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RESEARCH ARTICLE

Effects of Metformin, Avocado Seed, and Diabetic Ingredients Infusion to Weight and Fasting Blood Glucose on Sucrose Diet Rats

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Abstract

Metformin, an oral hypoglycemic drug which has metabolic effects and weight loss after 6–9 months; however, after 18 months, these effects disappear. Oral hypoglycemic drugs with no effect on raising the weight are needed. The objective of the study is comparing the effects of metformin, avocado seed infusion (AS), and diabetic ingredients/ DI (green chiretta, Java tea, and bitter grapes) in increasing weight and fasting blood glucose of rats with sucrose diet. The research was conduct at the Pharmacology Laboratory, Faculty of Medicine Universitas Kristen Maranatha in February–August 2017. The results showed that metformin within six weeks reduced weight (75.55%) compared to control (+) with a hypercaloric diet (114.36%). Metformin and hypercaloric diet in rats for 14 weeks showed a 125.66% increase in weight, higher than control (+) (114.36%), although not significant ($p>0.05$). Weight in rats with hypercaloric and AS diet for 14 weeks was 94.30% and 81.68% in DI was lower than control (+) (114.36%), but not significant ($p>0.05$). Fasting blood glucose (FBG) of dietary hypercaloric rats and metformin was 123.75 mg/ dL, higher than control (+), which was 85.75 mg/dL ($p<0.01$), whereas FBG infusion of AS and DI during 14 weeks: 85.75 mg/dL, and 99.50 mg/dL, not significant to control (+) ($p>0.05$). In conclusions, metformin increased rats body weight even though not significantly and fasting blood glucose in rats fed a hypercaloric diet for 14 weeks, while avocado seed infusion and diabetic ingredients infusion did not.

Key words: Avocado seed, diabetic ingredient, fasting blood glucose, metformin, weight

Efek Metformin, Infusi Biji Alpukat, dan Infusi Ramuan Diabetes terhadap Berat Badan dan Glukosa Darah Puasa pada Tikus Diet Sukrosa

Abstrak

Metformin, obat hipoglikemik oral berefek metabolik dan menurunkan berat badan (BB) setelah 6–9 bulan, namun setelah 18 bulan efek ini hilang. Diperlukan obat hipoglikemik oral yang tidak berefek meningkatkan BB. Tujuan penelitian ini membandingkan efek metformin, infusi biji alpukat (BA), dan infusi ramuan diabetes/RD (sambiloto, kumis kucing, dan bratawali) dalam meningkatkan BB dan glukosa darah puasa pada tikus diet sukrosa. Penelitian dilaksanakan di Laboratorium Farmakologi, Fakultas Kedokteran Universitas Kristen Maranatha periode Februari–Agustus 2017. Hasil penelitian menunjukkan metformin dalam waktu 6 minggu mengurangi penambahan BB (75,55%) dibanding dengan kontrol (+) diet hiperkalori (114,36%). Pemberian metformin dan diet hiperkalori pada tikus selama 14 minggu menunjukkan kenaikan BB 125,66%, lebih tinggi dibanding dengan kontrol (+) (114,36%), walaupun tidak signifikan ($p>0,05$). Berat badan pada tikus dengan diet hiperkalori dan infusi BA selama 14 minggu adalah 94,30% dan RD 81,68%, lebih rendah dibanding dengan kontrol (+) (114,36%), namun tidak signifikan ($p>0,05$). Glukosa darah puasa (GDP) tikus diet hiperkalori dan metformin adalah 123,75 mg/dL, lebih tinggi dibanding dengan kontrol (+) 85,75 mg/dL ($p<0,01$), sedangkan GDP infusi BA dan RD selama 14 minggu adalah 85,75 mg/dL dan 99,50 mg/dL, tidak signifikan terhadap GDP kontrol (+) ($p>0,05$). Simpulan, metformin meningkatkan berat badan tikus walau tidak signifikan dan meningkatkan glukosa darah puasa pada tikus diet hiperkalori selama 14 minggu, sedangkan infusi biji alpukat dan ramuan diabetes tidak.

Kata kunci: Berat badan, biji alpukat, gula darah puasa, metformin, ramuan diabetes

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Introduction

Metformin is a widely used drug for type 2 diabetes mellitus treatment. The hypoglycemic effect of metformin caused by decreasing production of liver glucose and increasing usage of glucose. Metformin has a beneficial effect on fat that can reduce fatty liver. AMP-activated protein kinase (AMPK) is the primary regulator at the cellular level for fat and glucose metabolism. Metformin activates AMPK that decrease the activity of acetyl-CoA carboxylase (ACC) in hepatocytes, induce fatty acid oxidation, and suppress the expression of the lipogenic enzyme. Thus, the effect of metformin on inhibiting glucose production in the liver and increasing usage of glucose by muscle cell is through AMPK activation. AMPK is a multisubunit enzyme that regulates to biosynthesis fat by its role in phosphorylating and inactivate acetyl-CoA enzyme. AMPK has a full function in metabolism, such as metabolism of fatty acid, uptake glucose by muscle, and glucose-stimulated genes associated with liver lipogenesis, include fatty acid synthase (FAS). Chronic activation of AMPK may include muscle hexokinase expression, and glucose transporter, which has the mimicry effect of extensive physical exercise. AMPK activation has the right approach for handling type 2 DM. Metformin has metabolic effects through activation of AMPK.[1] Metformin used in the treatment of type 2 diabetes mellitus and has an additional effect of reducing weight.[2]

The results of a meta-analysis of 11 studies published in 1995 about a patient that was given metformin or sulfonylurea 6–52 weeks, including nine studies that obtained information about changes in body weight.[3] The use of sulfonylureas associated with increased body weight seen in all studies.[3–5] Weight loss in metformin was seen in 7 studies, increasing body weight in 2 studies.[3] The metformin decreases body mass index (BMI) –1.38 (95% KI –1,93 to –0,82) kg/m^2 after six months while the effect of giving metformin over 12 months of treatment the results were not significantly different compared to placebo. Weight loss with metformin achieved after 6–9 months; then after 18 months, the BMI returns to its BMI before treatment.[6]

The BMI correlates with the development of type 2 diabetes mellitus. Every 1 kg increase in excess weight has a risk of 49% for the development of type 2 diabetes mellitus within ten years.[7] Women of childbearing age who are obese have a risk of getting type 2 diabetes 2.63 times greater than women of childbearing age who are not obese.[8]

Therefore, research on blood glucose-lowering agents that do not cause weight gain needs to be developed, especially for the treatment of diabetes mellitus. Traditionally, people treat diabetes mellitus with avocado seed. A study conducted an assessment of the antidiabetic activity of avocado seed extract (*Persea americana* Mill) with glucose tolerance test method, with the resulting decrease of concentration of glucose.[9–12] Also, the community also uses diabetic ingredients consisting of green chiretta (*Andrographis paniculata* (Burm. f.) Nees), Java tea (*Orthosiphon stamineus* Benth), and bitter grapes (*Tinospora rumphii* Boerl) to treat diabetes mellitus.[13–18] Both the avocado seeds and the diabetic ingredients (green chiretta, Java tea, and bitter grapes) are expected not to have the effect of increasing body weight when used as an oral hypoglycemic drug. This study was conducted to obtain oral hypoglycemic drugs that did not affect increasing body weight, and the aim was to compare the effects of metformin, avocado seed infusion (AS), and diabetic ingredients/DI infusion (green chiretta, Java tea, and bitter grapes) on increasing body weight of rats with sucrose diet.

Methods

The design of this study was an experimental laboratory study with experimental animals Wistar rats aged two months with a hypercaloric diet in the form of drinking water 20% sucrose (w/v). This research conducted at the Pharmacology Laboratory, Faculty of Medicine Universitas Kristen Maranatha in February–August 2017.

The treatment groups (n=4) are (1) Metformin A group, rats were given a hypercaloric diet for eight weeks, then hypercaloric diet & metformin for six weeks; (2) Metformin B group, rats were given a hypercaloric diet+metformin for 14 weeks; (3) Avocado seeds A group, rats were given a hypercaloric diet for eight weeks, then hypercaloric diet+AS infusion dose of 0.5 g/kgBW for six weeks; (4) Avocado seeds B group, rats were given a hypercaloric diet+AS infusion dose of 0.5 g/kgBW for 14 weeks; (5) Diabetes ingredients infusion A group, rats were given a hypercaloric diet for 8 weeks, then hypercaloric diet+DI infusion (green chiretta, Java tea, and bitter grape = 1:1:2) dose of 0.5 g/kgBW for 6

weeks; (6) Diabetes ingredients infusion B group, rats consumed a hypercaloric diet+DI infusion (green chiretta, Java tea, and bitter grapes = 1:1:2) dose of 0.5 g/kgBW for 14 weeks; (7) Positive control, rats were given a hypercaloric diet for eight weeks and hypercaloric diet for six weeks; and (8) Negative control, rats were given pellets and distilled water without a hypercaloric diet for 14 weeks.

The measured data is the weight of each group at then was performed a statistical test with the one-way ANOVA and the Tukey HSD test with alpha=0.05.

This research approved by the Research Ethics Committee of the Faculty of Medicine Universitas Kristen Maranatha-RS Immanuel Bandung with letter number: 230b/KEP/VIII/2017.

Results

The study began with weighing the weight of experimental animals before treating. The results of rats body weight measurements before and after treatment has presented in Table 1.

Discussion

The results showed that experimental animals of rats fed a hypercaloric diet with sucrose administration of 20% (w/v) in drinking water for 14 weeks showed an increase in body weight of 114.36%. Pre-experimental weight was 159.5 gram, and after 14 weeks of the hypercaloric diet, the weight of rat was 341 gram. Weight of the rat without hypercaloric diet was 157.75 gram, and after 14 weeks the rat weighed 295.75 gram, increase 87.80%. Weight of rat that were given a hypercaloric diet in 8 weeks and after that was given hypercaloric diet and metformin in 6 weeks was 157 gram and became 276.25 gram after 14 weeks, increase 75.55%. This result shows that metformin can reduce weight in 6 weeks compare to hypercaloric diet rats (114.36%) and negative control (87.80%). Giving metformin and a hypercaloric diet in rats for 14 weeks showed a weight gain of 125.66%, a pretreatment body weight of 162.5 grams to 363.75 grams after treatment. This result shows an increase of weight in rats that with metformin and hypercaloric diet in 14 weeks, the enhancement is higher (125.66%) compare to hypercaloric diet in 14 weeks only (114.36%), even though the difference is not significant ($p>0.05$).

Being overweight and obese increases the risk of cardiovascular disease, various types of cancer, and various other health problems.[19]

Table 1 Measurements of Rats Weight Before and After Treatment

Groups	Weight of Rats in Group (gram)							
	MA	MB	AS-A	AS-B	DI-A	DI-B	K+	K–
Before treatment								
Rat 1	141	166	159	180	175	188	163	189
Rat 2	156	177	132	169	172	149	158	140
Rat 3	161	154	172	168	172	154	168	158
Rat 4	170	153	164	170	170	191	149	144
Mean	157	162.5	156.75	171.75	172.25	170.5	159.5	157.75
Treatment in 8 weeks								
Rat 1	186	261	277	195	282	260	278	276
Rat 2	260	291	220	252	281	327	275	218
Rat 3	194	206	236	297	283	301	268	251
Rat 4	335	279	270	233	244	237	282	241
Mean	243.75	259.25	250.75	244.25	272.5	281.25	275.75	246.5
Treatment in 14 weeks								
Rat 1	228	397	278	307	297	244	349	340
Rat 2	316	296	299	363	328	364	330	247
Rat 3	241	422	296	347	294	352	333	309
Rat 4	320	340	289	315	338	237	352	287
Mean	276.25	363.75	290.5	333	314.25	299.25	341	295.75

The result of one-way ANOVA $p \geq 0.05$, MA: metformin A group, MB: metformin B group, AS-A: avocado's seed A group, AS-B: avocado's seed B group, DI-A: diabetes ingredients A group, DI-B: diabetes ingredients B group, K+: positive control, K–: negative control

Table 2 Percentage of Rats Weight Increase After 14 Weeks

Rats	Percentage of Rats Weight Increase							
	MA	MB	AS-A	AS-B	DI-A	DI-B	K+	K–
1	61.70	139.16	74.84	70.56	69.71	29.79	114.11	79.89
2	102.56	67.23	126.52	114.79	90.70	144.30	108.86	76.43
3	49.69	174.03	72.09	106.55	70.93	128.57	98.21	95.57
4	88.24	122.22	76.22	85.29	98.82	24.08	136.24	99.31
Mean	75.55	125.66	87.42	94.30	82.54	81.68	114.36	87.80

The result of one-way ANOVA p≥0.05, MA: metformin A group, MB: metformin B group, AS-A: avocado's seed A group, AS-B: avocado's seed B group, DI-A: diabetes ingredients A group, DI-B: diabetes ingredients B group, K+: positive control, K–: negative control

Table 3 Fasting Blood Glucose Level in Rats After 14 Weeks Treatment

Rats	Fasting Blood Glucose Measurement in Each Group (mg/dL)							
	MA	MB	AS-A	AS-B	DI-A	DI-B	K+	K–
1	88	113	108	79	94	89	83	96
2	107	122	118	91	103	89	101	104
3	108	119	116	95	95	110	80	93
4	122	141	111	78	106	110	79	103
Mean	106.25	123.75	113.25	85.75	99.5	99.5	85.75	99

The result of one-way ANOVA p≥0.05, MA: metformin A group, MB: metformin B group, AS-A: avocado's seed A group, AS-B: avocado's seed B group, DI-A: diabetes ingredients A group, DI-B: diabetes ingredients B group, K+: positive control, K–: negative control

Table 4 Tukey HSD Test Result of Fasting Blood Glucose Level in Rats After 14 Weeks Treatment

	Fasting Blood Glucose Measurement (mg/dL)							
	MA 106.25	MB 123.75	AS-A 113.25	AS-B 85.75	DI-A 99.5	DI-B 99.5	K+ 85.75	K– 99
MA 106.25		NS	NS	NS	NS	NS	NS	NS
MB 123.75			NS	**	*	*	**	*
AS-A 113.25				*	NS	NS	*	NS
AS-B 85.75					NS	NS	NS	NS
DI-A 99.5						NS	NS	NS
DI-B 99.5							NS	NS
K+ 85.75								NS
K– 99								

NS: not significant, *significant, **very significant, MA: metformin A group, MB: metformin B group, AS-A: avocado's seed A group, AS-B: avocado's seed B group, DI-A: diabetes ingredients A group, DI-B: diabetes ingredients B group, K+: positive control, K–: negative control

Therefore, oral hypoglycemic agents that can reduce glucose and do not increase of weight need to be developing. Research that assesses the antidiabetic activity of avocado seed extract (*Persea americana* Mill), with glucose tolerance test method with the result of lowering blood glucose levels has conducted by Zuhrotun.[20] Phytochemical screening of simplicia and ethanol extract of avocado seeds showed polyphenols, tannins, flavonoids, triterpenoids, quinones, monoterpenoids, and sesquiterpenoids.

Also, the community used diabetic ingredient consisting of the green chiretta (*Andrographis paniculata* [Burm. f.] Nees), the Java tea (*Orthosiphon stamineus* Benth), and the bitter grape (*Tinospora rumphii* Boerl). The bitter grape has the main content: diterpene lactone, including andrographolide, and andropanoside. The green chiretta effect includes antipyretic, antimalarial, and anti-inflammatory. Java tea has the main content: glycoside orthophony, essential oil, saponin, saxophone, and potassium salt. The effects of Java tea include diuretics effect. The bitter grape has the main content: berberine alkaloids, columbine, picroretoside glycosides, and picroretin bitter substances. Bitter grape's stem has the effect of lowering blood glucose levels.[17,18] Both the avocado seeds and the diabetic ingredients that consist of green chiretta, Java tea, and bitter grape which have the potential as oral hypoglycemic drugs, should not have the effect of increasing body weight.

This study showed an increasing weight on rats that were given hypercaloric diet and avocado's seed in 14 weeks was 94.30%, lower than the positive control (114.21%), even though is not significantly different ($p>0.05$). The body weight of rats with a hypercaloric diet and diabetic ingredients infusion for 14 weeks showed an increasing rats weight 81.20%, lower than the increase in body weight of rats who received a hypercaloric diet only (114.36%), even though isn't significantly different ($p>0.05$).

The study also showed that average of fasting glucose levels in rats given metformin and a hypercaloric diet was 123.75 mg/dL, higher than fasting blood glucose levels in rats with a 14 weeks hypercaloric diet (85.75 mg/dL) with significantly different ($p<0.01$), with a mechanism that needs to be studied and examined further. Whereas, an average of fasting blood glucose levels of rats that received a hypercaloric diet and avocado seed infusion for 14 weeks was 85.75 mg/dL, an average of fasting blood glucose levels of rats receiving a hypercaloric diet and diabetes ingredients infusion was 99.50 mg/dL. Both of these fasting glucose levels were not significantly different ($p>0.05$).

Conclusions

Metformin increased rats body weight even though not significantly and fasting blood glucose in rats fed a hypercaloric diet for 14 weeks, while avocado seed infusion and diabetic ingredients infusion did not increase rats body weight and fasting blood glucose compared to controls who received a 14 weeks hypercaloric diet.

Conflict of Interest

The authors declare no conflict of interests.

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