 2001). Muscle insulin sensitivity is markedly increased after muscle contractions (Cartee et al., 1989; Garetto, Richter, Goodman, & Ruderman, 1984; Jensen & Richter, 2012; Richter, Garetto, Goodman, & Ruderman, 1982). Therefore, any intervention that could elevate plasma insulin or enhance muscle insulin sensitivity after exercise could facilitate restoration of muscle glycogen stores, and thus serves as a useful recovery agent.

Opuntia ficus-indica (OFI) is one of the approximately 200 species of the Opuntia genus, which belongs to the Cactaceae family (Feugang, Konarski, Zou, Stintzing, & Zou, 2006). This popular herbal plant, also called prickly pear cactus, nopal, or Indian fig cactus, is commonly found in Mexico, the United States, and Mediterranean countries. The cladodes, as well as the richly colored fruits, of OFI are eaten in the form of various food preparations, largely by Mexican descendants (Rodriguez-Fragoso, Reyes-Esparza, Burchiel, Herrera-Ruiz, & Torres, 2008). OFI administration already is being used as an adjuvant therapy in a number of pathologies such as diabetes, hypercholesterolemia, obesity, alcohol-induced hangover, colitis, diarrhea, benign prostatic hypertrophy, and atherosclerosis (Feugang et al., 2006). With regard to the potential of OFI use in insulin resistance or diabetes, several research groups have already demonstrated the blood-glucose-lowering impact of OFI in animals (Butterweck et al., 2011; Enigbokan, Felder, Thompson, Kuti, & Ekpenyong, 1996; Ennouri et al., 2006) and humans (Frati-Munari et al., 1989; Godard et
al., 2010). For instance, a combination of extracts from OFI cladodes and fruit skins lowered blood glucose levels while increasing basal plasma insulin levels in rats, which indicates a direct action on insulin secretion at the site of pancreatic beta cells (Butterweck et al., 2011). Furthermore, Ennouri et al. reported that administration of a diet supplemented with OFI powder seeds during 9 weeks reduced blood glucose concentration in rats. Liver, as well as muscle, glycogen content increased after the OFI administration. These findings seem to indicate that the enhanced peripheral glucose disposal due to OFI ingestion is at least partly due to stimulation of muscle glucose uptake and glycogen synthesis. However, these findings were obtained in rats and can therefore not be simply extrapolated to humans. Nonetheless, the effectiveness of 400 mg OFI to stimulate peripheral glucose disposal after an oral glucose load has also been shown in prediabetic humans (Godard et al., 2010). However, in that study serum insulin concentrations were not measured, so the impact of OFI ingestion on serum insulin response after glucose intake in humans is unknown. The same study also looked at the effects of chronic OFI supplementation (400 mg/day for 16 weeks), but effects on blood glucose were similar to acute intake of a similar dose. However, negative side effects on blood parameters reflecting liver and kidney function were absent.

Data on the effect of OFI on glucose metabolism in healthy individuals are currently lacking. In elite sports, particularly endurance sports, there is a continuous search for methods to stimulate postexercise restoral of muscle glycogen depots (Burke et al., 2011), since the magnitude of glycogen stores when commencing exercise is an important determinant of endurance-exercise performance (Bergstrom, Hermansen, Hultman, & Saltin, 1967; Karlsson & Saltin, 1971; Walker, Heigenhauser, Hultman, & Spriet, 2000). Therefore, interventions that facilitate the rate of muscle glycogen resynthesis after glycogen-depleting exercise—for instance, elevating the concentration of circulating insulin (van Loon, Saris, Kruitjiphoop, & Wagemakers, 2000)—can enhance exercise performance. Against this background, the purpose of the current study was to investigate whether OFI administration in conjunction with high-dose glucose intake, either before or after an endurance-exercise bout, can elevate plasma insulin concentration and thereby stimulate glucose disposal from the circulation in healthy, physically active men. We postulated that OFI intake facilitates the peripheral disposal of oral glucose by stimulating insulin secretion.

### Materials and Methods

#### Subjects

Six healthy, physically active young men (for subject characteristics, see Table 1) volunteered to participate in the study, which was approved by the local ethics committee (K.U. Leuven). Subjects gave their written, informed consent after they were informed of all experimental procedures and risk associated with the experiments. Subjects were instructed not to participate in any moderate- or high-intensity exercise for the 48 hr before the tests.

#### Preliminary Testing

Two weeks before the start of the study, the subjects performed a maximal incremental-exercise test (initial load 60 W + 35 W per 3 min) on a bicycle ergometer (Avantronic Cyclus II, Leipzig, Germany) to determine rate of maximal oxygen uptake (VO2max) and the corresponding workload. Heart rate (Polar, Kempele, Finland), VO2, and VCO2 (Cortex Metalyzer II, Leipzig, Germany) were continuously measured during the test. The workload that corresponded with ~75% of VO2max was calculated for each individual and eventually used during the experimental sessions (202 ± 5 W).

#### Study Protocol

The study was organized as a randomized, double-blind, placebo-controlled, crossover design. All subjects participated in two experimental sessions with a 2-week interval in between. In each experimental session they underwent a 2-hr oral glucose tolerance test (OGTT) both before (OGTTR) and after a 30-min submaximal endurance exercise bout (OGTTEx). In the evening before the experimental sessions, subjects received a standardized carbohydrate-rich dinner (860 kcal, 73% carbohydrates, 14% fat, 13% protein), after which they remained fasted until an OGTT was started the next morning. After the ~10- to 12-hr overnight fast, subjects arrived between 8 and 9 a.m. in the laboratory. During the first experimental session they received 1,000 mg OFI extract or placebo (PL; see Study Supplementation). Next, an intravenous catheter was inserted into an arm vein for repeated blood sampling during the experiment. Thirty minutes after the ingestion of the supplement, a 2-hr OGTT was started. First, a baseline blood sample was taken (t0). Thereafter, the subjects received 75 g of glucose dissolved in 300 ml water as a bolus and for the next 2 hr were seated in a comfortable chair. Additional blood samples (5 ml) were collected 30, 60, 90, and 120 min after glucose ingestion (t0 to t120). Whenever a venous blood sample was taken, a capillary blood sample (~10 μl) was also collected from the earlobe. Immediately after this OGTT, the subjects received an additional dose of 1,000 mg OFI or PL. Thereafter, they performed a cycling-exercise bout on a calibrated cycle ergometer (Avantronic Cyclus II, Leipzig, Germany). For methods to stimulate postexercise restoral of muscle glycogen, see Table 1.)

### Table 1  Subject Characteristics, $M \pm SE, n = 6$

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>21.0 ± 1.6</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>78.1 ± 6.0</td>
</tr>
<tr>
<td>VO2max (ml·min⁻¹·kg⁻¹)</td>
<td>63 ± 3</td>
</tr>
<tr>
<td>Maximal workload (W)</td>
<td>317 ± 5</td>
</tr>
<tr>
<td>Workload at ~75% VO2max</td>
<td>202 ± 5</td>
</tr>
</tbody>
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The subjects started with a 10-min warm-up (5 min at 50 W and 5 min at 100 W) and subsequently cycled for 30 min at a workload corresponding to ~75% of their previously measured VO2max and cadence fixed at 90–100 rpm. During the exercise, heart rate was continuously measured (Polar, Kempele, Finland). On completion of the exercise bout, the subjects returned to their chair and another 2-hr OGTT was started. The procedure was largely identical to the first OGTT, in that the t0 blood sample was taken 5 min after termination of the exercise bout, whereafter the subjects received the oral glucose bolus. Different from the OGTT, an additional glucose bolus was administered at t60. After the last blood sample was collected (t120) the first experimental session was terminated. Two weeks later the subjects returned to the laboratory to participate in the second experimental session, involving the administration of the other treatment (OFI vs. PL).

### Study Supplementation

The study supplementation consisted of capsules containing either 333.3 mg OFI extract (OpunDia, Finzelberg, Germany) or a similar amount of LUVOS Heilerde (PL). OFI and PL capsules were identical in appearance. OpunDia is a preferred blend of OFI cladode and fruit-skin extract containing 75% cladode extract and 25% fruit-skin extract (for both, extraction solvent: water; DER (drug-to-extract ratio) 2–4:1; 50% native extract, 50% collagen hydrolysate as excipient). All plant materials of OFI were obtained from a U.S.-based cultivation operation having breeding experience since 1923 (Bunch, 1996). Voucher specimens of the drug material are deposited at PhytoLab, Vestenbergsgreuth, Germany. The dose of 1,000 mg OFI was selected based on a preliminary dose-response study (Figure 1) involving 5 other young healthy subjects (age 21.8 ± 0.6 years, body weight 72.9 ± 4.0 kg, VO2max 64 ± 6 ml · min⁻¹ · kg⁻¹). They reported to the laboratory in the fasted state between 8 and 9 a.m. on four different occasions and with a 1-week interval in between. On arrival, they received capsules containing either placebo or 500, 1,000, or 1,500 mg of OFI extract. Treatments were administered in a randomized order. Thirty minutes after ingestion of the supplement, a 2-hr OGTT was started following an identical protocol as the basal OGTTs described above. Venous blood samples were collected into vacuum tubes containing silica clot activator (BD Vacutainer, NJ, USA). Tubes were centrifuged (1,500 rpm for 15 min at 4 °C) and the supernatant was stored at −80 °C until later analysis. Serum insulin was assayed by chemiluminescence using the Siemens DPC kit and according to the manufacturer’s instructions. Capillary blood samples were immediately analyzed for blood glucose concentration (Glucocard X-meter, Arkray Inc., Kyoto, Japan).

### Data Calculations and Statistical Analyses

The positive incremental areas under the glucose curve (AUCGLUC) and the insulin curve (AUCINS) were calculated as previously described (Wolever & Jenkins, 1986; Wolever, Jenkins, Jenkins, & Josse, 1991). The differences between the two conditions (PL or OFI) were analyzed by Student’s paired t tests using the Statistica statistical software package. A probability level of p ≤ .05 was considered statistically significant. All data are expressed as M ± SE.

### Results

#### OGTT

Baseline concentration of blood glucose (~4 mmol/L) was similar between OFI and PL (Figure 2[A]). Blood
glucose peaked at \( t_{30} \) and gradually decreased thereafter. In comparison with PL, OFI tended to decrease blood glucose at \( t_{30} \) (–6%, \( p = .10 \)), and the decrease was significant at \( t_{60} \) (–10%, \( p = .02 \)). Values beyond \( t_{60} \) were not significantly different between the groups (\( p \geq .21 \)). Nevertheless, OFI reduced the 2-hr AUCGLUC by about 25% (\( p = .03 \), Figure 2[B]). Against the face of unchanged fasted glycemia, the administration of OFI increased fasted serum insulin concentration from 7 U/L to 10 U/L (\( t_{0} \); \( p = .01 \)). In addition, at \( t_{30} \) serum insulin was significantly higher in OFI than in PL (\( p = .03 \), Figure 2[C]). However, from \( t_{60} \) insulin values were similar between the groups (\( p \geq .18 \)). As a result of this, the AUCINS was not significantly different between OFI and PL (\( p = .21 \), Figure 2[D]).

**OGTTEX**

After OGTTR the subjects exercised for 30 min, whereafter OGTTEX was started. Blood glucose and serum insulin values at \( t_{0} \) were similar between OFI and PL (Figure 3[A]). In contrast with the OGTTR, in this OGTTEX subjects received a glucose bolus (75 g) at both \( t_{0} \) and \( t_{60} \), which maintained a high glucose level throughout the 2-hr OGT. Compared with PL, at \( t_{60} \) but not at the other time points blood glucose concentration was significantly reduced by OFI (–11%, \( p = .04 \); Figure 3[A]). However, overall AUCGLUC was substantially lower in OFI than in PL (–37%, \( p = .03 \); Figure 3[B]). Against the face of this lower glycemia due to OFI, neither single serum insulin values nor AUCINS was significantly different between OFI and PL (\( p \geq .23 \); Figure 3[C] and 3[D]).
Heart Rate During Exercise

Heart rate was continuously monitored during exercise. In PL, heart rate was stable at ~175 beats/min throughout the exercise bout (174 ± 4 beats/min at Minute 10 vs. 176 ± 4 beats/min at Minute 30, \( p = .34 \)). In OFI, heart rate increased from the start (162 ± 6 beats/min at Minute 10) to the end (167 ± 6 beats/min at Minute 30; \( p = .003 \)) of exercise but was consistently ~10 beats/min lower than in PL (\( p = .005 \)).

Discussion

In the current study, we investigated the effect of an OFI cladode and fruit-skin extract on blood glucose and plasma insulin increments due to high-dose carbohydrate ingestion, before and after exercise, in young healthy male volunteers. We postulated that acute OFI administration could stimulate glucose-induced insulin secretion and thereby facilitate the peripheral disposal of oral glucose. In agreement with our hypothesis, we report here that OFI enhanced the insulin response to ingestion of a high glucose dose at rest, and insulin values were higher, albeit nonsignificantly, during recovery after an endurance-exercise bout. This also resulted in lower circulating blood glucose levels just after the increased insulin levels, which conceivably indicates facilitated glucose uptake into insulin-sensitive peripheral tissues including muscle.

It is the prevailing opinion that blood glucose homeostasis has a high priority in metabolic regulation. In this regard, glucoregulation stimulates rapid clearance of...
ingested glucose from the circulation, to prevent excessive hyperglycemia during episodes of high-rate glucose absorption. The primary finding of the current study is that administration of an OFI extract, compared with PL, suppressed the degree of blood glucose increase due to an oral glucose bolus. This is evidenced by a reduction of the 2-hr AUCGLUC by ~25% before (Figure 2[B]) and by ~35% after (Figure 3[B]) a 30-min endurance-exercise bout. The effect of OFI was most prominent in the early stage of the OGTTs when blood glucose concentrations were peaking to the highest levels (Figure 2[A] and 3[A]). The decreased blood glucose levels after OFI corroborate data from earlier studies showing the potential of OFI to stimulate blood glucose disappearance after glucose administration. For instance, in a study using an extract identical to that in the current study, Butterweck et al. (2011) showed that OFI administration in rats (6 mg/kg body weight) suppressed hyperglycemia during intraperitoneal glucose infusion. In the current study in healthy volunteers, we used an OFI dose of 10–15 mg/kg body weight, which also proved to be effective to suppress the blood glucose response to glucose ingestion. However, in a recent study in prediabetic obese male and female individuals it was found that only 400 mg of an identical extract (~5 mg/kg body weight) consistently decreased blood glucose values throughout a 2-hr OGTT (Godard et al., 2010). Nevertheless, in the current study a dose of 1,000 mg OFI was selected because this amount was needed to increase insulin levels in a healthy young population (Figure 1).

The precise physiological mechanism underlying the glucose-lowering effect of OFI is still unclear. However, it has been suggested that OFI can stimulate peripheral glucose disposal via stimulation of insulin secretion (Butterweck et al., 2011). In support of such a presumption, we demonstrated that OFI administration stimulated the early increase in serum insulin concentration on glucose ingestion. Elevated serum insulin levels were found at 0 and 30 min during the basal OGTT (Figure 2[C]), and insulin concentration was also higher, albeit not significantly, at 30 min into the postexercise OGTT (Figure 3[C]). Still, the increase was not consistent, which caused total AUCINS during the two OGTTs to not be significantly different between OFI and placebo. However, this may be due to the small number of observations (N = 6) in the current protocol, which resulted in low statistical power (less than 30%). Our current findings are concurrent with the aforementioned report by Butterweck et al. showing elevated serum insulin concentrations due to oral OFI administration in rats. Clearly, our current findings together with the earlier observations by others (Butterweck et al., 2011; Godard et al., 2010) indicate the potential of OFI to augment insulin secretion in response to glucose ingestion. However, the exact mechanisms underlying this effect remain to be elucidated. In this regard, it is interesting to note that OFI increased plasma insulin already in the fasted state, as well as stimulating the glucose-induced increment in plasma glucose. This may indicate that glucose-induced insulin secretion and glucose-independent insulin production are stimulated by OFI intake.

Both before and after exercise the higher serum insulin concentrations caused by OFI preceded the drop in blood glucose concentration. This observation is important because it indicates that the higher degree of insulin stimulation, per se, probably largely accounted for the enhanced rate of peripheral glucose disposal by OFI. It is well documented that skeletal muscle is responsible for ~75% of insulin-stimulated peripheral glucose uptake after dietary carbohydrate intake (DeFronzo, Ferrannini, Sato, Felig, & Wahren, 1981; Shulman et al., 1990). An enhanced metabolic action of insulin in skeletal muscle is usually observed after exercise, including improvements in glucose transport, glycogen synthase activity, and glycogen synthesis (Jensen & Richter, 2012; Mikines, Sonne, Farrell, Tronier, & Galbo, 1988; Perseghin et al., 1996; Richter et al., 1982). Furthermore, after muscle contractions glucose transport and glycogen synthase activity in muscle cells are stimulated via an insulin-independent mechanism (Garetto et al., 1984; Ivy & Holloszy, 1981; Richter, Mikines, Galbo, & Kiens, 1989), which can act synergistically with insulin to further increase peripheral glucose clearance (Richter et al., 1989). In such scenarios, it is reasonable to postulate that the greater blood glucose clearance with OFI intake is probably largely caused by further enhancement of insulin-stimulated glucose uptake in muscle tissue, which due to the prior exercise bout has an elevated degree of insulin sensitivity. Furthermore, the elevated circulating insulin level due to OFI will facilitate the conversion of the glucose imported into the muscle cells into glycogen via stimulation of the glycogen-synthase enzyme. It remains to be elucidated whether OFI has the potential to stimulate postexercise muscle glycogen resynthesis.

Besides skeletal muscles, liver is another important tissue involved in insulin-stimulated clearance of oral glucose from the circulation (Pagliassotti & Cherrington, 1992). In this regard, it is important to mention that there are already some data to indicate that OFI can stimulate the disposal of glucose into muscle, as well as hepatic glycogen. In one study in rats, it was found that administration of a diet enriched in OFI powder seeds for 9 weeks caused a robust increase in muscle and liver glycogen content, while blood glucose concentration markedly diminished (Ennouri et al., 2006).

In endurance sports, athletes are consistently engaged in glycogen-depleting exercise (De Bock, Derave, Ramaekers, Richter, & Hespel, 2007; Van Proeyen, Szlufcik, Nielens, Ramaekers, & Hespel, 2011). Rapid repletion of glycogen stores between training sessions and competitions is pivotal to maintain exercise-training capacity and improve performance (Burke et al., 2011). Therefore, as a rule, after exercise endurance athletes ingest ample amounts of carbohydrates (Burke et al., 2011). The elevated glucose supply causes an insulin boost (Kaastra et al., 2006; van Loon, Saris, Kruisjhoop, & Wagemakers, 2000; van Loon, Kruisjhoop, Verhagen, Saris, & Wagemakers, 2000) and thereby stimulates muscle glucose uptake and rates of glycogen replenishment.
insulin secretion, can be an additional factor to stimulate postexercise muscle glycogen resynthesis.

It is also important to note that exercise heart rates were consistently suppressed by ~10 beats/min due to OFI intake. This finding is in keeping with an earlier report by Schmitt, Fouillot, Nicolet, and Midol (2008) showing lower resting heart rates (~9 beats/min, p < 0.1) in elite athletes after intake of an OFI extract corresponding to 5 g fresh fruit per kilogram body weight. In that study, the lower heart rates induced by OFI were tentatively explained by increased parasympathetic activity. We did not measure heart rate at rest, so we cannot determine whether the lower heart rates seen during exercise were due to lower basal heart rates or, rather, to suppressed exercise-induced increases in heart rates, which would indicate suppressed orthosympathic drive to the heart (Nakamura, Yamamoto, & Muraoka, 1993; Robinson, Epstein, Beiser, & Braunwald, 1966). Clearly, the precise physiological mechanism underlying the effect of OFI to reduce heart rate remains to be elucidated.

In conclusion, the current study provides novel evidence that OFI cladode and fruit-skin extract can increase plasma insulin and thereby facilitate the disposal of an oral glucose load from the circulation. This reduction in blood glucose was more explicit after exercise than in a basal state. Future research is warranted to investigate whether the increased glucose disposal by OFI is channelled into muscle glycogen and as such might be a useful ingredient to stimulate postexercise muscle glycogen restoral in athletes.

Acknowledgments

The authors thank all subjects for participating in this study. They also thank Dr. Ruud Van Thiemen for medical assistance during the experiments. Björn Feistel and Bernd Wobbroel from Finzelberg, Germany, kindly supplied OpunDia extract.

PhytoLab GmbH & Co. KG, Vestenbergsgreuth, Germany, sponsored this study.

Ivo Pischel is an employee of PhytoLab GmbH & Co. KG, Germany, and was involved in the study design but not in any data generation or processing. Finzelberg GmbH & Co. KG, Germany, has applied for patents for OpunDia, e.g., US 2010323045 (A1)—EXTRACT FORMULATION OF OPUNTIA FICUS INDICA (Priorities: US20080741562 20081106; EP20070120081 20071106; US20070002058 P 20071106; WO2008EP65048 20081106).


References


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