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BOVINE COLLAGEN EFFECT IN MAINTAINING BLOOD SUGAR AND BODY WEIGHT STABILITY IN DIABETIC RATS

(EFEK KOLAGEN SAPI DALAM MENJAGA STABILITAS GULA DARAH DAN BERAT BADAN PADA TIKUS DIABETES)

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ABSTRACT

Diabetes causes degenerative processes to occur earlier, for example, during hyperglycemia, with increased levels of Advanced Glycation End Products (AGEs) damaging the body's metabolism. Consuming anti-diabetic medications lowers blood sugar levels; however, hypoglycemia, which can be life-threatening, often occurs. Additionally, patients with diabetes experience uncontrolled weight loss or weight gain. This study aims to test the potential of bovine collagen in maintaining stable blood sugar levels and body weight in rats induced with diabetic. A total of 24 seven-month-old Wistar rats were divided into four groups: negative control group; positive control group induced with streptozotocin at 50 mg/kg body weight (BW) and given water as placebo; a group induced with streptozotocin at 50 mg/kg BW and

treated with bovine collagen at a dose of 2x 400 mg/kg BW/day; and a third group of healthy rats receiving bovine collagen at the exact dosage. All groups were treated for four weeks, during which body weight and blood sugar levels were monitored. The results indicated that diabetic rats treated with bovine collagen had better weight control than the positive control group in the first week ($p = 0.033$); however, in subsequent weeks, bovine collagen did not affect body weight. Blood sugar levels in the four groups of rats during the first, second, and third weeks showed that bovine collagen significantly reduced blood sugar levels in diabetic rats from the first to the third week ($p < 0.05$). Additional doses or administering antioxidant flavonoids may be necessary from the second week onward to maintain weight stability.

Keywords: body weight; bovine collagen; diabetic; blood sugar levels

ABSTRAK

Diabetes melitus menyebabkan proses degeneratif terjadi lebih awal saat hiperglikemia dengan produk glikasi lanjutan atau Advanced Glycation End Product (AGEs) meningkat merusak metabolisme tubuh. Mengkonsumsi obat anti diabetes berefek menurunkan kadar gula darah namun sering mengakibatkan kondisi hipoglikemia yang dapat membahayakan nyawa. Selain itu, pasien diabetes melitus juga mengalami penurunan berat badan. Penelitian ini bertujuan untuk menguji potensi bovine collagen dalam menjaga kestabilan gula darah dan berat badan pada tikus yang diinduksi diabetes melitus. Sample 24 tikus wistar umur 7 bulan, dibagi empat kelompok, yaitu kelompok kontrol negatif; kelompok kontrol positif yang diinduksi streptozotocin 50 mg/ kg BB dan pemberian placebo air; kelompok tikus yang diinduksi streptozotocin 50 mg/ kg BB dan bovine collagen dengan dosis 2x 400 mg/kg BB/hari; kelompok ketiga tikus sehat yang diberi bovine collagen dengan dosis 2x 400 mg/kg BB/hari; kelompok keempat kontrol negatif. Semua kelompok diperlakukan selama 4 minggu, diamati berat badan dan gula darah. Hasilnya tikus diabetes yang diberi bovine collagen

berat badannya lebih terkontrol dibandingkan dengan kontrol positif (p=0,033) pada minggu pertama, sedangkan pada minggu selanjutnya bovine collagen tidak berefek pada BB. Kadar gula darah empat kelompok tikus minggu ke-1, ke-2 dan ke-3 (p<0,05) menunjukkan bovine collagen terbukti dapat menurunkan kadar gula darah pada tikus diabetes minggu pertama sampai minggu ketiga. Kemungkinan pada minggu ke-2 dan selanjutnya dibutuhkan tambahan dosis atau pemberian flavonoid antioksidan untuk menjaga kestabilan berat badan.

***Kata kunci**: berat badan; bovine collagen; diabetes melitus; kadar gula darah*

INTRODUCTION

Diabetes is a metabolic disorder that accelerates degenerative processes during hyperglycemia, characterized by elevated levels of Advanced Glycation End Products (AGEs) that impair body metabolism. High blood sugar levels, characteristic of diabetes, promote the formation of **AGEs**. These harmful compounds form when sugar molecules bond with proteins, including collagen. Physically, they lead to decreased elasticity by thickening the epidermis, weakening the dermis, and hardening connective tissues. Because AGEs impair cardiovascular function, cause joint problems, slow lipid metabolism, decrease muscle mass creation, and speed up skin aging, their accumulation offers serious health hazards.[1]

Typically, diabetic affects obese individuals since obesity can lead to diabetic conditions due to disrupted carbohydrate metabolism, followed by disturbances in other metabolic processes.[2] As insulin efficiency decreases over time, the body resorts to lipid breakdown (lipolysis) to compensate for energy deficiencies caused by impaired glucose utilization.[3] This can result in weight loss among those suffering from diabetes. While consuming anti-diabetic medication reduces blood sugar levels, it often

precipitates potentially lethal conditions like hypoglycemia.[4]

Hydrolyzed Collagen Peptides (HC), smaller, more readily absorbed molecules, are one type of oral collagen supplement that has become a viable alternative for delaying aging.[5] Fish and terrestrial mammals like cows are the sources of these peptides. Twenty-four hours after oral collagen, hydroxyproline glycine, and serine-hydroxyproline-glycine are found in the bloodstream and then build up in the skin.[6] Supplements containing collagen from pigs, cattle, and marine sources may be promising anti-aging options.[7]

The three main types of collagen found in supplements are types I, II, and III: Whereas Type II collagen comes from chicken and cows, Type I Collagen comes from marine fish. Collagen products have become increasingly popular in many nations due to scientific and technological breakthroughs, both as dietary supplements and for cosmetic purposes.[8]

Because it contains fewer amino acids, mammalian collagen is more thermally stable than fish collagen. Compared to collagen collected from cows, the structural connections in marine collagen are weaker. Fish collagen needs to be processed to create crosslinking before it can be used as a biomaterial in tissue engineering.[7]

This study aims to assess the potential of bovine collagen in stabilizing blood sugar and body weight in rats induced with diabetes mellitus.

METHOD

The study used a true experimental study that was done at an animal Laboratory at the Medical Faculty of Jenderal Achmad Yani University, Cimahi, West Java, Indonesia, and received ethical approval from the Faculty of Medicine's Ethics Committee at Jenderal Achmad Yani University under the number 018/UH2.10/2024 dated October 11, 2024.

The design of the study was randomized entirely, using 24 healthy Wistar rats (*Ratus novergicus*) calculated based on the Federer formula with four treatment groups, i.e. $(t-1)(r-1)>15$, where t represents the number of treatment groups (4 groups) and r denotes the number of replications (with $r=6$). The inclusion criteria were Wistar rats aged 7 months weighing 150-300 grams. The rats were randomly divided into four experimental groups: Group 1 consisted of diabetic rats that were given bovine collagen for four weeks; Group 2 included healthy rats that received bovine collagen for four weeks; Group 3 comprised diabetic rats that were given water as a placebo; and Group 4

served as the negative control group with healthy rats that received no treatment. The inclusion criteria for the Wistar rats were healthy, active, not depressed, aged 7 months, weighing 150-300 grams, and having blood sugar levels between 70-149 mg/dL (normal). Exclusion criteria included a weight loss of more than 20% during the adaptation period, while dropout criteria included death or signs of depression during the study. The research method employed was an experimental post-test-only design, with the observed parameters being blood sugar levels and body weight.[9-11]

Diabetic condition in the rats was induced using an injection of streptozotocin at a dose of 32 mg dissolved in 1 mL of Aquabidest, administered at a dose of 50 mg/kg body weight in a single injection at the beginning of the study.[12]

Pure bovine collagen was obtained by extracting collagen from beef bones, separating the fat, drying, grinding, demineralizing, and undergoing multiple extraction stages, followed by neutralization and purification. The final product was a fine powder of bovine collagen hydrolysate with a molecular weight of 1000-3000 daltons, produced by a small-medium enterprise in Sidoarjo, East Java. The dosage administered per oral intake was 1 mL (equivalent to 26.6 mg of bovine collagen) per rat. The equipment used included an oral feeding tube for administration, an Accu-Chek device for measuring blood sugar levels, blood sugar test strips, and a scale with a precision of three decimal places for weighing the rats.[1,4,10]

The observations made on the rats over four weeks were analyzed using one-way ANOVA to compare body weight and blood sugar levels among Groups 1, 2, 3, and 4. Before this analysis, homogeneity and normality tests were conducted, and the test results showed normal and homogeneous distributed data. The ANOVA test showed significant differences between the groups, so the test was continued with the Tukey post hoc test.

RESULT

Observation of Rat Body Weight

Table 1 shows the average body weight of the mice weighed weekly. Observing the four groups of rats over four weeks revealed notable differences. The negative control rats (K (-)) exhibited a consistent increase in body weight over the four weeks, with a steady rise each week, although there was a non-significant decrease in the final week. Healthy rats receiving bovine Collagen (P1) showed

fluctuating increases in body weight throughout the four weeks. This fluctuation may have been influenced by reduced activity levels while housed and having a good appetite, allowing them to consume all provided food. Additionally, the effects of bovine collagen may contribute to muscle mass development (anabolic mechanism), resulting in increased body weight in conjunction with elevated metabolic rates (caloric expenditure).[17]

Table 1. Rat Body Weight

Groups	Rat Body Weight (grams) by week					
	BW-Pre	**BW-0**	**BW-1**	**BW-2**	**BW-3**	**BW-4**
K (-)	192.4±9.5	195.7±8.1	203.6±8.4	204.9±9.7	212.1±11.9	196.3±10.3
K (+)	205.4±16.4	207.9±18.2	214.7±17.9	213.1±14.5	214.0±14.8	206.9±14.0
P1	201.9±12.9	203.3±13.6	214.57±17.0	206.6±19.0	211.6±19.2	206.9±18.3
P2	205.9±8.3	207.9±8.5	199.6±11.7	200.6±9.6	202.6±9.37	201.4±11.5

Note: BW refers to the body weight of the rats, K (-) is the negative control, K (+) is the group of rats induced with streptozotocin and given a water placebo, P1 is the group of rats given bovine collagen, and P2 is the group of rats induced with streptozotocin and given bovine collagen.

Diabetic rats receiving a placebo (K (+)) demonstrated a significant increase in body weight during the first and second weeks, which remained high until week four. It can be attributed to elevated blood sugar levels during weeks one and two, leading to decreased lipolysis metabolism and subsequent weight gain, causing general weakness. In these diabetic rats, eye secretions indicated poor health and reduced activity levels.[12] Changes in rat body weight can be more clearly compared between groups, as illustrated in Figure 1.

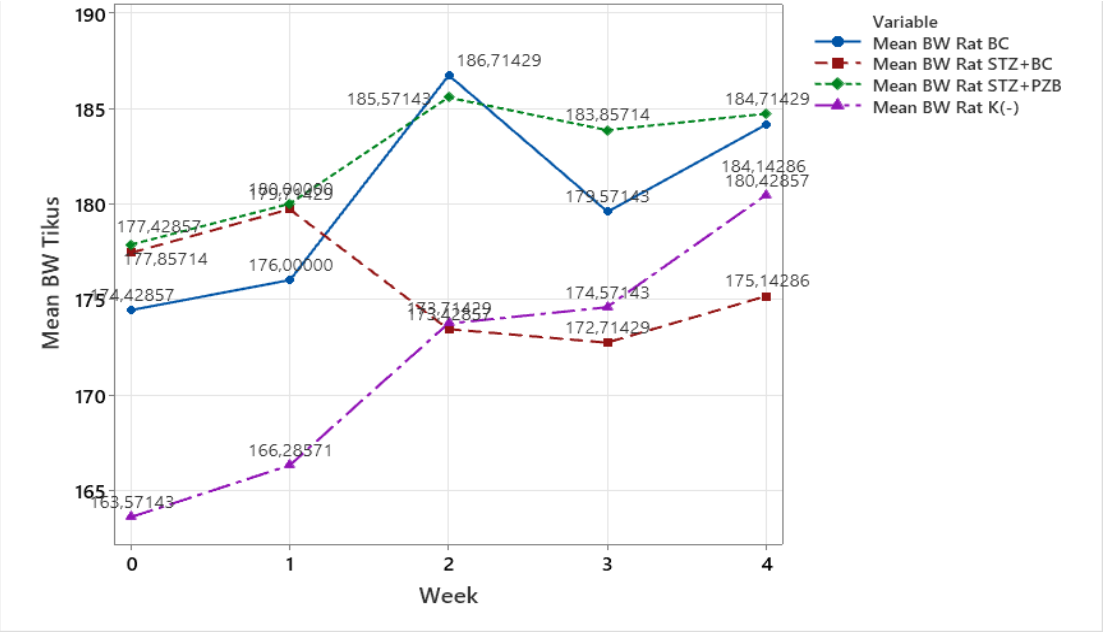

Figure 1. Graph of Body Weight (BW) of rats in four groups over four weeks.

Diabetic rats receiving bovine Collagen (P2) showed a slight increase in body weight to 179 grams during the first week, followed by a slight decrease in the second week, and then a minor increase again in the third week (172 grams) and fourth week (175 grams). The increase in body weight for diabetic rats treated with bovine collagen tended to stabilize during weeks three and four due to the mechanism by which bovine collagen enhances anabolic metabolism, where peptides from collagen serve as primary components for muscle mass. Collagen plays a role in reducing ghrelin levels, a "hunger" hormone that triggers appetite.[18] Figure 1 indicates that bovine collagen supports metabolic function as an anti-obesity agent in diabetic rats, consistent with the findings of Miguel López-Yoldi (2024) regarding the effects of oral collagen as an anti-obesity treatment. [13]

Observation of Blood Sugar Levels in Rats

The blood sugar levels of rats are observed in Table 2.

Table 2. Blood Sugar Levels in Rats

Groups	Blood Sugar Levels (mg/dl) by week					
	BSG-Pre	**BSG-0**	**BSG-1**	**BSG-2**	**BSG-3**	**BSG-4**
K (-)	133.1±21.1	127.1±13.2	121.1±12.4	109.1±8.6	117.9±15.3	121.9±14.5
K (+)	351.4±137	202.6±118	180.6±50.0	166.3±66.6	129.0±35.2	152.9±44.9

P1	122.7±11.5	137.3±17.6	119.2±14.4	127.8±11.4	108.6±19.5	120.1±11.4
P2	311.0±169	341.6±165	226.3±109	186.6±109	156.3±27.6	230.7±81.0

Note: K (-) refers to the negative control, K (+) denotes the group of rats induced with streptozotocin and given a water placebo, P1 is the group of rats receiving bovine collagen, and P2 is the group of rats induced with streptozotocin and given bovine collagen.

The observations in Table 2 regarding the blood sugar levels of the four groups of rats over four weeks indicate that the negative control rats maintained relatively stable normal blood sugar levels. Similarly, healthy rats receiving bovine collagen also exhibited stable blood sugar levels comparable to those of the negative control group. It suggests that bovine collagen does not significantly affect blood sugar levels in healthy rats.

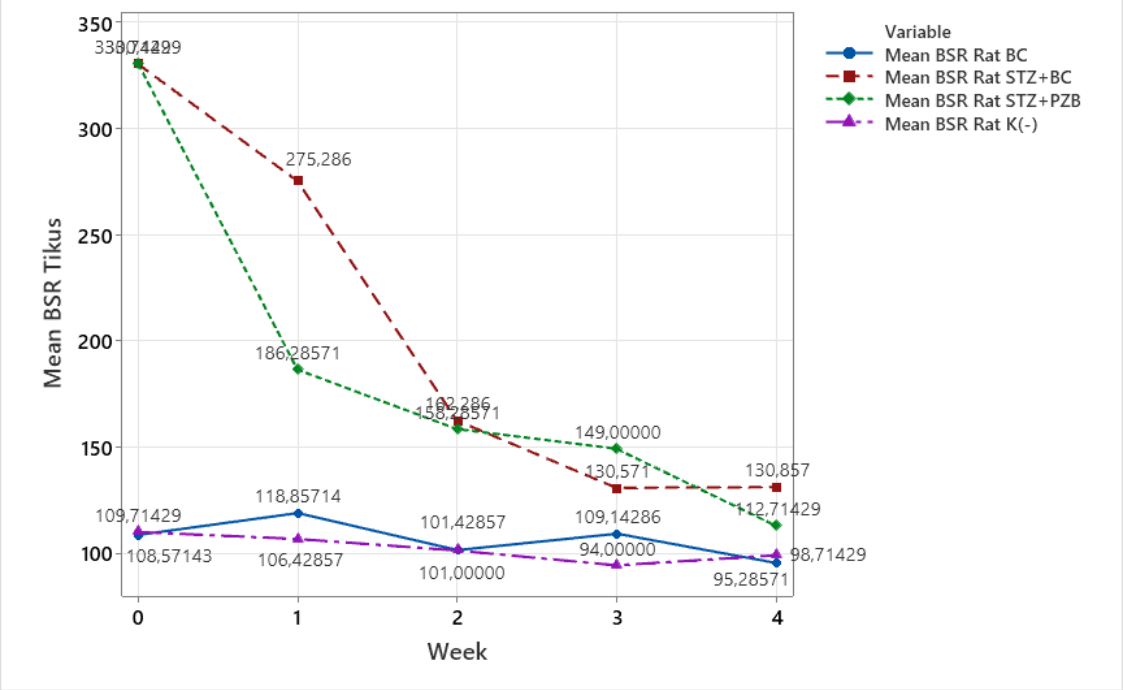

Figure 2. Graph of blood sugar levels in rats from four groups over four weeks.

As illustrated in Figure 2, diabetic rats treated with bovine collagen had a starting blood sugar level exceeding 330 mg/dL (severe hyperglycemia) on day zero.

Subsequently, their blood sugar decreased to 226 mg/dL (moderate hyperglycemia) by the first week, continuing to decline until reaching normal levels of 102 mg/dL by the fourth week. This gradual reduction in blood sugar levels indicates that treatment with bovine collagen effectively lowers blood sugar in diabetic rats, stabilizing it at normal levels by weeks three and four. The findings align with research by Sneedeker JG et al.(2023), which states that hyperglycemia triggers the

accumulation of AGEs, potentially accelerating aging processes. To address hyperglycemia and prevent aging, bovine collagen, composed of amino acids, may help repair damage to pancreatic beta cells responsible for insulin production.[14]

Insulin is crucial for regulating blood sugar levels, allowing them to return to normal.[17] That is, managing diabetes requires more than just anti-diabetic medications; it should also include combinations of flavonoids, collagen, and amino acids. Bovine Collagen is a vital source of amino acids for maintaining stable blood sugar levels in diabetic conditions. [1,16,18]

In contrast, diabetic rats receiving a placebo as a positive control exhibited an initial blood sugar level of 351 mg/dL (severe hyperglycemia) on day zero. By the first week, their blood sugar drastically dropped to 180 mg/dL (mild hyperglycemia), and by week four, it further declined to 152 mg/dL. The steep decrease in blood sugar during the first week poses a risk of hypoglycemia, characterized by symptoms such as weakness and decreased consciousness, which can be life-threatening.[19] Therefore, it can be concluded that the reduction in blood sugar levels among diabetic rats treated with bovine collagen is safer compared to those without bovine collagen treatment, as it helps prevent drastic drops in blood sugar (hypoglycemia). [20-21]

This study was conducted over four weeks, with a single induction of streptozotocin at a dose of 50 mg/kg body weight at the beginning. The rapid increase in blood sugar levels necessitated that they returned to normal by weeks three and four. Future research is recommended to repeat streptozotocin induction during week three to observe differences in blood sugar levels between diabetic rats receiving treatment and those in the positive control group. [10,16,18,22]

Based on the statistical analysis of the body weight of rats from week one to week four, the data showed a normal and homogeneous distribution. The data were analyzed using one-way ANOVA. The results of the ANOVA analysis can be seen in Table 3.

Table 3. Results of ANOVA Analysis of Body Weight in Four Groups of Rats Over Four Weeks

4 Groups	P. Value for Week-				
	0	1	2	3	4
	0.060	0.033	0.171	0.422	0.470

From week 0 to week 1, the P value (0.033) indicates a significant difference in body weight among the four groups of rats. However, from week 2 to week 4, the P

value was greater than 0.05, suggesting that there was no significant effect of bovine collagen on the body weight of the rats. It may be necessary to use a higher dose or a combination of other antioxidant substances that work synergistically for muscle mass formation. Therefore, to maintain the body weight of diabetic rats during the first week, bovine collagen may still be effective; however, from week 2 onwards, a higher dose or a combination of other supportive antioxidants is required. According to Yoldi (2024), bovine collagen acts as an anti-obesity agent in diabetes; thus, after consuming bovine collagen from weeks 2 to 4, the body weight of the rats remained more stable compared to both positive and negative control groups, which tended towards obesity. [13]

The statistical analysis of blood sugar levels in rats from week one to week four showed that the data were normally distributed and homogeneous. The data were analyzed using one-way ANOVA. The results of the ANOVA analysis can be seen in Table 4, which presents blood sugar levels from week 1 to week 4.

Table 2. Results of ANOVA Analysis of Blood Sugar Levels in Four Groups of Rats Over Four Weeks

4 Groups	P. Value for Week-				
	0	1	2	3	4
	0.001	0.033	0.017	0.042	0.075

The P value was below 0.05, indicating that bovine collagen maintained blood sugar stability until week 3. However, the blood sugar level at week 4 had a P value above 0.05, possibly due to the effect of streptozotocin induction at a dose of 50 mg/kg body weight, causing a short-term increase in blood sugar levels. Consequently, by weeks 3 and 4, blood sugar levels returned to normal. Future research is suggested to repeat the streptozotocin induction in week 3. [9,12]

DISCUSSION

Bovine collagen is a protein formed by very long amino acid chains after treatment with technology. It can incorporate water into the net and has the potential anti-obesity effects, increasing its water retention capacity in an acid pH medium stimulating gastric condition. In a previous study, collagen digestibility was tested using a pepsin digestion test. Postprandial levels of ghrelin in response to collagen supplementation thus collagen showed a low digestibility (<60%) and high swelling capacity (>1900%) in vitro.[13]

In humans with overweight and

obesity, this collagen significantly reduces body weight. Collagen reduces the sensation of hunger and increases fullness and satisfaction. Bovine collagen supplementation in diabetes helps to maintain blood sugar and prevent obesity by reducing the sensation of hunger and maintaining body weight. These may increase the quality of life in diabetes.[23]

The lack of effect of bovine collagen in the second week suggests that additional doses or the administration of antioxidant flavonoids may be necessary to maintain body weight stability.[22] The combination of other herbal ingredients could enhance its effects on blood sugar levels and body weight, one of which is Epigallocatechin gallate (EGCG), a polyphenol from green tea extract known to reduce inflammation and excess weight. When EGCG is combined with bovine collagen, which contains proline, it enhances antioxidant activity in the body, impacting blood sugar stability and body weight.[24] Chronic states of oxidative stress disequilibrium in the redox balance are typically associated with obesity and diabetes. Early difficulties in people with diabetes arise from dysfunction in the endothelium, the inner layer of blood vessels. Antioxidant-related dietary and lifestyle changes may be a useful preventative measure for diabetics.[25]

In rats with STZ-induced diabetes, EGCG has been shown to lessen the death of pancreatic B cells. It has been demonstrated that EGCG tea reduces body mass, decreases interstina lipid absorption, and increase insulin sensitivity in obese mice. EGCG stimulates insulin action and prevents hyperglycemia in vitro.[24]

In conclusion, combining EGCG and bovine collagen may be a supportive treatment for diabetics who want to maintain their body weight and avoid complications. Therefore, further research on combining bovine collagen and herbal antioxidants is encouraged. [18,21,26]

CONCLUSION

Based on the results and analysis, oral administration of bovine collagen in diabetic rats effectively maintained body weight stability during the first week; however, it did not significantly affect body weight stability in subsequent weeks. The oral administration of bovine collagen was proven to maintain blood sugar stability from week 1 to week 3.

CONFLICT OF INTEREST

There is no conflict of interest in this study.

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