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Review Article

Prophylactic Role of Butyrate Fermented in Aloe vera Gel to Type-2 Diabetic Patients and Obesity Subjects: Case Reports of Obesity-Prone Individuals

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Abstract

Diabetes mellitus is characterized by an increased level of blood glucose and impairment in the metabolic functions of carbohydrates, fats, and proteins. Beneficial effect of butyrate fermented in *Aloe vera* gel to type-2 diabetes patients and obesity subjects was discussed in the present review. In case reports, a possible prophylactic role of *Aloe vera* juice in long time ingestion to obesity-prone subjects was observed.

Keywords: *Butyrate; Aloe vera; Type-2 Diabetic Patients; Obesity*

Introduction

The rising incidence of type-2 diabetes among children and adults is related to the epidemic of obesity. The distinctions between type-1 (insulin-dependent) and type-2 (non-insulin-dependent) diabetes mellitus are becoming increasingly blurred both clinically, where β-cell insufficiency is the shared characteristic. Obesity is associated with an increased risk of developing insulin resistance and type-2 diabetes. In obese individuals, adipose tissue releases increased amounts of non-esterified fatty acids (NEFAs), glycerol, hormones, pro-inflammatory cytokines and other factors that are involved in the development of insulin resistance [1]. Increased release of NEFAs is observed in type-2 diabetes and in obesity, and it is associated with insulin resistance in both conditions. Insulin resistance is associated with body mass index at any degree of weight gain. Insulin sensitivity also differs completely in lean individuals because of differences in body fat distribution [2].

Diabetes and obesity are chronic disorders that are on the rise worldwide. Body mass index has a strong relationship to diabetes and insulin resistance. In an obese individual, the amounts of NEFA, glycerol, *et al*. that are involved in the development of insulin resistance are increased. Insulin resistance with impairment of β-islet cells function leads to the development of diabetes. Gaining weight in early life is associated with the development of type 1 diabetes. NEFA is cornerstone in the development of insulin resistance and in impairment of β-islet cell function [3]. Weight gain and obesity are major risk factors for conditions and diseases ranging from insulin resistance and

type-2 diabetes mellitus to atherosclerosis and the sequelae of nonalcoholic fatty liver disease. The link between obesity and inflammation has therefore raised the important question of whether obesity-induced inflammation plays a pathogenic role in the development and progression of these disorders. Shoelson., *et al*. reviewed the rapidly expanding body of animal and clinical data that support potential roles for inflammation in the pathogenesis of insulin resistance and type-2 diabetes mellitus [4]. Present review is focused on butyrate fermented in *Aloe vera* gel to type-2 diabetic patients and obesity subjects. Case reports: Prophylactic role of *Aloe vera* juice ingestion to obesity subjects.

Possible hypoglycemic effect of *Aloe vera* high molecular weight fractions on type-2 diabetic patients

Aloe vera high molecular fractions (AHM), which was prepared by patented hyper-dry system, produced significant decrease in blood glucose level sustained for 6 weeks of the start of the study. Treatment of 15 outpatient clinic of diabetic patients (nine males and six females) with AHM may relief vascular complications probably via activation of immune-system with no hepatic and nephrotoxicity [5].

Possible efficacy of *Aloe vera* gel metabolites in long-term ingestion to insulin sensitivity

The obesity as a primary source of diseases brings about metabolic dysfunction followed by inflammatory insulin resistance. The metabolites of aloe polymannose moiety; such as manno-oligosaccharide and short chain fatty acid, synergistically modulated insulin sensitivity on tissues. A possible putative efficacy of *Aloe vera* gel metabolites, such as short chain fatty acids, in long-term ingestion to insulin sensitivity were reviewed [6]. Symbiotic effect of butyrate-producing endophytic microbiota and *Aloe vera* gel containing non-digestible carbohydrates was discussed on slowing ageing design: butyrate efficacy for insulin sensitivity and sirtuin activation through histone deacetylase inhibition *in vitro* study [7].

Efficacy of *Aloe vera* supplementation on prediabetes and early non-treated diabetic patients

A systematic review and meta-analysis of randomized controlled trials

Zhang., *et al*. [8] performed a systematic search of PubMed, Embase, and Cochrane Central Register of Controlled Trials until 28 January 2016. A total of five randomized controlled trials (RCTs) involving 415 participants were included. Compared with the controls, *Aloe vera* supplementation significantly reduced the concentrations of fasting blood glucose (FBG) weight mean difference, glycosylated hemoglobin A1c (HbA1c), triglyceride, total cholesterol (TC), and low-density lipoprotein-cholesterol (LDL-C) levels. The evidence from RCTs showed that *Aloe vera* might effectively reduce the levels of FBG, HbA1c, triglyceride, TC and LDL-C, and increase the level of HDL-C on prediabetes and early non-treated diabetic patients.

Sodium butyrate supplementation or increasing intestinal butyrate production is a potential mean of improving the body's glucose metabolism and obesity profile

Sodium butyrate (NB), obtained by fermenting dietary fiber via intestinal microflora or endophytic bacteria in *Aloe vera* gel [9] was shown to improve the activity of some antioxidant enzymes *in vivo*. Tang., *et al*. [10] investigated the term changes of mitochondrial energy metabolism and redox homeostasis in skeletal muscles and clarify the regulatory mechanism and dose effect of NB on skeletal muscle in male Sprague-Dawley rats. The author showed that NB activates antioxidant pathway, improves the antioxidant capacity of obese rat tissues and promotes glucose metabolism.

Butyrate to combat obesity and obesity-associated metabolic disorders

Evidence is increasing that disturbances in the gut microbiome may play a significant role in the etiology of obesity and type-2 diabetes. The short chain fatty acid butyrate, a major endo product of the bacterial fermentation of carbohydrate, such as aloe polysaccharide, or the endophytic bacterial product in *Aloe vera* gel, is reputed to have anti-inflammatory properties and positive effects on body weight control and insulin sensitivity. Dueren., *et al*. [11] showed the animal studies indicating that butyrate administered via various routes,

e.g. orally, positively affects adipose tissue metabolism and functioning, energy and substrate metabolism, systemic and tissue-specific inflammation, and insulin sensitivity and body weight control. A limited number of human studies demonstrated inter-individual differences in clinical effectiveness suggesting that outcomes may depend on the metabolic, microbial, and lifestyle-related characteristics of the target population.

The effectiveness of Aloe-based drink in reducing glycated albumin and insulin resistance of metabolic syndrome

Aisya., *et al*. [12] investigated the effect of aloe-based drink on glycated albumin (GA) and insulin resistance (IR) in metabolic syndrome (Mets). This study aimed to investigate the effect of aloe-based drink on GA and IR in Mets. Thirty-eight Mets subjects were divided into two groups: treatment group (n = 19) which was provided by 165 g/d of Aloe-based drink for 4 weeks: and the control group (n = 19). Both groups were given education regarding of management of Mets. Compared to control group, the change of GA and HOMA-IR in intervention group were significantly different. Aloe-based drink was proven to reduce GA and IR in the Mets.

Increased gut microbiota diversity and abundance after fasting

An impaired gut microbiota has been reported as an important factor in the pathogenesis of obesity. Weight reduction has been mentioned to improve gut microbial subpopulations involved in inflammatory processes. Remely., *et al*. [13] investigated the pilot study: overweight people underwent a fasting program with laxative treatment for 1 week followed by a 6-week intervention with a probiotic formula. Gut microbiota were analyzed on the basis of 16s rRNA with a quantitative real time polymerase chain reaction. The author found that an increased in microbial diversity over the study period and no significant changes in abundance of total bacteria, although *Faecalibacterium prausnitzii* showed an increase over the study period. The results showed that caloric restriction affects gut microbiota by proliferating mucin-degrading microbiota subpopulations.

Structural changes in gut microbiome after Ramadan fasting

Ozkul., *et al*. [14] studied the changes in gut microbiota composition and diversity of 9 adult subjects after Ramadan fasting. Stool samples were collected before (baseline) and at the end of the Ramadan fasting (after 29 days). Linear discriminant analysis effect size (LEfSe) analysis revealed that *Butyricicoccus, Bacteroides, Faecalibacterium, Roseburia, Allobacterium, Eubacterium, Dialister* and *Erysipelotrichia* were significantly enriched genes after the end of Ramadan fasting. A limited sample size pilot study led to compositional changes in the gut microbiota. Our early case report suggested that the successive ingestion of *Aloe vera* juice for ten years provided high concentration of the butyrogenic microbiome *Faecalibacterium* spp. in fecal [15].

Fasting intervention and its clinical effects on the human host and microbiome

The health promoting potential of a balanced gut microbiotas status modulated by calorie restriction (CR) posits a possible lose link between gut microbiota (GM) and healthy aging. Short chain fatty acids generated from intestinal bacterial fermentation may act as mediators between the microbiota and the immune system. In earlier report a putative prophylactic role of butyrate from endophytic bacteria fermentation of *Aloe vera* gel was described to suggest that the consumption of fermented extract of *Aloe vera* gel may be beneficial for health and QOL as an immune modulation, and the effects of *Aloe vera* gel on GM status and CR were described. Intestinal microbiota producing butyrate might be developed for the therapeutic purpose to increase insulin sensitivity in humans with CD [16].

Experimental trials in organisms ranging from yeast to humans have shown that various forms of reducing food intake (caloric restriction) appear to increase both overall and healthy lifespan, delaying the onset of disease and slowing the progression of biomarkers of aging. Forstund [17] reviewed that the gut microbiota is considered one of the key environmental factors strongly contributing to the regulation of host health. Many studies investigating gut microbiota have been performed and have shown strong associations between specific microorganisms and metabolic diseases including overweight, obesity, and type-2 diabetes mellitus as well as specific gastrointestinal disorders, neurodegenerative diseases, and even cancer. There is substantial evidence for the efficacy of fasting in improving in-

sulin signaling and blood glucose control, and in reducing inflammation, conditions for which, the gut microbiota has been identified as a site of both risk and protective factors. Accordingly, human gut microbiota, both in symbiont and pathobiont roles, have been proposed to impact and mediate some health benefits of fasting and could potentially affect many of these diseases. Thus, fasting consistently enriches widely recognized anti-inflammatory gut commensals such as Faecalibacterium and other SCFA producers, which likely mediates some of the health effects through immune system and barrier function impact.

Divertive use of the diabetes drug (Mounjaro; Tirzepatide) to obese subjects

FDA news release [18]

The U.S. Food and Drug Administration approved Mounjaro (tirzepatide) injection improve blood sugar control in adults with type 2 diabetes, as an addition to diet and exercise.

Type 2 diabetes, the most common form of diabetes, is a chronic and progressive condition in which the body does not make or use insulin normally, leading to high levels of glucose (sugar) in the blood. More than 30 million Americans have type 2 diabetes. Despite the availability of many medications to treat diabetes, many patients do not achieve the recommended blood sugar goals. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GLP) are hormones involved in blood sugars control. Mounjaro is administered by injection under the skin once weekly, with the dose adjusted as tolerated to meet blood sugar goals.

Obesity was common among study participants, with an average body mass index of 32 to 34 kilograms/height in meters squared reported at the time of enrollment. Among patients randomized to the maximum recommended dose, the average weight loss with Mounjaro was 15 pounds more than placebo when neither were used with insulin and 23 pounds more than placebo when both were used with insulin. The average weight loss with the maximum recommended dose of Mounjaro was 12 pounds more than semaglutide (Novo Nordisk, Denmark), 29 pounds more than insulin degludec (genetical recombination) and 27 pounds more than insulin glargine (genetical recommendation biosimilar). Those patients receiving insulin without Mounjaro tended to gain weight during the study.

The FDA granted the approval of Mounjaro (Tirzepatide) for clinical trial, phase III, to Eli Lilly and Co.

Higher glucose levels; risk of dementia in people with or without diabetes

Crane., *et al*. [19] investigated whether higher glucose levels increase the risk of dementia in people without diabetes. Among participants without diabetes, higher average glucose levels within the preceding 5 years were related to an increased risk of dementia with a glucose levels of 115 mg per deciliter as compared with 100mg per deciliter, the adjusted hazard ratio for dementia was 1.18. Among participants with diabetes, higher average glucose levels were also related to an increased risk of dementia; with a glucose level pf 190 mg per deciliter as compared with 160 mg per deciliter, the adjusted hazard ratio was 1.40. The results suggested that higher glucose levels may be a risk factor for dementia, even among persons without diabetes.

Association of butyrate fermented in *Aloe vera* gel with Alzheimer's disease and dementia progression

The relationship between Alzheimer's disease and related dementia with butyrogenic microbiota and butyrate fermented was discussed in the prevention of human physiological disease such as Alzheimer's disease and dementia progression [20]. In case report it was suggested that the efficacy of hypotensive, hypoglycemic, antianginal, and cognition enhancer drug for a frail female patient needed the nurse care level 2, may be supported with daily ingestion of *Aloe vera* juice with the drug and multivitamin modulating from the nurse care level 2 into 1 and providing an important role in the modulation of brain homeostasis.

The effects of *Aloe vera* extract powder on depression in prediabetic patients

Prediabetes state is a condition of abnormal blood glucose level between normal and diabetic states that involves impaired fasting glucose and impaired glucose tolerance. It is a major risk factor for type-2 diabetes. The World Health Organization considers fasting blood

glucose equivalent to 100 - 125 mg/ml as the prediabetic state. Depression is on the list of risk factors suggested by the American Diabetes Association for the preliminary screening of diabetes. Foadoddini and Morfrad [21] examined a double blind randomized controlled trial study, conducted on 72 prediabetic patients. After sampling, the patients were allocated to three groups: *Aloe vera* 300 mg, *Aloe vera* 500 mg and placebo. The participants in the two first groups received pure *Aloe vera* extracted powder capsules twice a day in the morning and evening for eight weeks. In addition, they completed Beck Depression inventory before and eight weeks after the intervention. After confirming the normality of the mean depression score variable by the Kolmogoroy-Smirnov test, the data was analyzed using ANOVA, Chi-square, and paired t-test. The author resulted the mean depression scores in the 500mg *Aloe vera* group decreased significantly after the 8th week of intervention.

Beneficial role of *Aloe vera* juice (AVJ) ingestion to obesity-prone individuals: Case reports

Case report 1: A 30 years old male who had body weight 108 kg and BMI 38.3 started carbohydrate restriction and weight training with AVJ ingestion for six months on June, 2019. His body weight changed from 108 kg to 78 kg and BMI from 38.3 to 27.6. His abdominal girth decrease: 112 cm to 89 cm, body fat percentage decrease: 36% to 17%, and blood pressure decrease: 135 to 120.

Case report 2: A 47 years-old female who had body weight 66.0 kg and BMI 26.4 started carbohydrate restriction and dietary one/day with AVJ ingestion 330 ml/day from March, 2020 for 6 months. Her body weight changed from 66.0 kg to 51.4 kg and BMI 26.4 to 20.6. The blood sugar value140 to 110 and HA1c changed from 6.2 to 6.0.

Case report 3: A 50 years female who had body weight 58.9 kg and BMI 24.5, started dietary two times per day and carbohydrate restriction for one month with AVJ ingestion 1000 ml/day. Her body weight changed from 58.9 kg to 55.8 kg, BMI from 24.5 to 23.2, and his west change: 89 cm to 76 cm.

Case report 4: A 50-years old female who had body weight 55.0 kg and BMI 21.3, started carbohydrate restriction and dietary one eat/day with AVJ 600 ml/day ingestion on April, 2022 for 6 months. Her body weight changed from 55.0 kg to 48.0 kg and from BMI 21.3 to 18.7.

Summary

Present review is focused on butyrate fermented in *Aloe vera* gel to type-2 diabetic patients and obesity subjects. Body mass or BMI is central to the development and rising incidences of type-1/2 diabetes and obesity subjects. Recently, mechanisms linking between obesity and type-2 diabetes drugs were widely discussed. *Aloe vera* gel positively affected the blood glucose and lipid levels in type-2 diabetic patients. A possible beneficial efficacy of *Aloe vera* juice ingestion in long time may participate to obesity and prone to obesity subjects.

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