

Effects of goat milk kefir fortified with vitamin D3 on Interleukin-18 levels in diabetic rats

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Effects of goat milk kefir fortified with vitamin D₃ on Interleukin-18 levels in diabetic rats¹Anggraeni, K.D., ^{1,2}Anjani, G., ^{1,2}Ardiaria, M., ^{1,2}Nissa, C., ³Huang, S.Y. and ^{1,2,3*}Panunggal, B.¹Department of Nutrition Science, Faculty of Medicine, Diponegoro University, Semarang, Indonesia²Center of Nutrition Research, Diponegoro University, Semarang, Indonesia³School of Nutrition and Health Sciences, Taipei Medical University, Taipei, Taiwan**Article history:**

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Hyperglycemia causes increased oxidative stress through an imbalance of reactive oxygen species and antioxidative mechanisms. It stimulates the production of inflammatory mediators and cytokines such as TNF- α , interleukin (IL)-1, and IL-18. Goat milk kefir and vitamin D₃ have potential as antioxidants and anti-inflammatory agents that can repair damage to pancreatic β cells. This study analyzed the effects of goat milk kefir fortified with vitamin D₃ on the IL-18 level in diabetic rats. An experimental randomized pre-post test with control group design was conducted on 20 male Wistar rats divided into four groups, namely negative control (K-), positive control (K+), treatment with unfortified kefir (P1), and treatment with kefir fortified with vitamin D₃. The intervention lasted 34 days. Fasting blood glucose and IL-18 levels were measured before and after intervention. Blood glucose and IL-18 levels were analyzed using the glucose oxidase p-aminophenol method and enzyme-linked immunosorbent assay, respectively. No significant increase in the IL-18 level was found in the P1 group with a median of 56.5 (10–252.7) pg/mL to 148.2 (106.8–428.3) pg/mL ($p = 0.465$) or P2 group with a median of 117.3 (91.8–146.8) pg/mL to 246.7 (168.8–311) pg/mL ($p = 0.068$), and no significant increase was observed in blood glucose levels in the P1 group (366.9 \pm 134.8 mg/dL to 462.1 \pm 156.9 mg/dL, $p = 0.357$) or P2 group (415.0 \pm 203.8 mg/dL to 258 \pm 129 mg/dL, $p = 0.463$). Goat milk kefir fortified with vitamin D₃ could maintain blood glucose and IL-18 levels.

1. Introduction

Diabetes mellitus is a metabolic multisystem disease caused by abnormalities in insulin secretion, action, or use, such that insulin secretion by pancreatic β cells is reduced (also called insulin resistance). Insulin is a hormone that regulates the balance of blood sugar levels. Abnormalities in insulin secretion can cause abnormal metabolism of carbohydrates, fat, and protein (Kemenkes RI, 2014). According to the International Diabetes Federation, hormonal insulin is produced by the pancreas and is used as a source of energy, but when the body produces less insulin, it can lead to hyperglycemia (Lathifah, 2017). Estimates of the prevalence of type 2 diabetes mellitus by the World Health Organization (WHO) were 6.4% in the age group of 20–79 years in 2010, and it is expected to increase to 7.7% by 2030. By 2030, Indonesia is expected to rank ninth worldwide in the epidemiological estimates of diabetes mellitus, with 20 million cases (Shaw *et al.*, 2010).

Hyperglycemia is a consequence of insulin resistance, leading to increased production of free radicals and oxidative stress that activate the transcription factor NF- κ B and trigger the production of inflammatory mediators and cytokines, such as interleukin (IL)-18, that are part of proximal cytokines. IL-18 is a pleiotropic proinflammatory cytokine that induces TNF- α production and is an early mediator of the inflammatory pathway; thus, IL-18 can be a sensitive marker of the chronic inflammatory process underlying insulin resistance (Escobar-Morreale *et al.*, 2004). The IL-18 concentration was found to be elevated in patients with type 2 diabetes and was associated with fasting blood glucose levels. The IL-18 concentration is increased in acute hyperglycemia through an oxidative mechanism (Krogh-Madsen *et al.*, 2006).

Vitamin D₃ is a precursor of vitamin D produced by ultraviolet (UV)-B radiation. Vitamin D can be obtained by dietary intake and plays a role in glucose tolerance

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and insulin sensitivity (Nakashima *et al.*, 2016). Vitamin D deficiency causes a decrease in insulin sensitivity because the concentration of 25(OH)D is low and requires vitamin D intake to improve sensitivity through vitamin D₃ fortification (Al-Shoumer, 2015; Talaei *et al.*, 2013). Vitamin D can increase insulin sensitivity by reducing proinflammatory agents involved in insulin resistance, including ILs and TNF- α , and also reducing NF- κ B activity (Bachali *et al.*, 2013).

Some studies have suggested that goat milk contains oligosaccharides that can reduce inflammation in the rat colon and probiotics that can significantly inhibit glucose intolerance, hyperglycemia, hyperinsulinemia, dyslipidemia, and oxidative stress in rats with diabetes (Ham *et al.*, 2008). Goat milk could reduce levels of IL-8, IL-6, TNF- α , and hs-CRP, but no association has been found between goat milk and IL-18 levels (Sunarti *et al.*, 2015). Because goat milk contains protein, fatty acids, amino acids, vitamins, and minerals but small amounts of vitamins D, C, B6, B12, and folic acid, it requires food fortification (Park *et al.*, 2007). Milk has perishable properties and thus requires intermediate processing techniques, namely milk fermentation. Kefir is one such fermented milk product (Hafidzoh and Agustini, 2014).

Kefir is a product of alcoholic acid fermentation that has a sour taste and a creamy consistency and contains complex probiotic bacteria such as *Lactobacilli*, *Lactococci*, *Leuconostoc*, *Acetobacter*, and yeast (Dianti *et al.*, 2018; Prado *et al.*, 2015). Kefir contains kefiran, an exopolysaccharide produced from lactic acid; has antitumor, antimicrobial, and anti-inflammatory functions; and can reduce blood sugar and cholesterol levels (Sunarti *et al.*, 2015; Dianti *et al.*, 2018; Nursiwi *et al.*, 2015). Kefir acts as a probiotic that can suppress the growth of digestive tract-causing bacteria because it can produce antimicrobial compounds such as bacteriocin, hydrogen peroxide, and various antibiotics (Hafidzoh and Agustini, 2014).

This study analyzed the effects of administering 2 mL/day of goat milk kefir fortified with vitamin D₃ on IL-18 levels in diabetic rats. To our knowledge, this is the first study to determine the effects of fortified kefir on IL-18 levels in diabetic rats, and no comprehensive and systemic overview of these topics has been published recently.

2. Materials and methods

This study was approved by the Ethics Committee of the Faculty of Medicine, Diponegoro University (No. 88/EC/H/FK-RSDK/VII/2018). This study was a pre-post control group design using *Rattus norvegicus*. Research

was conducted from July to September 2018 at the animal research laboratory of the Faculty of Medicine of Diponegoro University, the Integrated Laboratory of Diponegoro University, the Semarang Health Laboratory, and the Research Center of Biotechnology of Gadjah Mada University. This study used 20 experimental *R. norvegicus* specimens weighing 180–300 g each. The calculation of sample sizes was based on WHO recommendations with a minimum of five samples in each group (WHO, 2000).

Healthy, active, normal, 8–12-week-old male *R. norvegicus* with a bodyweight of 180–300 g and fasting blood glucose levels of >150 mg/dL after streptozotocin (STZ) induction were included in this study. The exclusion criteria of this study were a bodyweight of <180 g and fasting blood glucose levels of <150 mg/dL. The dropout criteria were behavioral changes or death during the course of the study. The dependent variable was the IL-18 level, and kefir fortified with vitamin D₃ was the independent variable. Rat species, age, sex, weight, feed, care, and enclosure environment were controlling variables.

The rats were randomly divided into four groups: animals without diabetes and with intervention (group 1, control); animals that were injected with STZ and nicotinamide (NA) without intervention (group 2, Diabetes 2); animals that were injected with STZ and NA plus kefir at 2 mL/day (group 3, P1); and animals that were injected with STZ and NA plus kefir fortified with vitamin D₃ at 242 IU/m at 2 mL/day (group 4, P2). The intervention was conducted for 35 days. The diabetic rats were induced with STZ at 65 mg/kg of bodyweight and NA at 230 mg/kg of bodyweight (Ghasemi *et al.*, 2014). The blood glucose level before intervention was measured 15 days after the induction period. The rats were considered diabetic when fasting blood glucose levels were >150 mg/dL. Collected data were rat bodyweights measured once a week and glucose and IL-18 levels before and after intervention. Glucose levels were analyzed using the enzyme-linked immunosorbent assay (ELISA) (Hung, 2005).

Collected data were statistically analyzed. The results were a comparison between the control and treatment groups. The normality of the data was analyzed using the Shapiro-Wilk test. Differences in the IL-18 level, blood glucose level, and body weight were analyzed using the paired *t* test if data were normally distributed and the parametric test (Wilcoxon test) if data were abnormally distributed. Differences in the effect of intervention between the treatment and control groups were analyzed using one-way analysis of variance if data were normally distributed and the Kruskal-Wallis test if

data were abnormally distributed (Sastroasmoro, 2014).

3. Results

3.1 Characteristics of samples before intervention

As detailed in Table 1, no significant differences were noted in the mean values of the initial criteria of the rats after STZ and NA induction, including bodyweight ($p = 0.021$), IL-18 level ($p = 0.075$), and fasting blood glucose level ($p = 0.057$).

3.2 Body weight, fasting blood glucose level, and IL-18 level before and after intervention

As detailed in Table 1, a significant increase in body weight was noted in the negative control group ($p = 0.06$) and positive control group ($p = 0.06$), whereas significant weight loss was observed in the treatment group with fortification ($p = 0.46$). No significant differences in body weight were noted between the groups before treatment ($p = 0.127$) and after treatment ($p = 0.197$).

A nonsignificant increase in the fasting blood glucose level was observed in the normal group (K-), the diabetic group (K+), the diabetic group administered kefir without fortification (P1), and the diabetic group administered fortified kefir (P2). The blood glucose level between the groups demonstrated significant differences before treatment ($p = 0.057$), whereas there were no significant differences after treatment ($p = 0.034$). No significant differences were observed in delta values between the groups ($p = 0.510$).

The IL-18 level increased in all the groups ($p =$

0.465, 0.144, 0.465, and 0.0648 in the control group, the diabetic group, the treatment group without fortification, and the treatment group with fortification, respectively). No significant differences were observed between the groups before treatment ($p = 0.075$) and after treatment ($p = 0.092$).

4. Discussion

Type 2 diabetes mellitus is a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances in carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, action, or both (American Diabetes Association, 2013). Insulin secretion can be affected by changes in synthesis and secretory granules (Sesti, 2006). Type 2 diabetes mellitus is associated with a low level of tissue inflammation that can be caused by various proinflammatory cytokines such as IL-1- β , IL-6, and TNF- α , chemokines and adipocytokines, epigenetics factors, and metabolic pathways. Chronic exposure to proinflammatory mediators stimulated by cytokine signals can inhibit the activation of insulin receptor signals from pancreatic β cells. The main consequence of insulin resistance is hyperglycemia. Hyperglycemia can increase free radical production through non-enzymatic glycosylation and NADH/NAD⁺ imbalances caused by the presence of glucose in cells. Hyperglycemia can induce oxidative stress caused by the imbalance between the reactive oxygen species (ROS) production and antioxidative mechanisms (de Carvalho Vidigal et al., 2012). Hyperglycemia can increase ROS production through an enzymatic process by activating NADPH oxidase in cardiomyocytes. ROS that occur in

Table 1. Body weight, blood glucose, and IL-18 levels before and after intervention

Initial Characteristics \ Groups	Control (K-)	Diabetes (K+)	Diabetes + Kefir (P1)	Diabetes + Kefir fortified with Vit. D ₃ (P2)	<i>p</i>
Body Weight (g)					
Before Intervention ¹	197.5 (183–209)	201 (198–214)	239 (205–261)	204 (182–230)	0.127
After Intervention ¹	232.5 (205–250)	259 (232–282)	207.5 (183–297)	189 (144–248)	0.197
<i>p</i>	0.06	0.06	0.46	0.46	
Fasting Blood Glucose (mg/dL)					
Before Intervention ²	114.7±18.1	220.0±155.9	366.9±134.8	415.0±203.8	0.057
After Intervention ²	137.0±5.5	274.8±65.6	462.1±156.9	258.0±128.9	0.011 *
Delta mean	22.3±20.2	54.8±118.8	95.2±175.4	106.1±252.9	0.510
<i>p</i>	0.115	0.424	0.357	0.463	
IL-18 Levels (pg/ml)					
Before Intervention ²	50.2 (28.7–72.1)	43.1 (30.7–57.5)	56.5 (10–252.7)	117.3 (91.8–146.8)	0.075
After Intervention ²	87.7 (7–156.7)	166.6 (43.5–217.7)	148.2 (106.8–428.3)	264.7 (168.8–311)	0.092
<i>p</i>	0.465	0.144	0.465	0.068	

¹Median (minimum–maximum)

²Mean ± standard deviation

* $p > 0.05$

hyperglycemia activate the transcription factor NF- κ B that is triggered by the production of inflammatory mediators and cytokines, such as TNF- α , IL-1, and IL-18, that are included in proximal cytokines. Proinflammatory cytokines can induce insulin resistance by interfering with glucose production and fatty acid utilization (Abel *et al.*, 2012). Increases in ROS are caused by high oxidative stress. Oxidative stress causes lipid peroxidation, proinflammatory cytokine production, and a decrease in immune response due to pancreatic β -cell damage (Brownlee, 2005). IL-18 is one of the proinflammatory cytokines that increase the inflammatory response in hyperglycemia and type 2 diabetes mellitus (Fischer *et al.*, 2005).

Weight loss can be caused by disturbances in protein and fat metabolism when the body is unable to acquire adequate energy from sugar and processes other substances such as fat into energy instead. Such uses of fat and protein cause weight loss in the long term (Rias and Sutikno, 2017). The weight analysis revealed no significant weight loss in the treatment groups with and without fortification that could be attributed to this mechanism.

The fasting blood glucose level analysis revealed a difference in the blood glucose level between the groups. The blood glucose levels of the K- group were different from those of the K+, P1, and P2 groups. This is because the K- group did not receive STZ and NA induction, whereas the other groups did. STZ is used for inducing diabetes in subjects by damaging pancreatic β cells, and NA is used after STZ injection to protect β cells. β -cell damage by STZ to GLUT-4 transporters causes damage to DNA that results in a corresponding increase in polymerase (PARP-1) to repair DNA. Increasing polymerase activity can reduce intracellular NAD(+) and adenosine triphosphate (ATP) and cause necrosis. It acts as a barrier by inhibiting the activity of PARP-1, NAD+, and ATP in cells. NA is an NAD that can increase intracellular NAD+ (Nurmawati, 2017). The purpose of STZ and NA is to damage pancreatic β cells. Pancreatic β -cell damage causes hyperglycemia and increases free radicals and oxidative stress, which lead to an increase in proinflammatory cytokines and require intervention to reduce blood glucose levels and suppress inflammatory conditions.

The intervention was performed in the treatment group by the administration of unfortified goat milk kefir and goat milk kefir fortified with vitamin D₃. Goat milk contains 250–300 mg/L of oligosaccharides, which is 4–5 times higher than in cow milk, that possess prebiotic and anti-infective properties. Goat milk has relatively low levels of fat globules and is easily digested (Ulusoy, 2015). Kefir is milk fermented with lactic acid bacteria

and yeast containing exopolysaccharides from kefir seeds (Nursiwi *et al.*, 2015). Kefir is useful as a probiotic drink with antioxidant and anti-inflammatory effects that can suppress the growth of digestive tract-causing bacteria because lactic acid bacteria produce antimicrobial compounds including bacteriocin, hydrogen peroxide, and various antibiotics (Hafidzoh and Agustini, 2014). Kefir not only reduced blood glucose but also lipid profiles in animals with diabetes (Nurmawati, 2017). Kefir supplementation can increase the activity of intestinal dipeptidase and reduce the Na⁺-dependent uptake of intestinal sugars that contribute to protein digestion and reduce glycemia (Urdaneta *et al.*, 2007). Antioxidants in kefir can remove free radicals such as superoxide, hydroxyl, peroxide, and ascorbic acid (Yilmaz-Ersan *et al.*, 2016).

The results revealed an increase in the blood glucose level in the K+ group. No significant increase in the blood glucose level was found in kefir treatment groups with or without fortification. A permanent hyperglycemic phase occurs 24 hrs after STZ induction caused by the loss of the first insulin response whereby insulin secretion is delayed and fails to restore prandial blood glucose in normal time, reducing insulin sensitivity in response to glucose and leading to hyperglycemia and failure to stimulate a reasonable insulin response (Marliyati and Roosita, 2016). In addition, STZ inhibits the Krebs cycle such that ATP production in the mitochondria is limited; this causes a reduction in pancreatic β -cell nucleotides and subsequently results in damage to pancreatic β cells and swelling of the pancreas gland after 2–4 days, which causes a change in insulin production or an increase in the blood glucose levels, thus disturbing rats' physiological processes (Nurmawati and Rahma, 2017).

The IL-18 findings revealed no significant increases in the treatment groups with or without fortification. This can be attributed to an increase in the blood glucose level that can lead to an increased IL-18 level in diabetes and hyperglycemia; this further increases inflammatory responses and induces increased IL-18 mRNA expression through active protein kinases, such as protein kinase C and active mitogen protein kinase, in the macrophage tissue. Thus, both the interventions using kefir with and without fortification did not have a significant effect on the IL-18 level (Altinova *et al.*, 2008; Uzu *et al.*, 2011). This result is reinforced by *in vitro* studies that have demonstrated that vitamin D₃ could reduce the production of inflammatory cytokines by suppressing the activation of NF- κ B and reducing the expression of proinflammatory cytokines. However, not all studies have reported the same results due to differences in the body's response to vitamin D and the

physiological properties of serum. In addition, diabetes is a proinflammatory condition, but the role of the immune system in diabetes may be relatively marginal to that of other autoimmune diseases such as inflammatory bowel disease and chronic hepatitis where the effect of vitamin D₃ is more prominent. Therefore, vitamin D₃ has anti-inflammatory properties that cannot be observed in the low-level systemic inflammation that occurs in type 2 diabetes mellitus (Mitri, 2014).

Kefir is a probiotic drink that can reduce several proinflammatory cytokines, such as TNF- α and IL-6, and increase anti-inflammatory cytokines, such as IL-10; however, probiotics have a direct effect on inflammatory responses by acting as ligands for innate immune receptors called Toll-like receptors (TLRs), thus affecting signaling pathways, including those of NF- κ B, mitogen-activated protein kinase, and phosphoinositide-3-kinase-protein kinase B/Akt (PI3K-PKB/Akt), and gamma receptors that are activated by proliferator-activated peroxisome (PPAR). Some probiotic species can release a substance that can cross epithelial cells to interact with innate immune cell receptors called nucleotide-binding oligomerization domain receptors (NLRs). Activation of NLRs can affect the formation of inflammation and NF- κ B signaling associated with the inflammatory response. Probiotics have the ability to affect NF- κ B and PPAR signaling, which in turn affects inflammation because both the transcription factors can produce proinflammatory signals including cytokines and chemokines. *Lactobacillus casei* is a probiotic bacterium. Activation of TLR and NLR causes inflammation that can activate caspase-1, which further activates the proinflammatory cytokines IL-1 β and IL-18; the increased IL-18 level is also believed to be affected by the action of probiotics contained in kefir (Lescheid, 2014; Thomas and Versalovic, 2010).

Another factor that causes an increase in the IL-18 level is an increase in body weight, which can trigger a state of oxidative stress due to an imbalance between pro-oxidants and endogenous antioxidants. These conditions cause ROS formation. Weight gain can increase the progression of immune cells in adipose tissues. Cytokines released by immune cells and adipose tissues can increase tissue inflammation (Netea and Joosten, 2016; Susantiningsih and Mustofa, 2018). IL-18 rapidly responds to inflammation, causing an increase in the IL-18 level (Schroder and Tschopp, 2010). In addition, an increase in the IL-18 level may be caused by complications of diabetes associated with tissue damage as a result of hyperglycemia, such as heart abnormalities, atherosclerosis, and diabetic nephropathy. IL-18 causes plaque destabilization and cardiac dysfunction due to increased macrophage infiltration and thickening of the

aortic wall. IL-18 can cause microangiopathy associated with diabetic nephropathy because it is directly related to a decrease in kidney function (Nakashima et al., 2016).

4. Conclusion

Both unfortified kefir and kefir fortified with vitamin D₃ maintained stable blood glucose and IL-18 levels in the normal range but did not improve them.

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