Anthocyanins increase serum adiponectin in newly diagnosed diabetes but not in prediabetes: a randomized controlled trial

LiPing Yang (yanglp6@mail2.sysu.edu.cn)
Sun Yat-Sen University https://orcid.org/0000-0001-6560-0478
Wenhua Ling
Sun Yat-Sen University
Yun Qiu
Sun Yat-Sen University
Yong Liu
Centre for Chronic Disease Control
Li Wang
Centre for Chronic Disease Control
Jing Yang
Centre for Chronic Disease Control
Changyi Wang
Centre for Chronic Disease Control
Jianping Ma
Centre for Chronic Disease Control

Research

Keywords: Anthocyanin, adiponectin, prediabetes

Posted Date: June 16th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-28039/v1

Version of Record: A version of this preprint was published on September 21st, 2020. See the published version at https://doi.org/10.1186/s12986-020-00498-0.

Abstract

Background

Epidemiological studies have suggested that adiponectin is associated with the development of insulin resistance and type 2 diabetes. This study first examined the effect of purified anthocyanins, a group of dietary flavonoids, on serum adiponectin in patients with prediabetes and newly diagnosed diabetes.

Methods

A total of 160 patients with prediabetes (n=90) or newly diagnosed diabetes (n=70) were randomly assigned to either the anthocyanins group or the placebo group for 12 weeks intervention. Serum adiponectin, a set of biomarkers related to glucolipid metabolism, anthropometric parameters, dietary intakes and physical activities were measured before and after intervention.

Results

Anthocyanins increased serum adiponectin compared with placebo (net change 0.46 ug/mL, 95%CI [0.03, 0.90], p=0.038) in the subjects with newly diagnosed diabetes. No significant difference in the change of adiponectin was observed between the two groups either in the overall subjects (0.02 ug/mL [-0.32, 0.36], p=0.906) or in prediabetes (-0.35 ug/mL [-0.85, 0.16], p=0.174). Anthocyanins also decreased fasting glucose (-0.5 mmol/L [-1, -0.04], p=0.035) in the subjects with newly diagnosed diabetes, and no such change was observed in those with prediabetes.

Conclusions

Anthocyanins supplementation for 12 weeks improved serum adiponectin and fasting glucose in patients with newly diagnosed diabetes, but not in patients with prediabetes.

Introduction

The prevalence of type 2 diabetes (T2DM) in conjunction with its cardiovascular complications are becoming the most serious health challenges worldwide. Adiponectin is a protein secreted predominantly by adipocytes and is known to be an important regulator of glucose and lipid homeostasis. A systemic review and meta-analysis conclusively showed a strong and consistent correlation between higher circulating adiponectin levels and lower risk of type 2 diabetes among different populations [1]. Another recent meta-analysis showed that hypoadiponectinemia was associated with the development of type 2 diabetes[2]. Adiponectin is shown to be a therapeutic target and prognostic marker for cardiometabolic diseases[3]. However, there are conflicting results about the associations between circulating adiponectin and the development and outcomes of cardiometabolic diseases[4, 5]. Some studies indicated that increased adiponectin levels were associated with decreased risks of coronary artery disease in type 2 diabetic patients[6], whereas other studies suggested that hyperadiponectinemia were associated with increased cardiovascular events and mortality in patients with diabetes[7], myocardial infarction[8] and heart failure[9]. So far, the relationship between circulating adiponectin and cardiometabolic disorders is complex and remind unclear.

Anthocyanins are a large group of phytochemicals, concentrated from the dark fruits and vegetables and are associated with health benefits. A cross-sectional study suggested that higher anthocyanin intake was associated with lower peripheral insulin resistance, inflammatory markers and improved adiponectin concentration[10]. Numerous interventional studies have revealed that anthocyanins or anthocyanin-rich extracts improved lipid profiles in cardiometabolic diseases, but few studies evaluated the effect of anthocyanins on circulating adiponectin. There is only one study that examined the effect of anthocyanins on serum adiponectin in patients with known type 2 diabetes, in which anthocyanins increased adiponectin and decreased fasting glucose [11]. Whether these effects could be extended to prediabetes or early untreated diabetes is unclear. Subjects with prediabetes or newly diagnosed diabetes are identified to avoid the influence of medications and are more appropriate to prospectively evaluate the efficacy of anthocyanins intervention. Accordingly, the aim of this study was to evaluate the effect of purified anthocyanins supplementation on serum adiponectin levels in patients with prediabetes or newly diagnosed diabetes.

Methods

Subjects

Participants aged 40-75 years were recruited from local communities in Guangzhou, China. They were initially screened by their recent fasting blood glucose records, and were further screened by a face-to-face interview and a 3-hour 75g oral glucose tolerance test (OGTT) to confirm their eligibility. Patients with prediabetes or newly diagnosed diabetes were eligible for this study. According to the diagnosis criteria of American Diabetes Association (ADA)[12], prediabetes is an intermediate state if the subjects met one of the following criteria: impaired fasting glucose (IFG, 5.6~6.9 mmol/L) or impaired glucose tolerance (IGT, 2-hour glucose7.8~11.0 mmol/L), or HbA1c 5.7~6.4%. Newly diagnosed diabetes were the subjects who exceeded the upper limit of the above criteria (fasting glucose >6.9 mmol/L, or 2-hour glucose>11.0 mmol/L, or HbA1c >6.4%), and have not taken any diabetic medications before the screening.

Participants were excluded if they had pre-existing diabetes or a history of hypoglycemic medical treatment, acute or chronic infectious diseases, untreated thyroid disease, serious liver and kidney dysfunction, use of glucocorticoid, suffering from traumatic injury or undertaking surgery in 6 months before enrollment; lactating or pregnant women, or individuals with polycystic ovarian syndrome. This trial was approved by the Ethics Committee of Sun Yat-Sen University, and written informed consent was obtained from each participant.

Study design

This study was a 12-week randomized placebo-controlled trial that registered at ClinicalTrials.gov as NCT02689765. The co-primary outcomes were the changes in fasting glucose and glycated hemoglobin A1c (HbA1c). Sample size calculation were based on the previous study[11], in which the differences for fasting glucose and HbA1c are 0.4 mmol/L (SD 0.6mmol/L) and 0.2% (SD 0.4%), respectively. It was calculated that 80 participants per group would be enough in this trial to provide a significant difference of the primary outcomes at 80% power and a level of alpha 0.05.

Eligible participants were randomly assigned to either the anthocyanins group (n = 80) or the placebo group (n = 80). The allocation sequences were determined by a computer-generated random-numbers table. The anthocyanins group consumed two anthocyanin capsules (Medox; Polyphenols AS, Norway) twice daily for a total of 320 mg anthocyanins. The dose of anthocyanins was determined based on our previous trials that performed in patients with T2DM[11] and dyslipidemia[13]. The control group consumed two identical packaged placebo capsules twice daily.

The participants were asked to maintain their habitual diet and physical activities, and to avoid consuming anthocyanin-rich foods, such as berries and grapes, during the whole study. Dietary analyses were conducted at baseline and 12 weeks of the study. Subjects were asked to provide a detailed three-day food records which were guided by a trained investigator. Compliance was assessed using a short questionnaire every 2 weeks. When compliance was less than 80%, subjects were excluded from the trial.

Outcome measures

At baseline and at the end of intervention, height and weight were measured by trained staffs, and body mass index (BMI) was calculated as weight divided by height squared (kg/m2). Waist circumference, hip circumference and blood pressures were measured by the same staffs. Fasting blood samples were collected after a fasting overnight and a 3-hour OGTT was performed (continue to collect blood samples at 30, 60, 120, 180 minutes after a 75 g glucose challenge).

Serum samples were centrifuged (15 min, 3000×g, 4 °C) within 30 minutes after the blood collection and were stored at -80℃. Fasting serum adiponectin was measured using an ELISA kit with a solid phase two-site enzyme immunoassay (Mercodia, Uppsala, Sweden). The average intra- and inter-assay CV for adiponectin were 3.1 and 5.4%, respectively.

Hemoglobin A1c was analyzed by the high-pressure liquid chromatography (HPLC) (Bio-Rad Laboratories, USA). Insulin and C-peptide were assayed by the electrochemical luminescence (Roche Diagnostics, Indianapolis, USA). Laboratory analyses of blood glucose, lipid profiles (total cholesterol, triglyceride, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol, apolipoprotein A-1 and apolipoprotein B), C-reactive protein (CRP), and safety variables (liver enzymes) were performed by using an automatic biochemical analyser (Mindray BS600, Shenzhen, China) following standard protocols.

Statistical Analysis

SPSS 22.0 (IBM Inc., Chicago, IL, USA) was used for statistical analysis, and R 3.5.3 (R Foundation, Vienna, Austria) was used for graphing. $P < 0.05$ was considered as significant. The per-protocol data set without imputation of missing data was used to data analysis. We used the unpaired Student's *t*-test (for continuous variables) and chi-square tests (for categorical variables) to evaluate the baseline differences between the anthocyanins and placebo groups. An independent Student's *t*-test was used to compare the differences between the two groups after intervention. We assessed the differences before and after the intervention

within each group by using a paired *t*-test. Multiple comparisons are statistically corrected by using false discovery rate (FDR).

Results

General characteristics of the subjects

A total of 160 eligible participants (80 each intervention group) with prediabetes (n=90) or newly diagnosed diabetes (n=70) were included in this trial. Baseline characteristics of all the randomized participants are presented in **Supplemental Table 1**. Participants in anthocyanins and placebo groups were comparable in terms of age, gender, education, lifestyle factors, dietary intakes and physical activities. Twenty participants (12.5%) lost from the study and two participants were in poor compliance, resulting in 138 cases finally analyzed. Relatively more dropouts were observed in the placebo group (n =13) than in the anthocyanins group (n = 3). The flow chart presented in **Figure 1** shows the allocation and finally available for each group.

More than 90% of the participants in each group consumed at least 85% of the supplements provided, and no significant difference was observed in the proportion of poor compliance between the two groups. Participants reported a total of 10 adverse events to the intervention, and the proportion of adverse events did not significantly different between the two groups (**Supplemental Table 2**). There are 3 participants reported abdominal pain (n = 1), diarrhea (n = 1) and skin rash (n = 1) in the placebo groups; 7 participants reported black stool (n = 5) insomnia (n = 1) and dizziness (n= 1) in the anthocyanins group. Within the subgroup of prediabetes and newly diagnosed diabetes, comparisons for baseline values indicated that the subjects among the two intervention groups had similar metabolic parameters (**Table 1**). No significant difference was observed between the anthocyanins and placebo groups in dietary intakes and nutrients in either the baseline or the end of the study (**Supplemental Table 3**).

Table 1 Baseline values of adiponectin and glucolipid metabolic parameters between the anthocyanins and placebo group for the participants classified with prediabetes and newly diabetes

	Prediabetes			Newly diabetes		
	Anthocyanins (n=41)	Placebo (n=49)	*P*	Anthocyanins (n=39)	Placebo (n=31)	*P*
Adiponectin (ug/mL)	6.05±2.48	6.49±2.28	0.41	5.93±2.4	5.77±1.62	0.762
Glucose metabolism						
Hemoglobin A1c (%)	5.8±0.42	5.63±0.43	0.074	6.49±0.53	6.46±0.48	0.854
Fasting glucose (mmol/L)	5.68±0.68	5.87±0.44	0.145	6.62±0.82	6.48±0.66	0.418
2-h glucose (mmol/L)	7.66±2.03	7.05±1.8	0.144	12.08±3.03	11.74±3.34	0.661
Fasting insulin (μU/mL)	11.58±5.79	11.22±5.6	0.773	11.49±7.12	13.21±6.6	0.314
2-h insulin (μU/mL)	81.45±53.51	82.12±71.98	0.961	102.56±68.11	109.42±71.86	0.686
Fasting C-peptide (ng/mL)	2.27±0.92	2.29±0.81	0.943	2.58±1.1	2.81±1.26	0.424
2-h C-peptide (ng/mL)	10.9±3.68	10.56±3.7	0.674	12.14±3.86	12.45±4.25	0.754
AUC Glucose	23.7±4.04	23.96±3.76	0.785	33.66±6.01	32.56±5.55	0.465
AUC Insulin	195.77±95.64	208.35±105.93	0.608	211.23±126.83	260.78±129.8	0.142
AUC C-peptide	25.72±7.44	25.47±6.22	0.875	26.64±7.35	29.86±8.47	0.121
HOMA-IR	2.94±1.6	2.91±1.39	0.937	3.41±2.39	3.91±2.18	0.383
HOMA-β	112.65±68.82	104.3±97.25	0.664	77.31±41.61	87.36±38.99	0.316
Lipids						
Total cholesterol (mmol/L)	5.99±1.2	5.99±1.03	0.996	6.24±1.17	6.06±1.46	0.57
Triglycerides (mmol/L)	1.7±0.9	1.69±1	0.949	1.73±1.14	1.8±1.58	0.822
HDL cholesterol (mmol/L)	1.45±0.39	1.48±0.34	0.693	1.48±0.37	1.43±0.34	0.528
LDL cholesterol (mmol/L)	3.35±0.88	3.28±0.82	0.67	3.43±0.94	3.33±0.99	0.654
Apo A-1 (g/L)	1.55±0.3	1.66±0.28	0.073	1.64±0.34	1.63±0.34	0.907
Apo B (g/L)	1.17±0.25	1.13±0.22	0.506	1.16±0.22	1.14±0.28	0.836
LDLHDL ratio	2.44±0.76	2.34±0.82	0.554	2.46±0.86	2.46±0.94	0.998
TGHDL ratio	1.33±0.93	1.29±1.08	0.848	1.32±1.21	1.42±1.49	0.77

AUC, area under the curve by 3-hour oral glucose tolerance test, were calculated according the trapezoidal rule.

HOMA-IR, homoeostasis model assessment of insulin resistance; HOMA-IR= FIns (mU/mL) ×FG (mmol/L)/22.5.

HOMA-β, homoeostasis model assessment of β-cell function; HOMA-β= FIns×20/(FG-3.5).

HDL, high-density lipoprotein; LDL, low-density lipoprotein; apo A-1, apolipoprotein A-1; apo B, apolipoprotein B; TG, Triglycerides.

P value was for the differences between the two groups, compared by independent student's *t*-test.

Changes in serum adiponectin

After 12 weeks intervention, serum adiponectin reduced both in the placebo group (-0.31 ug/mL [-0.55, -0.06], *p*=0.015) and anthocyanins group (-0.29 ug/mL [-0.53, -0,05], *p*=0.021). There was no significant difference in the net change of serum adiponectin between the anthocyanins and placebo group in the overall subjects (0.02 ug/mL [-0.32, 0.36], *p*=0.906) (**Figure 2 A**).

In the subgroup of prediabetes, serum adiponectin reduced in the anthocyanins group (-0.51 ug/mL [-0.86, -0.16], *p*=0.006) but not in placebo group (-0.17 ug/mL [-0.53, 0.2], *p*=0.365), and the net change between the two groups was nonsignificant (-0.35 ug/mL [-0.85, 0.16], *p*=0.174) (**Figure 2 B**). In the subgroup of newly diabetes, there was a significant reduction of serum adiponectin in the placebo group (-0.48 ug/mL [-0.8, -0.16], *p*=0.004), whereas a null change in the anthocyanins group (-0.02 ug/mL [-0.33, 0.3], *p*=0.917), and the net change of adiponectin between the two groups was statistically significant (0.46 ug/mL [0.03, 0.90], *p*=0.038) (**Figure 2 C**).

Changes in markers for glucose and lipid metabolism

Compared with placebo, anthocyanins decreased fasting glucose (-0.5 mmol/L [-1, -0.04], *p*=0.035) in the subjects with newly diagnosed diabetes (**Supplemental Table4**), and increased serum apo A-1 (0.15 g/L [0.03, 0.26], *p*=0.016), decreased apo B (-0.1 g/L [-0.17, -0.03], *p*=0.008) in the subjects with prediabetes (**Supplemental Table5**). Similar changes in apo A-1 and apo B were observed in the overall subjects. No significant change was observed in the inflammatory marker such as C-reactive protein, the anthropometric measurements such as the body weight, BMI, waist and hip circumferences, and blood pressures either in the overall subjects or in the subgroups (data will be submitted on request).

Discussion

To our knowledge, this is the first study to examine the effect of purified anthocyanins supplementation on serum adiponectin in patients with prediabetes and newly diagnosed diabetes. This study showed that 320mg/day of purified anthocyanins supplementation for 12 weeks improved serum adiponectin and decreased fasting glucose, independent of hypoglycemic agents, in patients with newly diagnosed diabetes, but not in patients with prediabetes.

Comparison with other studies

Few intervention studies have investigated the effect of anthocyanins on circulating adiponectin in cardiometabolic diseases. A previous trial from our laboratory that conducted in well-controlled type 2 diabetic patients has showed that purified anthocyanins increased serum adiponectin and decreased fasting glucose, but without avoiding the potential interactions with medications[11]. Thus, we rigorously tried to assure that our participants did not take any hypoglycemic drug or presented any other chronic inflammatory disease that could interfere with the results. At present study, we observed significant improvements of adiponectin and fasting glucose in the participants with newly diagnosed diabetes, but not in those with prediabetes, which may be due to the less hyperglycemia status of prediabetes.

There are three trials using anthocyanins-rich supplements in patients with metabolic syndrome that reported the changes in adiponectin. Black raspberry treatment for 12 weeks significantly improved serum adiponectin levels (net change 1.9 ug/mL) and vascular endothelial function [14]. Consuming cranberry juice for 60 days increased serum adiponectin levels (graphic display), whereas no effect on inflammatory markers [15]. Anthocyanins-rich grape powder increased plasma adiponectin in subjects with non-dyslipidemia (net change 1.1 ug/mL), but decreased plasma adiponectin in subjects with dyslipidemia (net change -1.7ug/mL), who might be exposed to a more inflammatory environment and were less responsive to the dietary intervention[16]. Our participants had a mean triglyceride of 1.8 mmol/L, a mean HDL of 1.46 mmol/L, and with approximately 50% within the metabolically normal range. Moreover, with a normal mean CRP of 2.2mg/L, it is not surprising to observe a less remarkable improvement in adiponectin (net change 0.46 ug/mL) in the subjects with newly diabetes and a nonsignificant change in prediabetes and the overall subjects.

Clinical implications of this study

In the patients with newly diagnosed diabetes, we observed a decrease of serum adiponectin in the placebo group, which reveals the change of adiponectin in the progression of diabetes, whereas anthocyanins prevented the reduction of adiponectin, leading to a mild but significant relative increment. Hypoadiponectinemia may be an important component of the pathogenesis in insulin resistance and type 2 diabetes[17]. Several epidemiological studies have demonstrated that hypoadiponectinemia was associated with the development of insulin resistance and T2DM, and suggested that adiponectin could be a novel target for the treatment of diabetes in near future[18, 19]. A cohort study performed in initially normoglycemic subjects showed that low serum adiponectin predicted development of impaired glucose regulation (IGR) and T2DM [20], and suggested that low level of adiponectin may play a key role in the pathogenesis of abnormal glucose metabolism. A nested case-control study has also shown that low levels of adiponectin predict the deterioration of insulin sensitivity[21]. Another case-control study suggested that decreased serum adiponectin might be an independent predictor for progression of type 2 diabetes[22]. Considered together, these studies suggest that anthocyanins may prevent the progression to diabetes by improving serum adiponectin and fasting glucose in newly diagnosed diabetes.

The improvement of adiponectin may has cardiovascular-protective implication, which is consistently with the clinical implications of the changes in apo A-1 and apo B[23, 24]. Hypoadiponectinemia may contribute to the pathogenesis of coronary artery disease[25]. A cohort study showed that hypoadiponectinemia might act as a predictor of the impairment of endothelium-independent vasodilation in early type 2 diabetic patients[26]. Another case-control study suggested that the lower level of adiponectin correlated with the indicators of vascular damage and contributed to cardiovascular risk in type 2 diabetic patients [27].

Possible mechanism

It has been demonstrated that adiponectin could increase hepatic insulin sensitivity and glucose utilization through activation of adenosine monophosphate (AMP) kinase and peroxisome proliferator-activated receptor-alpha (PPARα) [28]. A previous experimental study from our laboratory has shown that anthocyanin

upregulated adiponectin secretion in adipocytes through transcription factor forkhead box O1 (FoxO1) in diabetic mice[29]. Basic studies have also demonstrated anti-diabetic activity of anthocyanins, which may be related to the activation of AMP-activated protein kinase and PPAR in adipose tissue and skeletal muscles[30]. Anthocyanin also might ameliorate insulin resistance via activation of insulin signaling and enhanced glucose transporter 4 (GLUT4) translocation, which increased glucose uptake and reduced the hyperglycemia associated with the metabolic disorders[31]. These studies may help to explain the reduction of fasting glucose in patients with newly diagnosed diabetes.

The potential cardiovascular-protective mechanism of anthocyanins is clearly understood. The previous study of our laboratory also found that anthocyanin protected against diabetes-related endothelial dysfunction[29]. In addition, basic and clinical studies have identified the anti-atherogenic function of adiponectin [32], and the positive effect in vascular inflammation and endothelial function[33]. Hypoadiponectinemia-induced inflammasome activation may be the molecular mechanism for diabetic vascular endothelial dysfunction[34]. On the other hand, adiponectin could improve endothelium-independent vasodilation by inducing the production of endothelial nitric oxide (NO) [35].

Limitation And Conclusion

The following limitations should be considered in the present study: first, there was possible incomplete blinding in this study because of the different contents of capsules, which may result in the relatively high dropout in the placebo group; second, there was no objective measure of compliance during the intervention period, and the data of serum anthocyanins or their metabolites was lacking. The complete clearance of anthocyanins in plasma needs 6~8 hours exceeded by 8~10 hours fasting[36]. Finally, we only measured total adiponectin rather than high-molecular-weight adiponectin. Nonetheless, data on the relevance of their distinction showed similar results[37, 38].

In conclusion, this randomized placebo-controlled trial showed that 12 weeks anthocyanins supplementation increased serum adiponectin and decreased fasting glucose in newly diagnosed diabetes but not in prediabetes. Additional long-term studies are needed to confirm the serial changes in adiponectin levels by anthocyanins intervention from normoglycemic individuals to prediabetes and new-onset diabetes.

Abbreviations

T2DM, type 2 diabetes; RCT, randomized controlled trial; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; FDR, false discovery rate; HbA1c, glycated hemoglobin A1c; LDL, low-density lipoprotein; HDL, high-density lipoprotein; C-reactive protein, CRP; apoA-1, apolipoprotein A-1; apo B, apolipoprotein B.

Declarations

Acknowledgements

The authors appreciate all the patients for their continuing participation in this study and all the medical staff for blood sample and data collection.

Funding information

This study was supported by the Key Project of National Natural Science Foundation of China (grant number 81730090) and the Health Technology Project of NanShan, ShenZhen (grant number 2019034).

Authors' contributions

Liping Yang: writing the manuscript; Wenhua Ling: study supervision; Yun Qiu and Jing Yang: data collection and curation; Li Wang: statistical analysis and visualization; Yong Liu: study resources; Changyi Wang and Jianping Ma: project adiministration and funding acquisition.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Sun Yat-sen University (No. 201503), and each participant provided written informed consent.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

References

1. Li S, Shin HJ, Ding EL, van Dam RM: **Adiponectin levels and risk of type 2 diabetes: a systematic review and meta-analysis.***JAMA* 2009, **302:**179-188.
2. Liu C, Feng X, Li Q, Wang Y, Li Q, Hua M: **Adiponectin, TNF-alpha and inflammatory cytokines and risk of type 2 diabetes: A systematic review and meta-analysis.***Cytokine* 2016, **86:**100-109.
3. Lopez-Jaramillo P: **The Role of Adiponectin in Cardiometabolic Diseases: Effects of Nutritional Interventions.***J Nutr* 2016, **146:**422S-426S.
4. Katsiki N, Mantzoros C, Mikhailidis DP: **Adiponectin, lipids and atherosclerosis.***Curr Opin Lipidol* 2017.
5. Menzaghi C, Trischitta V: **The Adiponectin Paradox for All-Cause and Cardiovascular Mortality.***Diabetes* 2018, **67:**12-22.
6. Schulze MB, Shai I, Rimm EB, Li T, Rifai N, Hu FB: **Adiponectin and future coronary heart disease events among men with type 2 diabetes.***Diabetes* 2005, **54:**534-539.
7. Bergmark BA, Cannon CP, White WB, Jarolim P, Liu Y, Bonaca MP, Zannad F, Morrow DA: **Baseline adiponectin concentration and clinical outcomes among patients with diabetes and recent acute**

coronary syndrome in the EXAMINE trial.*Diabetes, obesity & metabolism* 2017.

8. Lindberg S, Pedersen SH, Mogelvang R, Bjerre M, Frystyk J, Flyvbjerg A, Galatius S, Jensen JS: **Usefulness of adiponectin as a predictor of all cause mortality in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention.***Am J Cardiol* 2012, **109:**492-496.
9. Tamura T, Furukawa Y, Taniguchi R, Sato Y, Ono K, Horiuchi H, Nakagawa Y, Kita T, Kimura T: **Serum adiponectin level as an independent predictor of mortality in patients with congestive heart failure.***Circ J* 2007, **71:**623-630.
10. Jennings A, Welch AA, Spector T, Macgregor A, Cassidy A: **Intakes of anthocyanins and flavones are associated with biomarkers of insulin resistance and inflammation in women.***J Nutr* 2014, **144:**202-208.
11. Li D, Zhang Y, Liu Y, Sun R, Xia M: **Purified anthocyanin supplementation reduces dyslipidemia, enhances antioxidant capacity, and prevents insulin resistance in diabetic patients.***J Nutr* 2015, **145:**742-748.
12. American Diabetes A: **Standards of medical care in diabetes–2013.***Diabetes Care* 2013, **36 Suppl 1:**S11-66.
13. Qin Y, Xia M, Ma J, Hao Y, Liu J, Mou H, Cao L, Ling W: **Anthocyanin supplementation improves serum LDL- and HDL-cholesterol concentrations associated with the inhibition of cholesteryl ester transfer protein in dyslipidemic subjects.***Am J Clin Nutr* 2009, **90:**485-492.
14. Jeong HS, Hong SJ, Lee TB, Kwon JW, Jeong JT, Joo HJ, Park JH, Ahn CM, Yu CW, Lim DS: **Effects of black raspberry on lipid profiles and vascular endothelial function in patients with metabolic syndrome.***Phytother Res* 2014, **28:**1492-1498.
15. Simao TN, Lozovoy MA, Simao AN, Oliveira SR, Venturini D, Morimoto HK, Miglioranza LH, Dichi I: **Reduced-energy cranberry juice increases folic acid and adiponectin and reduces homocysteine and oxidative stress in patients with the metabolic syndrome.***Br J Nutr* 2013, **110:**1885-1894.
16. Barona J, Blesso CN, Andersen CJ, Park Y, Lee J, Fernandez ML: **Grape consumption increases anti-inflammatory markers and upregulates peripheral nitric oxide synthase in the absence of dyslipidemias in men with metabolic syndrome.***Nutrients* 2012, **4:**1945-1957.
17. Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K: **Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome.***J Clin Invest* 2006, **116:**1784-1792.
18. Achari AE, Jain SK: **Adiponectin, a Therapeutic Target for Obesity, Diabetes, and Endothelial Dysfunction.***Int J Mol Sci* 2017, **18**.
19. Hafiane A, Gasbarrino K, Daskalopoulou SS: **The role of adiponectin in cholesterol efflux and HDL biogenesis and metabolism.***Metabolism* 2019, **100:**153953.
20. Jalovaara K, Santaniemi M, Timonen M, Jokelainen J, Kesaniemi YA, Ukkola O, Keinanen-Kiukaanniemi S, Rajala U: **Low serum adiponectin level as a predictor of impaired glucose regulation and type 2 diabetes mellitus in a middle-aged Finnish population.***Metabolism* 2008, **57:**1130-1134.
21. Lindsay RS, Funahashi T, Hanson RL, Matsuzawa Y, Tanaka S, Tataranni PA, Knowler WC, Krakoff J: **Adiponectin and development of type 2 diabetes in the Pima Indian population.***Lancet* 2002, **360:**57-58.
22. Banerjee A, Khemka VK, Roy D, Poddar J, Roy TKS, Karnam SA: **Role of Serum Adiponectin and Vitamin D in Prediabetes and Diabetes Mellitus.***Canadian journal of diabetes* 2017.

23. Walldius G, Jungner I, Aastveit AH, Holme I, Furberg CD, Sniderman AD: **The apoB/apoA-I ratio is better than the cholesterol ratios to estimate the balance between plasma proatherogenic and antiatherogenic lipoproteins and to predict coronary risk.***Clinical chemistry and laboratory medicine* 2004, **42:**1355-1363.
24. McQueen MJ, Hawken S, Wang X, Ounpuu S, Sniderman A, Probstfield J, Steyn K, Sanderson JE, Hasani M, Volkova E, et al: **Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case-control study.***Lancet (London, England)* 2008, **372:**224-233.
25. Stojanovic S, Ilic MD, Ilic S, Petrovic D, Djukic S: **The significance of adiponectin as a biomarker in metabolic syndrome and/or coronary artery disease.***Vojnosanit Pregl* 2015, **72:**779-784.
26. Li H, Xiao Y, Liu H, Chen XY, Li XY, Tang WL, Liu SP, Xu AM, Zhou ZG: **Hypoadiponectinemia predicts impaired endothelium-independent vasodilation in newly diagnosed type 2 diabetic patients: an 8-year prospective study.***Chin Med J (Engl)* 2011, **124:**3607-3612.
27. Spurna J, Karasek D, Kubickova V, Goldmannova D, Krystynik O, Schovanek J, Zadrazil J: **Relationship of Selected Adipokines with Markers of Vascular Damage in Patients with Type 2 Diabetes.***Metab Syndr Relat Disord* 2018, **16:**246-253.
28. Yamauchi T, Kamon J, Ito Y, Tsuchida A, Yokomizo T, Kita S, Sugiyama T, Miyagishi M, Hara K, Tsunoda M, et al: **Cloning of adiponectin receptors that mediate antidiabetic metabolic effects.***Nature* 2003, **423:**762-769.
29. Liu Y, Li D, Zhang Y, Sun R, Xia M: **Anthocyanin increases adiponectin secretion and protects against diabetes-related endothelial dysfunction.***Am J Physiol Endocrinol Metab* 2014, **306:**E975-988.
30. Rozanska D, Regulska-Ilow B: **The significance of anthocyanins in the prevention and treatment of type 2 diabetes.***Adv Clin Exp Med* 2018, **27:**135-142.
31. Luna-Vital D, Weiss M, Gonzalez de Mejia E: **Anthocyanins from Purple Corn Ameliorated Tumor Necrosis Factor-alpha-Induced Inflammation and Insulin Resistance in 3T3-L1 Adipocytes via Activation of Insulin Signaling and Enhanced GLUT4 Translocation.***Mol Nutr Food Res* 2017, **61**.
32. Kishida K, Funahashi T, Shimomura I: **Molecular mechanisms of diabetes and atherosclerosis: role of adiponectin.***Endocr Metab Immune Disord Drug Targets* 2012, **12:**118-131.
33. Han SH, Sakuma I, Shin EK, Koh KK: **Antiatherosclerotic and anti-insulin resistance effects of adiponectin: basic and clinical studies.***Prog Cardiovasc Dis* 2009, **52:**126-140.
34. Zhang J, Xia L, Zhang F, Zhu D, Xin C, Wang H, Zhang F, Guo X, Lee Y, Zhang L, et al: **A novel mechanism of diabetic vascular endothelial dysfunction: Hypoadiponectinemia-induced NLRP3 inflammasome activation.***Biochimica et biophysica acta* 2017, **1863:**1556-1567.
35. Xi W, Satoh H, Kase H, Suzuki K, Hattori Y: **Stimulated HSP90 binding to eNOS and activation of the PI3-Akt pathway contribute to globular adiponectin-induced NO production: vasorelaxation in response to globular adiponectin.***Biochem Biophys Res Commun* 2005, **332:**200-205.
36. McGhie TK, Walton MC: **The bioavailability and absorption of anthocyanins: towards a better understanding.***Mol Nutr Food Res* 2007, **51:**702-713.
37. Kizer JR, Benkeser D, Arnold AM, Mukamal KJ, Ix JH, Zieman SJ, Siscovick DS, Tracy RP, Mantzoros CS, Defilippi CR, et al: **Associations of total and high-molecular-weight adiponectin with all-cause and**

cardiovascular mortality in older persons: the Cardiovascular Health Study.*Circulation* 2012, **126:**2951-2961.

38. Kizer JR, Arnold AM, Benkeser D, Ix JH, Djousse L, Zieman SJ, Barzilay JI, Tracy RP, Mantzoros CS, Siscovick DS, Mukamal KJ: **Total and high-molecular-weight adiponectin and risk of incident diabetes in older people.***Diabetes Care* 2012, **35:**415-423.

Figures

Figure 1 The CONSORT flowchart of the study

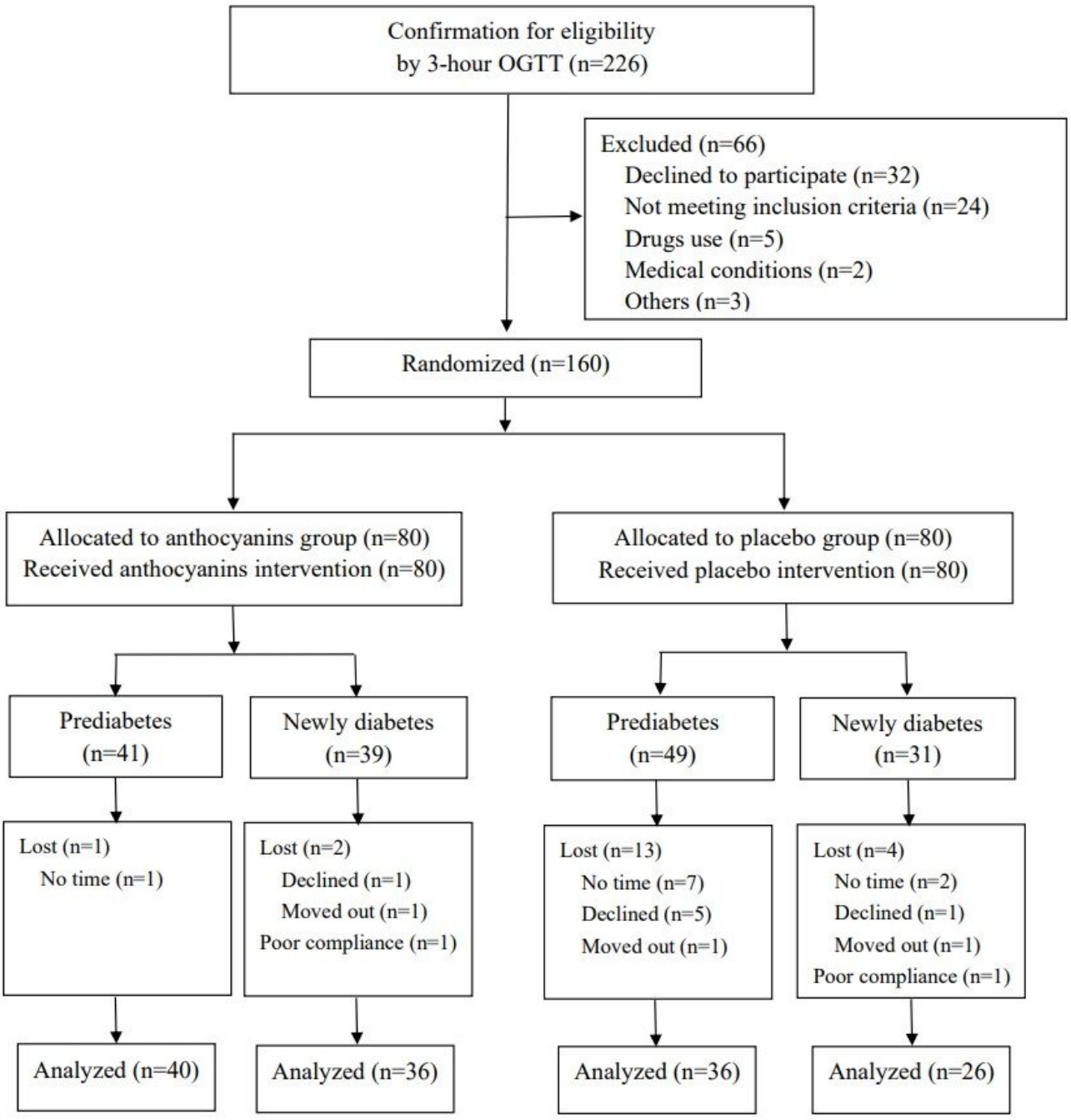

Figure 1

The CONSORT flow diagram for participants

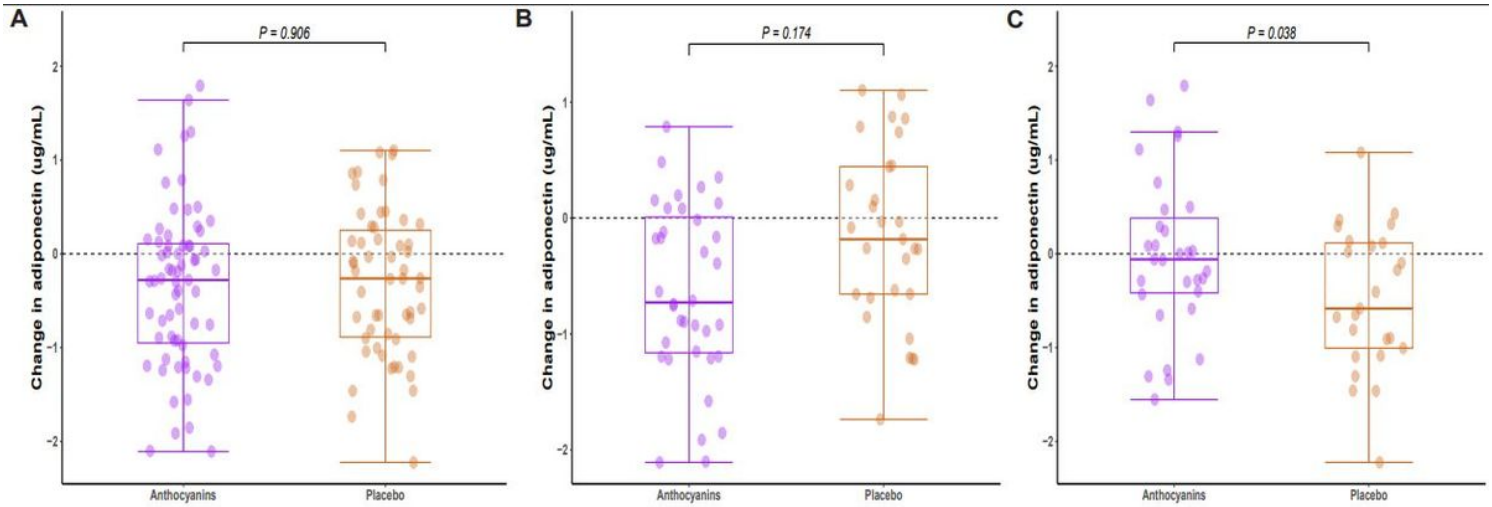

Figure 2

Changes in serum adiponectin after 12 weeks of treatment with anthocyanins or placebo. (A) changes in serum adiponectin in the overall subjects, (B) changes in serum adiponectin in the subjects with prediabetes, (C) changes in serum adiponectin in the subjects with newly diagnosed diabetes.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementaltables.docx
- Highlights.docx