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Research Article
The Effects of Replacement of Dietary Fiber with FiberCreme™ on Lowering Serum Glucose and Improvement of Lipid Profile in Hypercholesterolemia-Diabetic Rats and Its Mechanism

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Abstract

Background and Objectives: Dietary fiber is an important component in the diet and has important effects on health, such as reducing plasma glucose and cholesterol levels. FiberCreme™ is a commercial nondairy creamer that uses a variety of oligosaccharides as a source of fiber to replace the glucose component of conventional creamer combined with healthy oils as a palatable functional ingredient .The objectives of this study were to determine the effects of the replacement of dietary fiber with FiberCreme™ on lowering glucose and improvement of the lipid profile of hypercholesterolemia-diabetic rats. The possible mechanism of lowering cholesterol and glucose level was also studied *in vitro*. **Materials and Methods:** The diets used included a standard diet and a FiberCreme™ diet. Standard diets were fed to the rats in the control-healthy (CH), control-diabetic (CD) and metformin (METF) groups. FiberCreme™ diets were given to rats in the FC50, FC100 and FC150 groups. **Results:** The results showed that the FC100 diet decreased glucose by 56%, which is similar to the decrease seen with metformin (59%). The FC100 diet also reduced total cholesterol, LDL cholesterol and triglycerides by 84.2 mg dL^{-1} (46%), 31.69 mg dL^{-1} (43%), 18.9 mg dL^{-1} (15%), respectively and increased the HDL level from 24.1-50.2 mg dL^{-1} (108%). **Conclusion:** The *in vitro* study indicated that one of the mechanisms of lowering glucose was through the inhibition of glucose absorption in the small intestine and the mechanism of lowering cholesterol was through bile acid binding to the FiberCreme™.

Key words: FiberCreme™, hypercholesterolemia, diabetes, dietary habits, dietary fiber, glucose absorption

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The increase in prosperity and food availability in Indonesia has brought negative impacts to human health. One of the negative impacts is the change of dietary habits that lead to low dietary fiber consumption. This change resulted in the increasing prevalence of degenerative diseases, such as coronary heart disease, hypertension and diabetes mellitus (DM). In the last decade, epidemiological studies have demonstrated the trend of increasing incidence rates and prevalence of diabetes mellitus type 2 (NIDDM) worldwide. Diabetes mellitus type 2 is the most common form of diabetes worldwide, accounting for 90-95% of cases globally and representing a health threat to the population. The International Diabetes Federation predicts that the number of diabetics worldwide will increase from 425 million in 2017 to 629 million by 2045[1]. One therapeutic strategy to prevent type 2 diabetes involves increasing the intake of dietary fiber[2].

FiberCreme™ is a commercial nondairy creamer that uses a variety of oligosaccharides as a source of fiber to replace the glucose component of conventional creamer combined with healthy oils as a palatable functional ingredient. Oligosaccharides (inulin, raffinose, oligofructose, palatinose, isomaltose and lactosucrose) decrease the incidence of chronic diseases, such as insulin resistance, diabetes mellitus, hypertension and metabolic syndrome[3,4]. Isomaltose-oligosaccharides (IMOs) are oligosaccharides with α (1→6) glucoside bonds. Isomaltose, isomalto-triose, panose and isomaltotetraose are major components of commercial IMOs[5]. Partially digested IMOs in the small intestine and undigested portions undergo fermentation in the colon by intestinal microflora. This fermentation results in the production of short-chain fatty acids (SCFAs), which are dominated by acetate, propionate and butyrate[6]. Research on the physiological effects of IMOs remains very limited. Wang *et al.*[7] reported that IMOs improved lipid profile in hemodialysis patients by decreasing total cholesterol (-17.6%), triglycerides (-18.4%) and increasing HDL (+39.1%). Thus, FiberCreme™, which is rich in oligosaccharides (IMOs), can be an alternative foodstuff to prevent hyperglycemia and dyslipidemia.

This study aimed to identify the potential of FiberCreme™ as a dietary fiber source in the prevention of hyperglycemia and dyslipidemia through *in vivo* studies. The effects of different doses of FiberCreme™ on glucose level and blood lipid profile was investigated using hypercholesterolemia-diabetic rats. Hypercholesterolemia was induced with a high hypercholesterolemia diet and diabetes was induced using streptozotocin nicotinamide (STZ-NA). Possible mechanisms of lowering cholesterol and blood glucose were studied *in vitro*.

MATERIALS AND METHODS

Materials: The main research material of FiberCreme™ was obtained from PT. Lautan Natural Krimerindo (LNK), Mojokerto, Indonesia.

Experimental animal: Thirty *Wistar* rats initially weighing 150-200 g and aged 2-3 months were obtained from the Center for Food and Nutrition Studies, Gadjah Mada University where the experiment was conducted. All rats were maintained in individual cages with natural light/dark cycle and stable ventilation at room temperature (25-30°C). The rats were allowed to acclimatize for five days and received AIN93M standard diet[8,9], as shown in Table 1.

After 5 days of acclimation, rats were randomly divided into two groups: the control-healthy group (CH) (n = 5) and the experimental group (n = 25). The control-healthy group

Table 1: The composition of the standard, hypercholesterolemia and FiberCreme™ diets (Composition per 1000 g diet)

Components	Standard diet (g)	Hypercholesterolemia diet (g)	FC50 diet (g)	FC100 diet (g)	FC150 diet (g)
Corn starch	620.7	608.7	618.84	618.84	618.84
Casein	140.0	140.0	138.90	137.80	136.70
Sucrose	100.0	100.0	100.00	100.00	100.00
Soybean oil	40.0	40.0	27.38	14.76	3.14
Alphacel	50.0	50.0	0.00	0.00	0.00
AIN 93 MX	35.0	35.0	34.06	33.13	32.19
AIN 93 VX	10.0	10.0	10.00	10.00	10.00
L-cystine	1.8	1.8	1.80	1.80	1.80
Choline bitartrate	2.5	2.5	2.50	2.50	2.50
FiberCreme™	0.0	0.0	40.59	81.17	121.76
Cholesterol	0.0	10.0	0.00	0.00	0.00
Sodium cholate	0.0	2.0	0.00	0.00	0.00
Total	1000.0	1000.0	1000.00	1000.00	1000.00

Standard: AIN93 diet, Hypercholesterolemia diet: Standard diet added with 1% cholesterol, FC 50 diet: FiberCreme™ diet contains levels equivalent to 50% standard DF, FC 100 diet: FiberCreme™ diet contains levels equivalent to 100% standard DF, FC 150 diet: FiberCreme™ diet contains levels equivalent to 150% standard DF

(CH) received an AIN93M standard diet. The experimental group was fed with a hypercholesterolemia diet (Table 1) for seven days and then, cholesterol levels were determined. Hyperglycemia was induced in rats by intraperitoneal injection of nicotinamide (NA) in a buffered saline solution (NaCl) 0.9% (230 mg kg^{-1} of body weight) followed by injection of streptozotocin (65 mg kg^{-1} of body weight) 15 min later. To prevent the possibility of death due to hypoglycemia, rats were given 1 mL of 10% glucose solution orally after induction[10].

Blood glucose analysis: During the intervention, blood samples were taken weekly until the end of the experiment (4 weeks). The blood samples were collected from the *supraorbital* vein of the eye using capillary tubes. Blood samples were transferred into an Eppendorf tube and centrifuged (4000 rpm) for 15 min until blood serum was obtained. Glucose analysis was performed using the GOD-PAP method[11]. A total of 10 µL serum was inserted into the test tube and then 1 mL of GOD-PAP glucose reagent was added. Serum and reagent were mixed using a vortex and then incubated at 20-25°C for 20 min. The absorbance was read at λ = 500 nm. The blanks and standards were prepared using same procedure. The standard concentration was 100 mg dL^{-1}. Blood glucose levels were calculated using the following equation:

$$\text{Blood glucose}\left(\frac{\text{mg}}{\text{dL}}\right)=\frac{\text{Absorbance sample}}{\text{Absorbance STD}}\times\text{Cons.STD}$$

Total cholesterol analysis: Total cholesterol was determined enzymatically using the CHOD-PAP method[12] pre- and post intervention. A total of 10 µL serum was loaded into the test tube and 1 mL CHOD-PAP cholesterol reagent was added. Serum and reagent were vortexed then incubated at 20-25°C for 20 min. Absorbance was read at λ = 546 nm. The procedure was performed for blanks and standards. The standard concentration was 200 mg dL^{-1}. Total cholesterol level was calculated using the following equation:

$$\text{Blood total cholesterol}\left(\frac{\text{mg}}{\text{dL}}\right)=\frac{\text{Absorbance sample}}{\text{Absorbance STD}}\times\text{Cons.STD}$$

LDL cholesterol analysis: Total LDL cholesterol levels pre- and post intervention were measured enzymatically using the CHOD-PAP method[13]. A total of 10 µL serum was inserted into the test tube and then, 1 mL CHOD-PAP cholesterol reagent was added. Serum and reagent were vortexed and then incubated at 20-25°C for 20 min. Absorbance was read at λ = 546 nm. The procedure was performed for blanks and standards. The standard concentration was 100 mg dL^{-1}. Total LDL cholesterol level was calculated using the following equation:

$$\text{Blood LDL cholesterol}\left(\frac{\text{mg}}{\text{dL}}\right)=\frac{\text{Absorbance sample}}{\text{Absorbance STD}}\times\text{Cons.STD}$$

HDL cholesterol analysis: HDL cholesterol was examined using CHOD-PAP method[14], pre- and post intervention. Blood samples were transferred to an Eppendorf and centrifuged (4000 rpm) for 15 min until blood serum was obtained. Then, 200 µL of serum was inserted into the test tube and 500 µL of HDL precipitant was added. The solution was mixed using a vortex and incubated at 20-25°C for 15 min. After incubation, the supernatant was separated via centrifugation at 3000 rpm for 20 min. A total of 100 µL supernatant was loaded to the test tube and 1 mL CHOD-PAP cholesterol reagent was added. The solution was mixed with a vortex and incubated at 20-25°C for 20 min. Absorbance was read at λ = 546 nm. The procedure was performed for blanks and standards. The standard concentration was 200 mg dL^{-1}. Total HDL cholesterol level was calculated using the following equation:

$$\text{Blood HDL cholesterol}\left(\frac{\text{mg}}{\text{dL}}\right)=\frac{\text{Absorbance sample}}{\text{Absorbance STD}}\times\text{Cons.STD}$$

Triglyceride analysis: Triglyceride levels pre and post intervention were examined using the GPOP-PAP method[15]. A total of 10 µL serum was transferred to the test tube and then, 1 mL CHOD-PAP cholesterol triglycerides was added. Serum and reagent were vortexed and incubated at 20-25°C for 20 min. Absorbance was read at λ = 546 nm. The procedure was performed for blanks and standards. The standard concentration was 200 mg dL^{-1}. The triglyceride level was calculated using the following equation:

$$\text{Blood triglyceride}\left(\frac{\text{mg}}{\text{dL}}\right)=\frac{\text{Absorbance sample}}{\text{Absorbance STD}}\times\text{Cons.STD}$$

Inhibition of glucose absorption *in vitro*: Inhibition of glucose absorption was determined using everted suc modified method as reported in a previous study[16]. The sample was diluted in 1.4% glucose solution and AquaDest was added to make the water content of the solution 67%. The pH was adjusted to 6 and the mucosal fluid was incubated

under oxygen. The everted suc was cannulated at one end, transferred to the incubation tube, kept at 37°C and contained aerated bicarbonate saline. Serosal fluid was taken from the cannulated everted suc and was analyzed for glucose concentration at 15, 30, 45 and 60 min.

***In vitro* assay of bile acid binding:** The binding capacity of bile acid was determined using a method previously reported by Kongo-Dia-Moukala *et al.*[17] with a few modifications. Standard cholic acid and deoxycholic acid were dissolved in 50 mmol L^{-1} phosphate buffer (pH 6.5) to make a 2 mM bile acid solution, which is the same concentration of bile acid in the human body (1.5-7 mM). The pH was adjusted to the physiological pH of the duodenum. Then, 100 mg of samples were mixed with 10 mL of 2 mmol mL^{-1} of bile acid and the individual substrate solution without samples was used as a blank. The tube was incubated at 37°C for 30 min in a shaking water bath and then centrifuged at 2000 rpm for 5 min. Then, 50 µL of supernatant was obtained and added to 5 mL of 70% sulfuric acid and 1 mL of new furfural solution (0.25%). After 80 min incubation at room temperature, the absorbance was measured at 510 nm. Duplicate assays were performed for each bile acid assay. The percentage of bound bile acid was calculated as:

$$\text{Bound (\%)} = \frac{Cc - Cs}{Cc} \times 100$$

where, Cc and Cs represent bile acid concentration in the control and samples, respectively.

Statistical analysis: SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis with one-way analysis of Variance (ANOVA) followed by Duncan's Multiple Range Test (DMRT) at the 95% confidence level.

RESULTS AND DISCUSSION

Feed consumption: Total feed intake values for CH, CD, METF, FC50, FC100 and FC150 during the observation (28 day intervention) were 341, 391, 353, 344, 355 and 354 g, respectively. The control-diabetic (CD) group had the highest feed consumption compared to the other diet groups. This finding is attributed the fact that the CD group included diabetic rats that will experience polyphagia[18]; which makes the total feed intake higher than that of other groups. Total feed intake for the FC50, FC100 and FC150 groups was higher than that for the CH group. FiberCreme™ is more palatable than the standard feed. This finding might be due to the oil content of FiberCreme™.

Body weight: The changes in the body weight among the groups of rats during the experiment showed that the CH, METF, FC50, FC100 and FC150 rats had significant increases in body weight at the end of the intervention period. On the other hand, the body weight of the CD group decreased from 230-188.2 g (7.29%). The CD group was the only group that lost weight but had the highest intake of feed. These results are similar to recent data reported by Ma and Mu[19], indicating that rats with diabetic conditions exhibited decreased weight although food intake is increased. Under diabetic conditions, the CD group cannot utilize the sugar in the blood as an energy source because it is unable to uptake glucose into the muscle[20]. As a result, the body will use the energy source of the muscle via breaking down proteins (called as *protein washing*) or fat from the muscles, resulting in weight loss. The CH group had the most significance weight gain (29.4 g) followed by the METF (27.2 g), FC150 (24.6 g), FC100 (23.8 g) and FC50 (17.0 g) groups at the end of the experiment. For the group fed the FiberCreme™ diet, the different amounts of FiberCreme™ lead to significant increases in body weight.

Glucose level: Glucose levels were measured weekly during the experimental period and the results are shown in Fig. 1. Glucose levels in the CD group increased from 266.8-295.5 mg dL^{-1}. For the METF, FC50, FC100 and FC150 groups, the glucose levels decreased by 59, 38, 56 and 53%, respectively. The METF group exhibited the lowest glucose levels (59% decrease) because metformin works by inhibiting the production of hepatic glucose, reducing intestinal glucose absorption and improving glucose uptake and utilization[21].

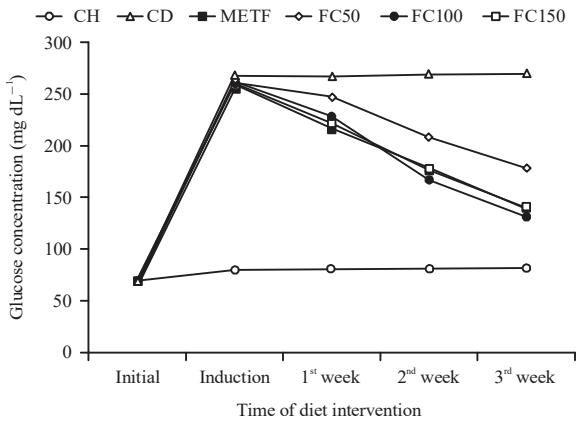

Fig. 1: Glucose concentration during 4 weeks of diet intervention

CH: Control-Healthy, CD: Control-Diabetic, METF: Diabetic-Metformin, FC50: Diabetic-FiberCreme™ 50, FC100: Diabetic-FiberCreme™ 100 and FC150: Diabetic-FiberCreme™ 150 group

Figure 1 demonstrates that FiberCreme™ decreased blood glucose levels in diabetic rats in a manner similar to metformin.

In this study, FiberCreme™ was used to replace 50, 100 and 150% fiber components in the diet. Regarding FC treatment, the FC100 group had the best effect on blood glucose reduction (56%). The hypoglycemic effect of FiberCreme™ was due to the isomaltose-oligosaccharides (IMOs), which is a fiber component of FiberCreme™. The hypoglycemic effect of dietary fiber was due to the inhibition of glucose absorption and increase in insulin sensitivity[22,23]. Similar features are noted between IMOs and inulin. Inulin is an oligosaccharide that has been widely studied for health benefits.

Rumessen *et al.*[24] reported that administering 20 g of inulin lowered the glycemic and inulin responses in healthy subjects. Other researchers reported that dietary inulin reduces glucose uptake and consequently lower postprandial hyperglycemia[25]. Hesta *et al.*[26] stated that the IMO diet has a decreased effect on blood glucose, resembling a diet high in fiber.

Cholesterol level: Cholesterol levels of the rats at the end of the experiment are presented in Fig. 2. The CH and CD groups exhibited slightly increased cholesterol levels during the experiment (2.90 and 2.57 mg dL^{-1}, respectively). Significant decreases in cholesterol were noted for the METF, FC50, FC100 and FC150 groups. Figure 2 demonstrates that the METF group had the most significant decrease (53%) followed by the FC100 (46%), FC150 (43%) and FC50 (15%) groups. These results are similar to previous reports that metformin has a good effect on lipid metabolism[27,28].

The results indicate that FiberCreme™ is effective in decreasing cholesterol levels, possibly due to the IMO component in FiberCreme™. IMO is an oligosaccharide that is a component of dietary fiber. Wang *et al.*[7] reported that IMO improves lipid profiles in hemodialysis patients (i.e., reduced total cholesterol via the use of Isomalto-oligosaccharide in the treatment of lipid profiles and constipation in hemodialysis patients). Other oligosaccharides, such as inulin, were also reported to have similar effects. Yamashita *et al.*[29] reported that in diabetics, consumption of 8 g inulin per day for 14 days can decrease cholesterol by 19 mg dL^{-1}. Causey *et al.*[30] reported that in a double-blind cross-over study of 12 volunteers with 20 g insulin consumed per day, inulin reduced cholesterol by 11 mg dL^{-1}.

Triglyceride levels: The data presented in Fig. 2 reveal significant decreases in triglyceride levels with FiberCreme™ treatment. Triglyceride levels are similar to total cholesterol

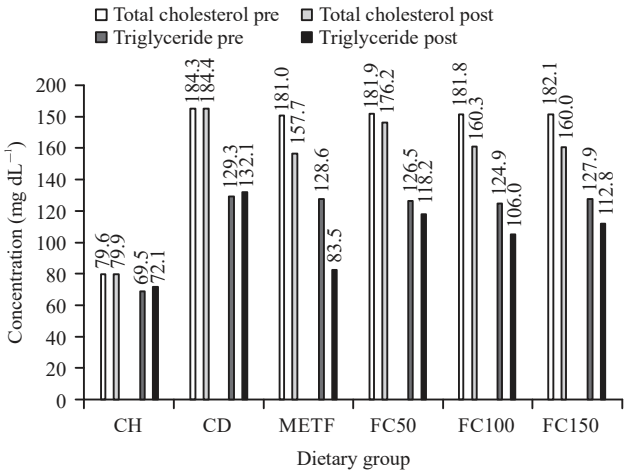

Fig. 2: Changes in total cholesterol and triglycerides of rats
CH: Control-Healthy, CD: Control-Diabetic, METF: Diabetic-Metformin, FC50: Diabetic-FiberCreme™ 50, FC100: Diabetic-FiberCreme™ 100 and FC150: Diabetic-FiberCreme™ 150 group

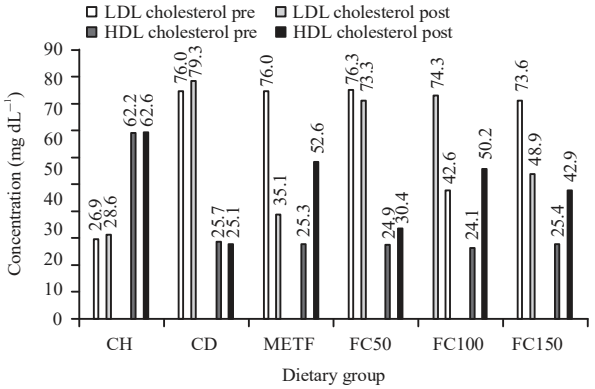

Fig. 3: Changes of LDL and HDL cholesterol levels in rats
CH: Control-Healthy, CD: Control-Diabetic, METF: Diabetic-Metformin, FC50: Diabetic-FiberCreme™ 50, FC100: Diabetic-FiberCreme™ 100 and FC150: Diabetic-FiberCreme™ 150 group

levels. The METF group had a higher decrease (-45.1 mg dL^{-1}). Among the group fed with FiberCreme™, the FC100 group had the most significant effect in decreasing the triglyceride levels (-18.9 mg dL^{-1}) followed by the FC150 (-15.1 mg dL^{-1}) and FC50 (-8.3 mg dL^{-1}) groups. This effect is attributed to the presence of oligosaccharide (IMO) in FiberCreme™. According to Tokunaga *et al.*[31] the addition of 10 and 29% oligofructose decreases triglyceride levels. Causey *et al.*[30] conclude that the consumption of 20 g of inulin per day reduces triglycerides by 40 mg dL^{-1}. Research on the effect of IMO on triglyceride has not been reported. In this study, FiberCreme™ (a non-dairy creamer containing IMO) showed that IMO can decrease triglycerides.

LDL level: Figure 3 presents LDL levels for all groups during the experiment. LDL levels in the CH group remained at

Table 2: *In vitro* bileacid (cholic acid and deoxycholic acid) binding of standard and FiberCreme™ diet (%)

Samples	Cholic acid binding (%)	Cholic acid binding relative to cholestyramine (%)	Deoxycholic acid (%)	Deoxycholic acid binding relative to cholestyramine (%)
Standard diet	7.63±0.80	9.96±1.04	4.48±0.12	6.77±0.18
FiberCreme™ diet	31.57±0.11	41.25±0.15	9.75±0.60	14.75±0.91
Cholestyramine	76.54±0.57	100	66.08±0.23	100

normal levels, while the CD group exhibited slightly increased levels (3.31 mg dL^{-1}). The METF group exhibited the most significant decrease (-40.90 mg dL^{-1}) followed by the FC100 (-31.69 mg dL^{-1}), FC150 (-24.69 mg dL^{-1}) and FC50 (-2.93 mg dL^{-1}) groups. The result showed that FiberCreme™ has a similar trend for LDL cholesterol and total cholesterol. The FC100 group is the most effective for both total cholesterol and LDL cholesterol compared to FC50 or FC150.

HDL level: The effect of FiberCreme™ on HDL was in contrast to its effects on LDL. HDL levels were increased during the experiment in the FiberCreme™ groups (Fig. 3). High HDL levels in the blood indicated that the risk of coronary heart disease is reduced. The FC100 group exhibited the greatest increase in HDL (26.16 mg dL^{-1}) followed by the FC150 (17.46 mg dL^{-1}) and FC50 (5.55mg dL^{-1}) groups. The increase in HDL in the FC100 group was almost similar to that in the METF group (27.29 mg dL^{-1}).

***In vitro* glucose inhibition:** The concentration of glucose in the serosal fluid increased during incubation and reached the maximum value at 60 min (7.2 mg L^{-1}) for a standard diet and at 75 min (3.05 mg L^{-1}) for the FiberCreme™ diet as shown in Fig. 4. Glucose concentrations in serosal fluid represent glucose absorption in the small intestine. Higher glucose concentrations in serosal fluid indicate higher absorption or lower inhibition. These data indicate a significant difference in the absorption of glucose and FiberCreme™ reduced glucose absorption more than a standard diet. These phenomena explain that FiberCreme™ plays an important role in the inhibition of glucose absorption in the small intestines, thereby lowering blood glucose concentration. This finding confirmed the hypothesis that one of the possible mechanisms of lowering glucose by dietary fiber was due to the inhibition of glucose absorption.

***In vitro* bile acid binding capacity of FiberCreme™ diet:** Binding of bile acids has been hypothesized as a possible mechanism for lowering cholesterol by dietary fiber[32]. To evaluate how the FiberCreme™ diet reduce cholesterol level, an *in vitro* study on the bile acid binding capacity to bile acid was conducted. The FiberCreme™ diet has a higher capacity for binding bile acids than the standard diet but a lower capacity than cholestyramine as shown in Table 2.

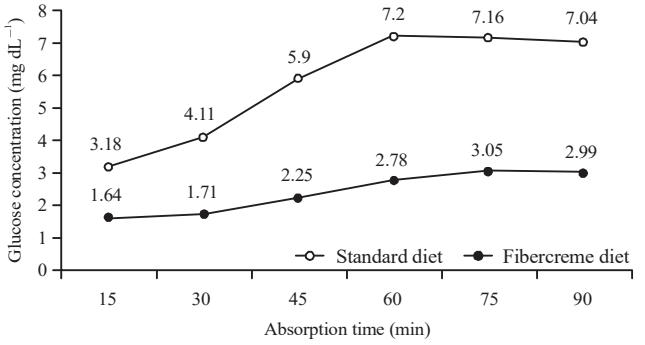

Fig. 4: Glucose concentration in serosal fluid

This result indicates that one of the mechanisms by which FiberCreme™ reduces cholesterol levelsin rats involves its capacity to bind bile acids. Binding bile acids increases the loss of bile acids through feces. Consequently, FiberCreme™ reduces the entero hepatic flow of bile acids to the liver. Therefore, the liver should produce more bile acids to be used to emulsify food lipids and cholesterol is required as the raw material of bile acids. The cholesterol was taken from the blood and the blood cholesterol was reduced.

CONCLUSION

It is concluded that replacement of dietary fiber with FiberCreme™ in the diet fed to hypercholesterolemia-diabetic rats for four weeks results in a significant decrease in glucose levels and improves the lipid profile. Replacement of 100% of the fiber source has the greatest effect on glucose reduction [146.4 mg dL^{-1} (56%)]. The result is almost similar to that obtained with metformin, which reduces glucose levels to 152.7 mg dL^{-1} (59%). The replacement of 100% of the fiber source (FC100) yields the greatest reduction in total cholesterol [84.2 mg dL^{-1} (46%)] and this result is similar to the use of metformin [96.1 mg dL^{-1} (53%)]. The diet also lowered LDL levels to 31.69 mg dL^{-1} (43), raised HDL levels to 26.16 mg dL^{-1} (108%) and lowered triglyceride levels to 18.9 mg dL^{-1} (15%). However, there is no significant effect on the water content of the digestive system. The effect on the weight of the digestive system is inconsistent with different FiberCreme™ dosages. The *in vitro* studied indicated that one of the mechanisms for reducing glucose was through

inhibition of absorption in the small intestine and the mechanism of reducing cholesterol occurred through bile acid binding by FiberCreme™.

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