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Beneficial effects on fasting insulin and postprandial responses through 7-day intake of New Zealand blackcurrant powder

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ABSTRACT

Background: Blood glucose and insulin are elevated after intake of carbohydrate, with levels returning to normal in about 2-3 hours after ingestion. We examined the effects of daily New Zealand blackcurrant intake over 7 days on fasting glucose and insulin levels and the responses of glucose and insulin during an oral glucose tolerance test (i.e. OGTT).

Methods: Seventeen healthy participants (9 males, 8 females, age: 24±8 years, body mass: 75.4±16.4 kg, height 172±11 cm, body mass index: 25.3±3.3) consumed 6 g·day^{-1} New Zealand blackcurrant (NZBC) powder for 7 days. Every 6 g of the serving contained 138.6 mg anthocyanins, 49 mg vitamin C, and 5.2 g of carbohydrates with total phenolic content 271.6 mg. A cross-over design was used. Participants completed one OGTT before starting the supplementation (day 0) and another OGTT after 7 days of the supplementation (day 7). For the OGTT, participants were seated and consumed 75 g of glucose dissolved in 250 mL water. Finger prick capillary samples were taken before and every 30 minutes for a total of 120 minutes after consuming the glucose drink. Following duplicate glucose analysis, blood samples were centrifuged and then plasma was separated and frozen (-20°C) for triplicate insulin analysis using a human 96-well insulin enzyme-linked immunosorbent assay (IBL international, Hamburg, Germany).

Results: NZBC had no effect on fasting glucose (control: 4.46±0.45; NZBC: 4.41±0.44 mmol·L^1, P=0.657), although there was a trend for fasting insulin to be 14.3% lower (control: 66.5±28.2; NZBC: 57.0±29.5 pmol·L^{-1}) (P=0.091). HOMA-IR was not different between the control and NZBC (1.81±0.73 vs 1.58±0.83) (P=0.126). With NZBC during the OGTT, plasma glucose at 60 min was 8.1% lower (control: 6.68±1.13; NZBC: 6.14±1.41 mmol·L^{-1}; P=0.016), insulin at 30 min was 18.4% lower (control: 337.1±228.3; NZBC: 275.0±136.4 pmol·L^{-1}; P= 0.021), and insulin at 60 min was 39.2% lower (control: 297.8±154.3; NZBC: 181.2±97.4 pmol·L^{-1}; P= 0.002). With NZBC during the OGTTs, areas-under-the-curve for plasma glucose (control: 752.6±79.4, NZBC: 709.8±93.3 mmol·L^{-1}·120 min) and insulin (control: 28443±12816, NZBC: 20406±7985, pmol·L^{-1}·120 min) were 5.7% (P=0.051) and 31.1% lower (P<0.001) respectively.

Conclusion: A trend for lower fasting insulin with normal glucose and lower areas under the curve for glucose and insulin suggests that repeated intake of New Zealand blackcurrant powder increases insulin sensitivity. This is the first observation of a high-anthocyanin containing berry powder to increase insulin sensitivity. Regular intake of New Zealand blackcurrant powder may be beneficial for the postprandial responses in people with type 2 diabetes or metabolic syndrome.

Keywords: Anthocyanins, Glycaemia, Insulinaemia, Berries, Blood Glucose, Diabetes, Metabolic Syndrome

INTRODUCTION

Blood glucose and insulin are elevated after consumption of carbohydrate, with levels returning to normal about 2-3 hours after ingestion. The acute intake of anthocyanin-rich blackcurrant drinks before a high carbohydrate meal reduced postprandial glucose and insulin levels [1]. Nutritional intervention studies on the acute effects of the intake of blackcurrant drinks do not provide information on potential adaptations with repeated intake (e.g. 7 days). In a cross-sectional study in females (*n*=1997), the repeated intake of one of the main anthocyanins in blackcurrant (i.e. delphinidin) was associated with lower fasting insulin levels [2]. Additionally, a higher consumption of anthocyanins was associated with a lower risk for type 2 diabetes [3]. However, the effects of repeated intake of blackcurrant powder on fasting glucose and insulin levels and postprandial glucose and insulin responses are unknown.

Postprandial blood glucose typically results in a peak value in the first 60 min with levels returning to normal in about 2 hours [1, 4]. It is the result of the digestive and absorption processes of food components in the mouth, stomach, and small intestine, in addition to the uptake of blood glucose by tissues for storage and as an energy source. Furthermore, a reduced ability to lower postprandial blood glucose in the first few hours after a meal with a high carbohydrate content may be indicative of a decrease in insulin sensitivity and/or insulin secretion. Abnormal glucose clearance may increase the risk for development of type 2 diabetes [5], likely associated with attenuation of endothelial relaxation in healthy subjects with a family history of diabetes [6].

In addition to the carbohydrate content of the dietary intake, other components may also affect the postprandial blood glucose response, with recent evidence indicating a role for the effects of

polyphenols [7] and more specifically anthocyanins [8]. Blackcurrant is high in content of the polyphenol anthocyanin [9, 10]. Blackcurrant components inhibit salivary and pancreatic α-amylase and intestinal α-glucosidase activity *in vitro* [11, 12, 13, 14]. The inhibition of α-amylase and α-glucosidase are causally linked with blunting of the *in vivo* postprandial blood glucose response following the intake of polyphenol and fibre-rich fruits and green tea [15]. Additionally, an anthocyanin-rich berry extract containing the anthocyanins present in blackcurrant (i.e. delphinidin and cyanidin) decreased acute glucose transport in human intestinal Caco-cells with 16 h exposure decreasing the expression of both sodium-dependent glucose transporter (i.e. SGLT1) mRNA and glucose transport 2 (i.e. GLUT-2) mRNA [16]. Therefore, *in vitro* studies provide observations that seem to indicate that anthocyanins can affect carbohydrate digestion and absorption *in vivo*. Recently, postprandial glucose and insulin responses were examined in an *in vivo* study with a group of men and postmenopausal women after the acute intake of a non-sugar added fruit drink with different doses of blackcurrant extract [1]. It was observed that the dose of 599 mg of blackcurrant anthocyanins reduced blood glucose in the first 30 min postprandial compared with no effect of an intake of 131 mg and 322 mg of anthocyanins [1]. To our knowledge, this was the first study with *in vivo* observations for beneficial effects of blackcurrant juice on the postprandial glucose and insulin response. However, nutritional intervention studies on the acute effects of the intake of blackcurrant drinks do not provide information on potential effects that may occur with repeated intake (e.g. 7 days) on fasting glucose and insulin levels. Fasting insulin and glucose levels have been linked with pre-diabetes diagnosis [17, 18]. The effect of repeated intake of blackcurrant on fasting glucose and insulin levels and the responses of glucose and insulin to carbohydrate intake are unknown.

The aim of the present study was to examine the effect of repeated intake of New Zealand blackcurrant powder on postprandial glucose and insulin in non-diabetic individuals. It was hypothesized that the intake of New Zealand blackcurrant powder would enhance insulin sensitivity in non-diabetic individuals. This is the first study to provide observations on the effects of the repeated intake of a blackcurrant powder on insulin sensitivity in humans.

METHODS

Participants

Ethical approval was obtained from the Ethics Committee of the University. Seventeen participants (9 males, age: 27±12 years, body mass: 79.3±15.0 kg, height: 177±8 cm, body mass index: 24.9±2.6 $kg \cdot m^{-2}$; 8 females, age: 23±2 years, body mass: 69.2±18.1 kg, height: 163±8 cm, body mass index: 25.7±4.5 $kg \cdot m^{-2}$) provided written informed consent. A health history questionnaire was completed and confirmed the absence of a pre-diabetic or diabetic state. Participants were healthy.

Design, supplementation and measurements

The study used a cross-over design. Participants visited the laboratory twice after an overnight fast for an oral glucose tolerance test (i.e. OGTT) and instructed to have identical dietary intake on the day before the OGTT. No placebo was provided for the control condition. Participants were tested

first for the control condition. For supplementation, participants were provided with 7 doses of 6 g of New Zealand blackcurrant (NZBC) powder (Sujon Berries, Nelson, New Zealand) in opaque plastic vials. Per 6 g serving, Sujon New Zealand blackcurrant powder contains 138.6 mg anthocyanin (total phenolic content 271.6 mg), 49 mg vitamin C, and 5.2 g of carbohydrates. For 6 days, participants were instructed to take 6 g of NZBC powder dissolved in water around breakfast. The 7th dose was taken 1 hr before attending the laboratory for the OGTT. For the OGTT, participants were provided with 75 g of glucose dissolved in 250 ml of water. Participants were seated for the duration of the OGTT with finger prick capillary blood samples taken at 0, 30, 60, 90, and 120 min after glucose intake. Blood glucose was measured immediately in duplicates (YSI 2300 Stat Plus, Yellow Springs Instruments Co. Inc., Yellow Springs, USA). The remaining samples were centrifuged (C2 Series, Centurion Scientific, Chichester, UK) at 5000 rpm for 5-min, providing about 90 µL of plasma. The plasma was pipetted and frozen at -20°C for insulin analysis. Plasma insulin samples were measured in triplicate (~25 µL of plasma for each measurement) using a human 96-well insulin enzyme-linked immunosorbent assay (IBL international, Hamburg, Germany). The insulin assay was based on the sandwich principle with the microtiter wells pre-coated with the antibody. The intensity of the colour developed was proportional to the concentration of insulin with absorbance values of each well determined at 450 nm with a microtiter plate reader (Tecan GENios, Männedorf, Switzerland).

Data and statistical analysis

The area under the curve for insulin and glucose (i.e. $AUC_{insulin}$ and $AUC_{glucose}$) were calculated using the trapezoid method and expressed as pmol·L^{-1}·120 min and mmol·L^{-1}·120 min respectively. Fasting insulin, fasting glucose, HOMA-IR [i.e. homeostatic model assessment of insulin resistance, (fasting glucose · fasting insulin)/22.5)], insulin and plasma glucose at either 30, 60, 90, or 120 min, $AUC_{insulin}$, $AUC_{glucose}$ and changes in AUCs for males and females were analyzed with paired and unpaired samples student t-tests. Statistical significance was accepted at $P<0.05$. Interpretation of $0.05>P\leq0.1$ was according to guidelines by Curran-Everett & Benos [19]. Data are presented as mean ± SD unless stated otherwise. Calculations and statistical analysis were conducted with GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego California USA).

RESULTS

NZBC had no effect on fasting glucose (control: 4.46±0.45; NZBC: 4.41±0.44 mmol·L^{-1}, P=0.66) (Figure 1) but there was a trend for fasting insulin to be 14.3% lower (control: 66.5±28.2; NZBC: 57.0±29.5 pmol·L^{-1}, P=0.091) (Figure 2), with 9 of the 17 participants having lower values.

HOMA-IR for control and NZBC was 1.81±0.73 and 1.58±0.83 respectively and not different (P=0.126). Plasma glucose during the OGTT was 8.1% lower at 60 min with NZBC (control: 6.68±1.13; NZBC: 6.14±1.41 mmol·L^{-1}; P=0.016) (Figure 1), with 13 participants having lower values. Insulin was 18.4% lower at 30 min with NZBC (control: 337.1±228.3; NZBC: 275.0±136.4 pmol·L^{-1}; P= 0.021), with 11 participants having lower values. Insulin was 39.2% lower at 60 min with NZBC (control: 297.8±154.3; NZBC: 181.2±97.4 pmol·L^{-1}; P= 0.002) (Figure 2), with 12 participants having lower values.

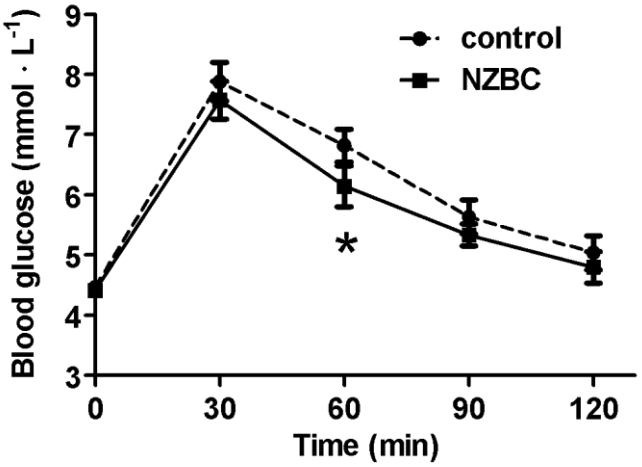

Figure 1. Postprandial blood glucose concentrations during the 2 hr oral glucose tolerance test. *, indicates difference between control and New Zealand blackcurrant (NZBC) powder at 60 min ($p<0.05$). Data are mean±SEM (*n*=17).

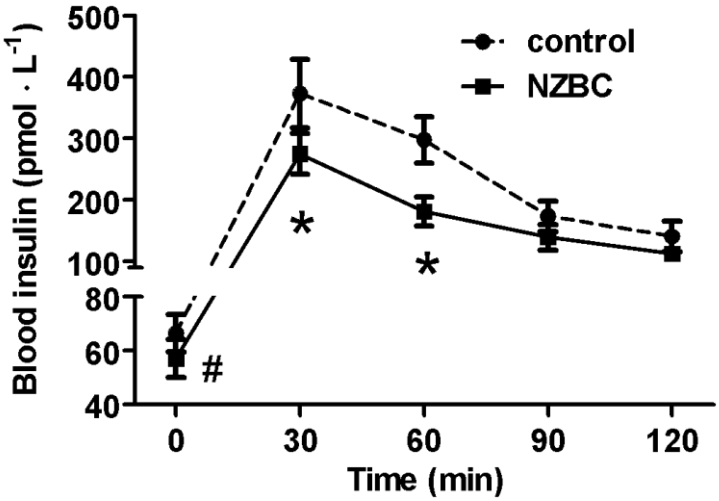

Figure 2. Postprandial blood insulin concentrations during the during the 2 hr oral glucose tolerance test. #, indicates a trend for a difference between the control and New Zealand blackcurrant (NZBC) powder for fasting insulin (P=0.091); *, indicates a difference between the control and NZBC powder at 30 and 60 min (P<0.05). Data are mean±SEM (*n*=17).

With NZBC during the OGTTs, there was a strong trend for lower $AUC_{glucose}$ (control: 752.6±79.4, NZBC: 709.8±93.3 mmol·L^{-1}·120 min, P=0.051) (Figure 3), with 11 participants having lower values. There was no difference between females and males for the change in $AUC_{glucose}$ with NZBC (P=0.374). With NZBC during the OGTTs, $AUC_{insulin}$ was 31.1% lower (control: 28443±12816, NZBC: 20406±7985, pmol·L^{-1}·120 min, P<0.001) (Figure 4), with 14 of the 17 participants having lower values. Compared to females, there was a trend for males to have larger changes in $AUC_{insulin}$ with NZBC (P=0.093).

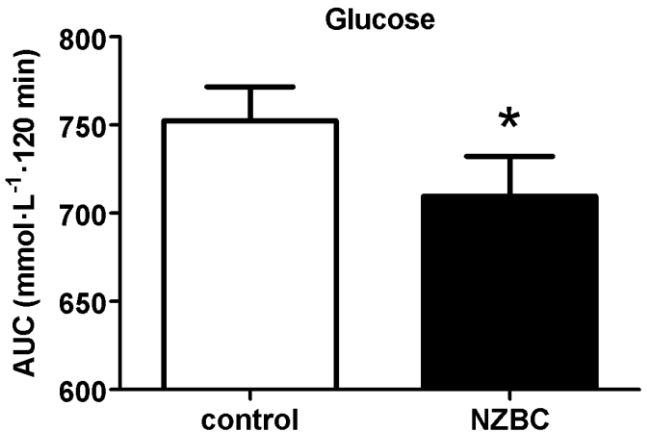

Figure 3. Postprandial area under the curve (AUC) for blood glucose during the 2 hr oral glucose tolerance test. *, indicates a difference between control and New Zealand blackcurrant powder (P<0.05). Data are mean±SEM (*n*=17).

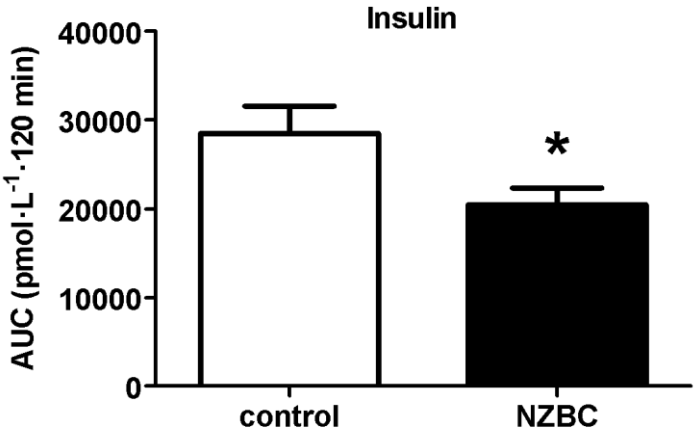

Figure 4. Postprandial area under the curve (AUC) for blood insulin glucose during the 2 hr oral glucose tolerance test. *, indicates a difference between control and New Zealand blackcurrant powder (P<0.05). Data are mean±SEM (*n*=17).

DISCUSSION

The present study provides novel observations in healthy individuals on the effects of a 7-day intake of a high anthocyanin-containing berry powder on fasting glucose and insulin, in addition to the glucose and insulin responses after high glucose intake (i.e. 75 g). We observed that 7-day intake of 6 g of New Zealand blackcurrant powder (i.e. ~138.6 mg of blackcurrant anthocyanins/day) tended to reduce fasting insulin by 14.3%, and reduced the area under the curve for glucose and insulin during an OGTT by 5.7% and 31.1% respectively. These observations suggest an increase in insulin sensitivity occurs through the intake of New Zealand blackcurrant powder intake.

Lower fasting insulin and normal fasting glucose in the present study confirms the observations of a cross-sectional study of 1997 females (18-76 years) on the habitual intake of polyphenol classes and insulin resistance [2]. It was reported that the habitual intake of the

anthocyanins delphinidin, malvinidin, peonidin, and petunidin reduced fasting insulin by 9.4%, but only in participants in the highest quintile (total anthocyanin intake of 39.9±15.0 mg·day^{-1}) compared to the lowest quintile [2]. In blackcurrant, the delphinidins (i.e. delphinidin-*3*-*O*-glucoside and delphinidin-*3*-*O*-rutinoside) make up 66% of the total blackcurrant anthocyanin content [20]. The main anthocyanins in blackcurrant are cyanidin-*3*-*O*-glucoside, cyanidin-*3*-*O*-rutinoside, delphinidin-*3*-*O*-glucoside, and delphinidin-*3*-*O*-rutinoside, which makes up about 98% of the total anthocyanin content [20]. We cannot exclude that the effects by the intake of all blackcurrant anthocyanins (intake 138.6 mg/day) were required to lower fasting insulin in the present study. Future studies may want to examine the effects of short-duration intake of other berry powders having different polyphenol composition on fasting insulin in healthy individuals. Intake of highbush blueberry powder for 90 days in Zucker fatty rats on high-fat and low-fat diets lowered fasting insulin with normal fasting glucose [21], while no effect was observed on fasting insulin and glucose with a 6 week intake of two smoothies a day containing each 22.5 g of blueberry bioactives in obese insulin-resistant men and women [22] and in adults with metabolic syndrome [23]. An acute intake of delphinidin-rich maqui berry extract lowered fasting insulin and glucose after 60 min in pre-diabetic individuals [24]. In the present study, fasting insulin was not measured before the final intake of New Zealand blackcurrant on the day of testing. Therefore, we can not exclude that the tendency to have lower fasting insulin in the present study was due to the final intake of New Zealand blackcurrant. The final intake of New Zealand blackcurrant contained 5.2 g of carbohydrates, an amount that is too small to cause a rise in blood glucose levels. Our observations of lower fasting insulin with normal fasting glucose may therefore be indicative of increased insulin sensitivity. However, HOMA-IR was not shown to be different with New Zealand blackcurrant intake, while 10 out of 17 participants had lower HOMA-IR values, Thus, the present study may have been underpowered.

As far as we know, our observations over a 2 hour period on the reduction of both the area under the curve for glucose and insulin during an OGTT by 7-day intake of New Zealand blackcurrant powder have not been examined in studies with other berries. Recently, it was observed in a study with a group of men and postmenopausal women that the acute intake of blackcurrant in a low sugar fruit drink with an anthocyanin content of 599 mg before a high carbohydrate meal (39 g starch and 23 gr sucrose) reduced blood glucose and insulin in the first 30 min postprandial compared to an intake of 131 mg and 322 mg of anthocyanins [1], with no changes in area under the curve for blood glucose and insulin over a 2 hour period for any anthocyanin content. The absence of a change in area under the curve for glucose and insulin was due to a rebound effect with higher glucose at 75 min and higher insulin and 75 and 90 min [1]. A rebound effect on glucose and insulin was not observed in the present study. Methodological differences between the present study and Castro-Acosta et al [1] with respect to carbohydrate intake, dietary restrictions for high polyphenol intake for 24 h, and subject characteristics complicates judgement of whether New Zealand blackcurrant powder was more potent for postprandial responses. However, the low dose intake of anthocyanins in the Castro-Acosta et al study (i.e. 131 mg) with blackcurrant in a fruit drink did not provide any significant findings [1] and was comparable with the intake in the present study (i.e. 138 mg). Additionally, in the present study, responses were observed after an overnight fast with no dietary restrictions and the glucose responses were examined after glucose intake. Therefore, there was no role of enzymes normally

involved in the breakdown of various carbohydrates into glucose, i.e. α-amylase and α-glucosidase. Future studies may want to examine the effect of New Zealand blackcurrant on the postprandial glucose and insulin responses after an intake of complex carbohydrates or a normal meal. Furthermore, future studies may want to examine sex-differences in insulin responses to blackcurrant intake in well powered studies. In the present study, hormonal status in females due to menstruation phase and/or intake of oral contraceptives was not considered when tested for the OGTT responses.

It would be of interest to examine the dose effects of chronic intake of New Zealand blackcurrant powder on postprandial responses as anthocyanin intake was much higher in Castro-Acosta et al [1]. We observed dose effects on cardiovascular function in rest with New Zealand blackcurrant extract [25]. The lower glucose response may be due to inhibition of intestinal absorption by reduced contribution of the active Na^+-dependent transport via sodium glucose co-transporter 1 and facilitated Na^+-independent transport via GLUT2 and/or an increase in insulin sensitivity. However, Castro-Acosta et al observed lower gastric inhibitory peptide with a high dose of blackcurrant intake [1]. Therefore, the lower insulin responses may be due also to an effect on gastric inhibitory peptide and/or a direct effect on the pancreatic functioning by intake of New Zealand blackcurrant powder. Furthermore, cyanidin-*3*-*O*-glucoside lowered postprandial hyperglycemia by an effect in part on GLUT-4 translocation in soleus muscle by activation of both insulin and AMPK-signalling pathways [26]. Additionally, *in vitro* studies have shown effects of the phenolic metabolites that result from blackcurrant intake on insulin and glucose handling [27]. For example, protocatechuic acid mimics insulin activity in visceral adipocytes [28], gallic acid induces GLUT4 translocation and glucose uptake activity in 3T3-L1 cells [29], and protocatechuic acid derived vanillic acid may ameliorate insulin-resistant insulin resistance in FL83B mouse hepatocytes [30]. However, supraphysiological concentrations of phenolic metabolites used in *in vitro* studies warrants caution when extrapolating to *in vivo* conditions.

CONCLUSIONS

A 7-day intake of New Zealand blackcurrant powder reduced fasting insulin and lowered glucose and insulin responses during an oral glucose tolerance test. Regular intake of New Zealand blackcurrant may reduce the risk for development of type II diabetes in healthy individuals. Future work should examine the effects of regular intake of New Zealand blackcurrant on postprandial responses in people with type II diabetics or metabolic syndrome.

Competing Interests: The authors have no financial interests or conflicts of interest.

Authors' Contributions: All authors contributed to this study.

Abbreviations: AUC, area under the curve; HOMA-IR, homeostatic model assessment of insulin resistance; NZBC, New Zealand blackcurrant; OGTT, oral glucose tolerance test

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