

A Review of the Hypoglycemic Effects of Vinegar and its Potential Benefit in Gestational Diabetes Mellitus (GDM)

Abstract

The current first line management for women with gestational diabetes mellitus (GDM) is dietary modification and exercise, which emphasizes the elimination or reduction of foods with high glycemic index. However, evidence suggests there may be a complimentary hypoglycemic effect of substances such as vinegar. This literature review explores vinegar's hypoglycemic effects, proposed physiological mechanisms of action, and whether these effects have been demonstrated during pregnancy with particular attention given to women affected by GDM.

MEDLINE, PubMed and Google Scholar were searched for randomized controlled trials and prospective cohort studies of vinegar ingestion by individuals affected by diabetes. Search terms used were delayed gastric emptying, postprandial glycemia and glycemic Index (GI).

Fifteen articles describing 21 studies were identified that evaluated the hypoglycemic effects of vinegar in groups of individuals without diabetes, with Type 1 diabetes (T1D), Type 2 diabetes, (T2D) or those at risk for diabetes, as well as hypoglycemic effects of vinegar in rats and intestinal human cells. Our review found that vinegar significantly reduced postprandial glucose, fasting blood glucose, and increased response to insulin. We found significant support for a proposed physiological mechanism for the hypoglycemic effects of vinegar, delayed gastric motility, inhibition of carbohydrate digestion, increased satiation with associated decreased caloric intake, and glycogen repletion in skeletal muscle and liver cells. There is strong evidence supporting vinegar as a complimentary component of nutrition therapy for nonpregnant individuals with diabetes, but a paucity of data evaluating the use of vinegar during pregnancy affected by GDM.

Keywords: Acetate; Acetic Acid; Acetic Acid Feeding; Antiglycemic; Antiglycemic Properties of Vinegar; Apple Cider Vinegar; Appetite; Delayed Gastric Emptying; Diabetes; Diabetes Mellitus; Fasting Glucose; (GDM) Gestational Diabetes Mellitus; Glucose; Glycemic Index (GI); Hyperglycemia; Insulin; Metabolism; Morning Hyperglycemia; Mortality; Nutrition; Postprandial Hyperglycemia; Postprandial Glycemia (PPG); Pregnancy; Satiety; Vinegar; Vinegar Ingestion; Type 2 Diabetes

Abbreviations: GI: Glycemic Index; PPG: Postprandial Glycemia; GDM: Gestational Diabetes Mellitus

Introduction

Gestational Diabetes Mellitus (GDM) is a common condition, in which pathologic insulin resistance develops during pregnancy that prevents maintenance of euglycemia. Depending on patient demographics, GDM affects approximately 1-25% of all pregnancies in the United States [1]. This medical complication is associated with an increase risk for maternal, fetal, and neonatal mortality and morbidity [1-3]. Poor health outcomes in gravidas affected by diabetes include but are not limited to maternal preeclampsia and future Type 2 Diabetes along with neonatal macrosomia and hypoglycemia, and birth injuries [3-7]. In fact, evidence shows that even without a diagnosis of diabetes, there is positive correlation with higher levels of glucose and perinatal mortality [8]. As a result, current GDM management guidelines promote strict glycemic control [1]. Initial management involves

lifestyle changes that emphasize moderate physical activity, caloric restriction and reduction of dietary glycemic load. If the patient remains unable to maintain target fasting blood glucose and postprandial targets, either insulin or oral hypoglycemic agents may be prescribed [9,10].

Compliance with current recommended dietary changes that emphasize the reduction of carbohydrate intake or consumption of foods that have a low glycemic index can be difficult for patients [11,12]. Complementary foods, however, that helps lower blood glucose without additional changes to the diet present a promising, simpler dietary approach to GDM management. Evidence suggests that acetic acid found in vinegars and pickled foods lowers postprandial and fasting glycemia [13-27]; thus, we undertook a literature review to explore these hypoglycemic effects, their proposed physiological mechanisms of action, and whether these effects have been shown in the pregnant population, and in particular, those with GDM.

Review Article

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Methods

An electronic literature search using MEDLINE, PubMed and Google Scholar were conducted. We searched for randomized controlled trials and prospective cohort studies of vinegar ingestion in populations affected by diabetes. We also searched for *in vitro* and animal experiments that explored vinegar's proposed mechanisms of action. Study variables and keywords used were Delayed Gastric Emptying, Postprandial Glycemia and Glycemic Index (GI).

The studies included randomized clinical trials and uncontrolled studies evaluating the hypoglycemic effects of acetic acid, or sodium acetate in healthy subjects, patients with insulin resistance, T1D, T2D or at high risk for developing T2D. We also evaluated *in vitro* experiments and animal experiments evaluating the hypoglycemic effects of vinegar. The literature search was limited to English language publications. Study endpoints were levels of postprandial blood glucose, insulin response, fasting blood glucose, and glycogen repletion in skeletal muscle and liver parenchyma, gastric motility and satiation.

Results

A fifteen articles consisting of 21 studies were identified that evaluated the hypoglycemic effects of vinegar, acetic acid, or pickled foods in healthy participants [13] T1D [8], T2D [4], those at risk for diabetes and those with insulin resistance [8], rats [4], as well as hypoglycemic effects of vinegar in intestinal cells [1] (Table 1). No study was found that explored the effects of vinegar in healthy pregnant women or in gravidas a diagnosis of GDM, T1D or T2D. The studies we reviewed were conducted in the United States [6], Japan [6], Sweden [4] Italy [1], and Greece [1] (Table 1). The fifteen articles consisted of thirteen randomized control trials, two uncontrolled trials, three animal experiments, and 1 *in vitro* experiment (Table 1). Eleven articles, described 16 trials, explored the effects of vinegar ingested with carbohydrates on postprandial blood glucose levels (PPG) [13-19,23-25]. Vinegar was found to reduce postprandial glucose, delayed glycemic response, or reduced the glycemic index of the carbohydrate ingested. Seven trials explored the effect of vinegar on the postprandial insulin response, of which six demonstrated a statistically significant reduction in insulin response [13,16,18,19,24,25]. Only two studies, both by Johnston et al. [17] explored the effect of vinegar on fasting glucose levels [17,26], one demonstrated that bedtime vinegar ingestion reduced morning fasting glucose [17], while the other demonstrated that ingestion of vinegar during meals over a 12 week period leads to a reduction in fasting blood glucose [26]. Additional studies attempted to account for these findings by exploring vinegar's potential mechanisms of action. Three studies explored the effect of vinegar on gastric motility, of which two found that it significantly delayed gastric motility [20,25]. One study explored the effect of vinegar on satiety and found a linear, dose-dependent response [24], while another confirmed vinegar ingestion led to decreased future caloric intake [17]. Finally, two other studies explored the effect of vinegar on skeletal muscle and liver parenchyma in rats and found that it was associated with increased glycogen repletion [22,27].

Effects on postprandial glycemia and the Glycemic Index

Of the 13 randomized control trials, 1 animal experiment and 2 uncontrolled trials that explored the effects of vinegar with ingestion of carbohydrates on postprandial blood glucose (PPG), found a reduction in either PPG or glycemic index (GI) [13-16,18,19,23,24-26], of which 10 were statistically significant (Table 1). Reductions were reported in healthy populations around the world [14-17,24,25], as well as among individuals with and without a diagnosis of diabetes (including those taking oral hypoglycemic agents) [18,23] and individuals identified as having prediabetes [18,26], and rats [13]. Reductions in PPG or GI were substantial, ranging from 19% to 54% (Table 1). Many studies reported statistically significant decreases in PPG, but presented the results in graphic form, which limited our ability of to quantify and compare findings [18,24,25]. Of the 2 trials that did not demonstrate a reduction in PPG [13,23], Ebihara et al. [13] study found that vinegar delayed the maximal glycemic response which is consistent with a decrease in GI. Johnston's et al. [18] reported that vinegar did not reduce the glycemic response in glucose ingestion, which is consistent with the theory that vinegar reduces the glycemic response to complex carbohydrates rather than monosaccharides.

Five of the 14 trials that demonstrated a postprandial glycemic reduction did not find a statistically significant difference ($p < 0.05$) (Table 1), many of which were in found in the T2D patients. In the 3 randomized control trials conducted by Johnston's et al. [18], the hypoglycemic effect of vinegar in insulin resistant patients was found to be statistically significant ($p = 0.014$) while the effect in individuals without diabetes and those with T2D were not significantly different. Similarly, Johnston et al. [23] study, the only other study that explored the glycemic response to vinegar among patients with T2D, also yielded reductions in PPG that were not statically significant ($p = 0.097$). While Johnston's et al. [23] study also yielded statistically insignificant reductions in PPG in healthy participants, many other studies exploring the hypoglycemic effects of vinegar among healthy participants did show a statistically significant reduction in PPG or GI [14-17,24,25]. Finally, Johnston's et al. [26] study also found a statistically insignificant decrease in PPG (-7.7 ± 6.9 mg/dl $p = 0.259$) among participants at risk for diabetes. While Johnston's et al. [26] have proposed small sample sizes as a potential cause of their large p values, many of the other studies cited here had similar sample sizes but yielded statistically significant results (Table 1).

It could be that other studies had statistically significant findings as they stratified their data according to time following ingestion of vinegar and meal, and as a result could present findings that were significant within a specific period. For example, Johnston's et al. [23] study measured PPG as the total area under the curve 120 min following the meal. Ostman et al. [24] on the other hand, found a statistically significant reduction in PPG at 30min with ingestion of 23g of vinegar, and 45min with ingestion of 28g of vinegar, which did not hold at later times. Similarly, Ostman [24] found a GI reduction for the meal with ingestion of 28g of vinegar 90min post ingestion, however such differences were not significant by 120min [24].

The variance in postprandial glycemic reduction and their statistic significance did not appear to correlate with the carbohydrate load given at the time of ingestion when comparing the studies (Table 1). Most studies used a carbohydrate load of 50-75g and reported comparable glycemic reductions. However, Johnston et al. [16] did find that vinegar consumption with a high glycemic meal (glycemic load=81) showed a statistically significant PPG reduction of 55% whereas when consumed with a low glycemic meal (glycemic load=48) the reduction in PPG was not statistically significant. The type of vinegar ingested did not appear to correlate with the hypoglycemic differences either. Whether apple cider vinegar, white vinegar, raspberry vinegar, pure acetic acid, or pickled foods was used, studies found statistically significant reductions in PPG or GI, suggesting that the acetic acid was the active compound (Table 1).

While most studies used 20g of standard 5% acetic acid vinegar, an amount equivalent to that found in salad dressing, corresponding to 1g of acetic acid [14,16-18,24-27], several studies documented doses using different measurement units [15,22,24] rendering it difficult for the authors to explore doses used and corresponding hypoglycemic effects (Table 1). To discern whether the hypoglycemic effect is dosage-dependent, however, Johnston's et al. [23] conducted a randomized control trial comparing 20g (1g acetic acid), 10g (0.5g acetic acid) and 2g (0.1acetic acid). They found that 10g of vinegar, the equivalent of 2 teaspoons, reduced PPG by 23-28% as compared to 2g or placebo ($p= 0.05$) [23]. Interestingly, they also found that 20g of vinegar (1g of acetic acid) only reduced the PPG by 6-12%, suggesting that while a minimum dose is needed for therapeutic effect, this effect may not be dose-dependent. Conversely, Ostman et al. [24] did find a negative linear relationship between PPG and vinegar dose ($r= -0.47$ $p= 0.001$), however, only 30min following ingestion.

A few studies also explored the effects of acetate on PPG to discern whether the hypoglycemic effects of acetic acid are due to acetataemia. Brighenti et al. [14] & Johnston et al. [23] found that sodium acetate did not reduce PPG despite leading to higher levels of acetataemia, suggesting that the mechanism of action of vinegar lies in its acidic properties and not the blood level of its salt [14].

Effects on fasting blood glucose levels

Two studies explored the effect of vinegar on fasting blood glucose (FBG). Johnston's et al. [26] study explored the effect of vinegar ingested before lunch and dinner on FBG among type 2 diabetics over a 12 week period [26]. This study's timeframe was unique in that all the other trials employed an intervention period of less than 1 week if not one day [13-16], and they found it significantly reduced FBG by 16.3 ± 4.9 mg/dl ($p= 0.05$) [26]. White et al.'s study also explored the effect of vinegar on FBG on individuals affected by diabetic. However, this trial evaluated bedtime ingestion of vinegar, which was found to decrease FBG by 4% ($p=0.046$) [17]. This reduction was seen even in those taking hypoglycemic agents. Although the vinegar was ingested with a sample of cheese, these were consumed after mealtime, which is perhaps why this reduction is not as large as the reduction seen in Johnston's et al. [26] study, nor as large as the reductions in PPG seen in other studies. Moreover, White's et al. [17] study found that

for patients with a typical FBG >7.2 mmol/l ($n=6$), fasting glucose was reduced 6% compared to a reduction of 0.7% in patients with a typical FBG <7.2 mmol/l, suggesting that the hypoglycemic effect of nighttime vinegar may be more pronounced in people with impaired insulin response than in healthy people.

Effects on insulin secretion

Seven trials demonstrated that vinegar not only reduced the glycemic response to meals, but also reduced the insulin response [13,16,18,24,27], of which six were statistically significant. Reductions in insulin response ranged from 20-30% (Table 1), comparable to reductions in blood glucose. Similar to effects on PPG, Ostman et al. [24] & Liljeberg et al. [25] found reductions in insulin to be statistically significant within a shorter timeframe post ingestion of the meal (less than 45min and 30 min respectively). Ostman et al. [24] also found a significant reduction in insulin index using a 90 min incremental area, but by 120min, the insulin index did not differ from the control. Additionally, Ostman et al. [24] found a negative linear relation between vinegar dose and insulin response ($r= -0.44$ $p= 0.02$), however, this was only true for 30 minutes post meal. While Johnston's et al. [17] demonstrated that peanuts attenuated the glycemic response to the test meal at amounts comparable to vinegar; they found that only vinegar significantly reduced the 60 minute insulin response. This implies that vinegar's hypoglycemic effect is not merely responsible for the hypoinsulinemic effect as peanuts also lowered postprandial glycemia and glycemic index. Brighenti et al. [14] propose that perhaps the cephalic phase response to oral vinegar can lead to changes in insulin secretion or gastrointestinal hormones that potentiate insulin secretion, while Johnston et al. [16] propose that vinegar improves insulin sensitivity.

Effects on satiation and decreased total caloric intake

After consumption of the intervention (vinegar + bagel or peanut butter + bagel), Johnston et al. [16] found that caloric intake was reduced by 200-275kcal for the remainder of the day ($p=0.111$). Although this reduction was not statistically significant, the regression analysis indicated that the 60 minute glucose responses to the test meals accounted for 11%-16% of the variance in later caloric ingestion ($p<0.05$). This finding is consistent with the evidence that low GI foods promote post-meal satiety and subsequent hunger [28]. Accordingly, using a subjective rating scale, Ostman et al. [24] found that vinegar promoted and prolonged satiety. In fact, they found a positive linear dose-response relationship ($r=0.41$ $p=0.004$) at every time interval explored. The control satiety went back to baseline after 90 min, whereas the satiety in the vinegar group was elevated throughout the experiment (120min) [24].

Effects on gastric motility

Three studies explored the effects of vinegar on gastric motility to identify a mechanism through which vinegar leads to delayed and decreased PPG and increased satiety [14,20,25]. Hlebowicz et al. [20] found that the gastric emptying rate, taken as a measurement of percent change in gastric antrum cross-sectional area using real time ultrasound, was reduced from 27% to 17% with the ingestion of vinegar in patients with T1D and diabetes

associated gastro paresis ($p < 0.05$) [20]. Similarly, Liljeberg et al. [25] using paracetamol absorption as a marker for gastric emptying rate, found that vinegar delayed the gastric emptying rate by approximately 20% ($p < 0.05$) in healthy, participants without diabetes [25]. Brighenti et al. [14] also using ultrasound and cross sectional area as a marker for gastric emptying rates, explored whether acetate had the same effect as acetic acid. They found no difference between the gastric emptying rates of the acetate versus acetic acid group, however, these findings were not statistically significant ($p = 0.789$) [14].

Effects on carbohydrate digestion

Ogawa et al. reviewed the effect of acetic acid on Caco-2 cells (a human intestinal cell line) to explore its effect on disaccharidases and glucose transport. Chronic treatment was found not to hinder cell growth or viability, nor did it affect glucose transport (measured using 3-O-methyl glucose), but rather, acetic acid was found to significantly suppressed sucrase in a time and concentration dependent manner. Similarly, the activity of maltase, trehalase, and lactase was found to be significantly decreased. Other acids tested including citric and lactic acid did not suppress sucrase activity [21]. In further exploration, acetic acid was found not to affect the transcription nor translation of sucrose but rather its enzymatic activity, indicating a post-translational mechanism of action.

Effects on glycogen repletion in skeletal muscle and liver

Fushimi et al.'s 2001 and 2002 experiments found that the addition of acetic acid to a glucose diet resulted in greater glycogen repletion in the liver and gastrocnemius muscle after food deprivation [22], and in the soleus muscle after exercise than glucose alone [27]. In Fushimi et al.'s [27] study, for example, a glucose diet with 0.4% acetic acid was found to increase the glycogen content in the soleus muscle by 1.3 fold (4.04 ± 0.41 mg/g tissue compared to 3.04 ± 0.29 mg/g tissue $p < 0.05$) and the ratio of glycogen synthase I by 10% ($47.0 \pm 0.7\%$ compared to $38.1 \pm 3.4\%$); however, no statistically significant difference was found in the glycogen content or glycogen synthase ratio of the gastrocnemius muscle and liver. The authors propose that glycogen repletion in skeletal muscle following exercise occurs prior to that in the liver and is dependent on the activation of glycogen synthase. Similarly, Fushimi et al. [22] reported that a glucose diet with 0.2% acetic acid increased the glycogen content in the gastrocnemius muscle and the liver following food deprivation ($p < 0.05$). Moreover, they found that acetic acid led to a statistically significant increase in glucose-6-phosphate and that the control group had a statistically significant decrease in fructose-1,6-bisphosphate/fructose-6-phosphate ratio ($p < 0.05$) in the gastrocnemius muscle. This suggests that acetic acid stimulates glycogen repletion in skeletal muscle by suppressing glycolysis [22]. In the liver, Fushimi et al. [22] (2001) found that xylulose-5-phosphate was significantly higher in the control group than in the acetic acid groups ($p < 0.01$), suggesting that acetic acid promotes glycogenesis by inactivating glycolysis (as low levels of xylulose-5-phosphate inactivate fructose-1,6-bisphosphate). They also found that acetic acid (0.2%) led to lower fructose

2,6-bisphosphate in the liver, suggesting that it also promotes glycogen repletion via gluconeogenesis [22].

Discussion

While these studies provide strong evidence that vinegar has a hypoglycemic effect, all of the intervention arms, with the exception of Johnston et al.'s [26] study, were carried out over a period of less than one week [13-27]; accordingly, no study has explored long-term indicators of elevated blood glucose including hemoglobin A1C (A1C0 levels nor long term health outcomes associated with elevated blood glucose such as cardiovascular disease and nephropathy. Thus while the hypoglycemic effects of vinegar confirmed in these studies represent promising therapeutic value, more studies are needed to confirm improved health outcomes and indicators.

In comparing the results of the studies and how each were conducted, it is important to note that all the studies that included lipid and protein products with the carbohydrate test meal saw a statistically significant reduction in PPG or GI [14,16,19], suggesting that other food products may confound or amplify the results of the vinegar treatment. This is consistent with Johnston et al.'s [16] study that found that peanuts had the same effect on PPG as did vinegar, reducing it by 55% ($P < 0.05$), and Sugiyama et al.'s [15] study found that dairy products and bean products reduced the GI of white rice as much if not more than vinegar products. Indeed, Ostman et al. [24] found that 18mmol of acetic acid ingested with white bread decreased the GI by 11%, but it was not statistically significant and nor did this treatment have any statistically significant effect on the insulinemic index (II); whereas Liljeberg et al. [25] who also used 18mmol of acetic acid but ingested with olive oil and cheese found a reduction in GI and II by 35% ($P < 0.05$). These findings suggest that lipids and proteins may have a synergistic or confounding effect on vinegar.

Many studies discussed in this paper provide evidence for the physiological mechanisms of vinegar that reduce blood glucose and insulin responses to food, including by decreasing gastric motility and increasing satiety, increasing insulin sensitivity, inhibiting disaccharidases, and reducing hepatic gluconeogenesis and glycogenolysis, but promoting hepatic and skeletal glycogen storage. Certain oral hypoglycemic medications, such as metformin and acarbose, harness some of these very mechanisms, and while the reductions in PPG and FBG captured in these studies are less than those generated in the trials of these pharmaceuticals, vinegar still presents a complementary adjuvant for diabetics or pre-diabetics [17]. While skeletal muscle and liver glycogen repletion was demonstrated in fatigued and food deprived rats, the findings may not be applicable to humans, and even if they are, could only be applied to patients who skip meals or rigorously exercise. It would be interesting to see if such findings are reproducible in sedentary and well feed rats. It is important to note that all these mechanisms of action were contingent on the ingestion of a meal with the vinegar. Accordingly, Johnston et al.'s [23] study found no change in PPG if vinegar was ingested 5h prior to a meal. White et al.'s [17] study, however, which demonstrated that nighttime ingestion of vinegar after mealtime leads to decreased morning fasting blood glucose suggests that there could be an alternative mechanism independent of the ingestion of food [17].

While the evidence for the hypoglycemic effects of vinegar presented in this paper are substantial and significant, there are limitations that merit discussion. Sample sizes were quite small; possibly resulting in findings that are non-significant, that are may not be representative of the general population or the targeted population explored (T2D, T1D, or with insulin resistance). Many of the trials were reviewed conducted by the one researcher (9 out of 21 by Johnston). Moreover, most of the human trials used healthy participants, limiting the generalizability of the findings to populations with insulin resistance, including women with gestational diabetes.

Most studies employed a crossover study method to ensure that individual differences in response to control and vinegar intervention would be held constant (Table 1). The rat studies by virtue of the nature of the experiment, sacrificing the animals to measure the glycogen content of tissues, meant that individual differences between rats could not be held constant, thus it is possible that the rats used in the experiment exploring the effects of vinegar had more glycogen in their muscles for other reasons. It is interesting to note that only Johnston's et al.'s studies were double blinded [16,18,23] perhaps rendering their results, which were often statistically insignificant, more reliable than others.

Conclusion

The object of our study was to review published reports of hypoglycemic effect of vinegar during normal pregnancy and in pregnancies affected by GDM. While no study was found that address our research question, we found strong evidence that vinegar ingestion is associated with a reduction in PPG, insulin response, and FBG among participants who healthy affected by or at risk for diabetes. Moreover, we identified proposed physiological mechanisms of action for vinegar effect on include decreased gastric motility, increasing satiety, inhibited disaccharidases metabolism, and increased hepatic and skeletal muscular glycogen storage. Many of these mechanisms are in fact harnessed by oral hypoglycemic pharmaceuticals. Our review provides compelling evidence to consider use of an additional tool to the current medical approach to the dietary management of diabetes, including GDM. Our review provides support for conducting adequately powered clinical studies to evaluate the hypoglycemic properties of vinegar when ingested by gravidas with a diagnosis of diabetes. Subsequent studies would be needed to evaluate effects of dietary vinegar on chronic disease outcomes including perinatal morbidity and long-term markers such as A1c levels. Vinegar is readily available, affordable, and used in a variety of cuisines. Therefore, is acetic acid by may present a viable tool to assist individuals attempting to achieve their glycemic targets.

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