

# **Evaluating the synergistic activity of Metformin and Apple Cider Vinegar in Type 2 diabetics**

## **ABSTRACT**

**Aims:** The aim of this study was to observe the effect of Apple Cider Vinegar (ACV) in combination with Metformin on the Body Mass Index (BMI) and glycemic control of newly diagnosed type 2 diabetic patients.

**Study design:** Single arm pre post quasi experimental clinical trial

**Place and Duration of Study:** Department of Medicine of a tertiary care hospital and a Diabetes and Endocrinology clinic, based in Karachi, Pakistan from April to July 2019.

**Methodology:** A total of 30 newly diagnosed type 2 diabetic patients were enrolled in the study (Males: 17; females: 13; age range: 27-55 years) after obtaining written informed consent. Body weight, BMI, Fasting Blood Sugar (FBS) and Hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) of each patient were assessed before and after 12 weeks of treatment with Metformin 750 mg plus 2 tablespoons of ACV per day. The baseline and post treatment values of the aforementioned were compared with each other.

**Results:** In all the 30 patients, assessed after 12 weeks of treatment the weight was significantly reduced from 85.66±18.30 kg. to 82.96±18.43 kg with a consequently significant change in the BMI from 29.38±5.08 kg/m<sup>2</sup> to 28.43±5.16 kg/m<sup>2</sup>. Moreover, the glycemic control, assessed as FBS and HbA<sub>1c</sub> also showed significant reduction in FBS (127.76±9.17 to 121.23±9.54) and HbA<sub>1c</sub> (7.14±0.29 to 6.92±0.29) after 12 weeks of treatment in all 30 patients ( $p < 0.01$ )

**Conclusion:** Apple Cider Vinegar seems to be effective therapy in combination with metformin for newly diagnosed type 2 diabetic patients in improving glycemic control as well as augmenting weight reduction.

**Keywords:** *Diabetes Mellitus, Metformin, Apple Cider Vinegar, Body Mass Index, Fasting Blood Sugar, Hemoglobin A<sub>1c</sub>*

## **1. INTRODUCTION**

With an alarming increase in the rate of incidence by over 90 percent in the past decade [1] diabetes mellitus is a major health concern contributing significantly to the global burden of disease [2] Type 2, previously known as Non-Insulin dependent DM, eventually leads to a state of chronic hyperglycemia resulting in a vast array of complications [3]

Although the precise molecular mechanism leading to type 2 diabetes is yet to be fully understood, it is principally the result of both genetic and environmental factors. The eventual pathophysiology is impairment of insulin secretion and insulin resistance, whereas the major environmental factors are a sedentary lifestyle, unhealthy eating habits and obesity amongst others [4]

BMI (Body Mass Index) is a crude measure of obesity in adults that categorizes them into groups based on the anthropometric measurements of weight and height, widely used in population based studies as an indicator of body fat [5]. Hence it could be postulated that an increase in BMI due to an increase in weight would predispose genetically susceptible individuals to the development of diabetes.

A member of the biguanide group, metformin seems to occupy the distinct position of being the first line or drug of choice for the oral treatment of type 2 diabetes [6]. A major factor that attributes to this seems to be the ability of metformin to bring about weight loss, in both diabetic and non-diabetic individuals [7]. Its antiglycemic property seems to be an effect of improving insulin sensitivity as well as decreased glucose synthesis by the liver, among other mechanisms [8].

The use of Vinegar for its medicinal properties dates back to many centuries ago [9], however there has been a recent upsurge of interest in one of its types, Apple Cider Vinegar as a therapeutic agent. Recent studies strongly suggest the antiglycemic properties of apple cider vinegar due to its glucose-lowering effects, both postprandially [10], as well as evident by decrease in Hemoglobin A<sub>1c</sub> [11]. Moreover multiple studies support the evidence of weight loss after treatment with apple cider vinegar hence highlighting its role in weight reduction as well [12],[13]. However these evidences are preliminary and warrant further research, Especially important to note, is that there is scarce evidence of the combined effect of herbs like apple cider vinegar with conventional therapy like metformin, on the glycemic control of type 2 diabetes patients. Hence, this study aims to observe the synergistic activity of metformin and apple cider vinegar in weight reduction as well as glycemic control of newly diagnosed type 2 diabetics.

## 2. PATIENTS AND METHODS

### 2.1 Clinical Trial Design and Setting

This is an open label single arm pre and post quasi experimental clinical trial. With 99% confidence interval, 95% power, and an effect size of 1.538, the minimum required sample size was calculated to be 12 using an online sample size calculator (<http://statulator.com/SampleSize/ss2PM.html>). A total of 30 patients (n=30) however were enrolled using the consecutive sampling technique over the duration of April to July 2019 (12 weeks for each patient) at the Department of Medicine of a tertiary care hospital and a Diabetes and Endocrinology clinic, both in Karachi, Pakistan.

### 2.2 Participant Criteria

A total of 30 patients with an age range in between 27-55 years having the following characteristics were included in this study:

- Newly diagnosed with Diabetes Mellitus Type 2
- Hemoglobin A<sub>1c</sub> in between 6.5% to 7.5%.
- No known allergies to apple or any kind of vinegar
- Able to understand and communicate effectively

All patients unable to meet the above mentioned criteria or those taking any therapy for Diabetes were excluded from the study.

### 2.3 Study Design:

A patient proforma enlisting biodata and relevant health conditions and allergies was administered after explaining the entire procedure of the study in detail and obtaining written informed consent from the patients. The newly diagnosed diabetic patients were given conventional therapy in the form of Metformin 750 mg OD whereas they were additionally

instructed to take 2 tablespoons of organically sourced Apple Cider Vinegar per day, for 12 weeks. The ACV bottles were all provided by the researcher from the same source to ensure uniformity.

Anthropometrically, the height was measured using a standard calibrated scale in feet and inches whereas the weight was measured in kilograms using a weighing scale with standard calibration with a maximum capacity of 125 kg. The Body Mass Index was then calculated by an online calculator via the formula :

Metric units:  $BMI = \text{weight (kg)} \div \text{height}^2 \text{ (m}^2\text{)}$ .

The parameters of glycemic control; Fasting Blood Sugar and Hemoglobin A<sub>1c</sub> were analysed at Ziauddin Laboratory, Karachi both at the start and at the end of 12 weeks for each patient

## 2.1 Statistical Analysis

The data analysis was done using the software SPSS version 20. Parametric numerical variables were expressed as mean and standard deviation whereas non parametric numerical variables were expressed as median and interquartile range. Categorical variables were expressed as frequencies and percentages. The pre and post comparison of weight and BMI was done using the paired t test whereas the Wilcoxon signed rank test was used for pre and post comparison of FBS and HbA<sub>1c</sub>. A *p* value of <0.01 was considered statistically significant.

## 3. RESULTS

The demographical features of the patients depicted a mean age of patients to  $41.56 \pm 7.70$  years. The gender distribution reflected a slight male predominance (56.7%) and a majority of the patients married (83.3%) (Table 1)

**Table 1: Demographical Characteristics of Patients Enrolled in the study(n=30)**

Demographical Characteristics		Mean±SD/n(%)
Age (years)		41.56±7.70
Gender	Male	17(56.7%)
	Female	13(43.3%)
Marital Status	Married	25(83.3%)
	Unmarried	5(16.7%)

The mean height observed among the 30 patients was 5.66±0.31. The weight of the patients observed before treatment with Metformin and Apple Cider Vinegar was 85.66±18.30 kg whereas after treatment it reduced significantly to 82.96±18.43 kg ( $p$  value <0.001). Similarly the BMI before treatment was 29.38±5.08 kg/m<sup>2</sup> which also showed a noteworthy reduction to 28.43±5.16 kg/m<sup>2</sup> ( $p$  value <0.001)(Table 2).

**Table 2: Anthropometric Parameters of patients before and after treatment with Metformin and ACV**

Anthropometric Parameters	Pre Intervention	Post Intervention	P value
	Mean ± SD	Mean ± SD	
Height (feet and inches)	5.66±0.31	--	--
Weight (kg)	85.66±18.30	82.96±18.43	<0.001*
BMI (kg/m <sup>2</sup> )	29.38±5.08	28.43±5.16	<0.001*

*Pre and post values obtained from paired t test*

*,\* shows significant  $p$  values of <0.01*

With consideration to the glycemic control of the patients (Table 3) there was a decrease in the Fasting blood Sugar levels of the patients from 127.76±9.17mg/dl to 121.23±9.54 mg/dl which was statistically significant ( $p$  value <0.001). In addition, the decline in Glycated Hemoglobin (HbA<sub>1c</sub>) was also observed from 7.14%±0.29 at the start and then 6.92%±0.29 by the end of 12 weeks of treatment.

**Table 3: Glycemic Control of Patients before and treatment with Metformin and ACV**

Parameters of Glycemic Control	Pre Intervention		Post Intervention		p-value
	Mean ± SD	Median(IQR)	Mean ± SD	Median(IQR)	
FBS(mg/dl)	127.76±9.17	130.5(121.7-134.2)	121.23±9.54	124.5(115.0-130.0)	<0.001*

<b>Hb A1c %</b>	7.14±0.29	7.2(6.9-7.4)	6.92±0.29	7.0(6.6-7.2)	<0.001*
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*Pre and post*

*values from the Wilcoxon-signed rank test*

*\* shows significant p values of <0.01*

UNDER PEER REVIEW

#### 4. DISCUSSION:

It is common knowledge that Diabetes Mellitus Type 2 is now one of the most prevalent chronic diseases around the globe, posing grave challenges to public health worldwide [14]. All in all, the risk factors mainly happen to be physically inactive lifestyles along with unhealthy eating habits [15], leading to obesity. Therefore weight gain is one of the major modifiable risk factors of the disease and can also be postulated to have an effect on glycemic control. The eventual pathophysiological change seems to be resistance to insulin in the body or ultimately loss of insulin production leading to a state of chronic hyperglycemia, which may cause multiple microvascular as well as macrovascular complications if left untreated [16].

Our study shows demographical features of male predominance in the study sample which is in line with the demographic profile of a cross-sectional study conducted on newly diagnosed type 2 diabetics in Pakistan, as well as a mean age of  $41.56 \pm 7.70$  years which is comparable to  $49.6 \pm 8.5$  years found in the same study reported by Naqvi et al [17].

The present study observes a significant reduction in the weight of the patients after treatment with combination of metformin and apple cider vinegar with a subsequent decline in the BMI (Table 2), highlighting the role of this combination as a possibly successful therapy to augment weight loss in type 2 diabetics. There are multiple studies that support the claim of weight loss by metformin [18],[19] and there is also emerging evidence of weight loss caused by apple cider vinegar [20], however there seems to be scarce information regarding the combination therapy of ACV with metformin.

Metformin is an established first-line drug for the treatment of diabetes mellitus type 2 due to its stellar advantage to bring about weight loss. [21],[22] However, in cases of inadequate control by metformin alone, different anti-diabetic agents may be administered in combination to achieve better glycemic control [23]. Also important to note is that metformin is widely reported for significant gastrointestinal distress, as well as Vitamin B<sub>12</sub> deficiency [24],[25].

Multiple studies carried out in humans and animals also suggest the anti-diabetic effect of apple cider vinegar when used alone. Halima et al reported decreased blood glucose level as well as increased antioxidant activity in diabetic rats after 4 weeks of administration of apple cider vinegar [26]. A study done by Mohammadpourhodki et al on 74 diabetic patients also reported significantly reduced FBS and HbA<sub>1c</sub> levels after 8 weeks of administration of ACV [27]. A recent clinical trial reports significant reduction in the fasting blood sugar and Hemoglobin A<sub>1c</sub> levels after administration of ACV in type 2 diabetic patients with poor glycemic control [28].

Our study observes a significant reduction in the level of both Fasting Blood Sugar as well as Hemoglobin A<sub>1c</sub> after the 12-week period of treatment with metformin and apple cider vinegar combination, showing the beneficial effects of this combination on glycemic control. Many reviews also support the claim of apple cider vinegar as an anti-diabetic remedy, in addition to other properties, like being an anti-oxidant, an effective weight loss agent, having a possible role in managing hyperlipidemia, as well as its potential role as an anti-hypertensive agent [29],[30],[31].

Moreover, a clinical trial reported by Gheflati et al also supports the notion of ACV improving glycemic control in type 2 diabetic patients [32]. Apple cider vinegar is prepared from fermented apples, the possible reason behind weight-reducing and glucose-lowering effects of ACV could be its chief active ingredient acetic acid [33]. Still at the molecular level the benefits of ACV should be explored to know its exact mechanism of anti-glycemic and weight-reducing effects.

Therefore, this study explores the niche of combination of conventional and herbal treatment, i.e. metformin and apple cider vinegar, respectively, which to the best of our knowledge is somewhat innovative. However, this trial is prone to bias due to a smaller sample size as well as the absence of a control group for comparison. Therefore, we strongly recommend clinical trials on larger sample sizes and comparative groups to strengthen the claim of this study.

#### 5. CONCLUSION

Our study examines the synergistic effect of Metformin, a first-line pharmaceutical agent with ACV, a traditional herbal remedy, revealing increased weight loss and improved glycemic control in newly diagnosed type 2 diabetic patients.

manifesting as significant decreases in BMI, FBS and HbA<sub>1c</sub>. However, it is preliminary and certainly requires more evidence on larger sample sizes and diverse populations and comparative studies with conventional treatment groups.

## CONSENT

This study was conducted in accordance with the Declaration of Helsinki. Ethical Approval was obtained from the institutional ethics board (Ethics Review Committee) of Ziauddin University. The patients were explained the entire procedure in detail and written informed consent was obtained with due diligence.

## ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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### **DEFINITIONS, ACRONYMS, ABBREVIATIONS**

DM: Diabetes Mellitus

BMI: Body Mass Index

FBS: Fasting Blood Sugar

HbA1c : Hemoglobin A1c (Glycated Hemoglobin)

ACV: Apple Cider Vinegar

OD: once daily