Available online at **www.ijmrhs.com**

ISSN No: 2319-5886

International Journal of Medical Research & Health Sciences, 2020, 9(2): 1-7

Comparison of Apple Cider Vinegar and Metformin Combination with Metformin Alone in Newly Diagnosed Type 2 Diabetic Patients: A Randomized Controlled Trial

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ABSTRACT

Objective: *This study aims to compare the effect of metformin monotherapy with the combination therapy of metformin and apple cider vinegar on the parameters of Body Mass Index and glycemic control of recently diagnosed type 2 diabetes mellitus patients.* ***Methods:*** *A total of 126 patients were enrolled in this open-label randomized controlled trial, divided into two parallel arms: Group I (Metformin 750 mg alone per day) and Group II (Metformin 750 mg+Apple Cider Vinegar 2 tablespoons per day) and assessed for weight, Body Mass Index, Fasting Blood Sugar and Hemoglobin A1c after which the post-treatment values of the aforementioned parameters were compared between the two groups. Informed consent from all patients and ethical approval from the institutional ethics board was obtained. A p-value of <0.05 was considered significant.* ***Results:*** *All the parameters underwent a significant reduction in the pre and post intra group comparison of each group (p-value<0.001). Moreover, a significant difference was found in the post-treatment comparisons of the Fasting Blood Sugar (p-value<0.001) and HbA_{1c} (p-value=0.04) in between the two groups. However, no significant difference was obtained in the post-treatment comparisons of weight and Body Mass Index in between the two groups.* ***Conclusion:*** *Apple Cider Vinegar in combination with Metformin appears to be more effective in improving glycemic control versus Metformin monotherapy.*

Keywords: Apple cider vinegar, Type 2 diabetes mellitus, Metformin, Randomized controlled trial

Abbreviations: FBS: Fasting Blood Sugar; HbA1c: Hemoglobin A1c; ACV: Apple Cider Vinegar; BMI: Body Mass Index

INTRODUCTION

First recognized by the folk of ancient Egypt centuries ago Diabetes Mellitus is a chronic metabolic disease that continues to be one of the major causes of death even today, worldwide [1]. Its major type, Type 2 Diabetes is a multifactorial and progressive disease. There is increasing evidence of obesity predisposing to the development of the disease even on a genetic level, along with consequent weight loss improving the outcome of the disease, hence highlighting the role of obesity as a major risk factor and weight loss as an alleviating measure [2,3]. Multiple studies highlight the crucial role of inflammation in the pathogenesis of type 2 diabetes including oxidative stress and DNA damage as well as alleviation via antioxidative pathways and mechanisms [4-6]. Pharmacologically classified a biguanide, Metformin has the reputation for being the drug of choice for Diabetes around the world [7]. Although the exact

molecular mechanism is unclear, but Metformin is an effective weight loss agent, hence playing a role in not just the treatment but also the prevention of Diabetes [8].Moreover, its antihyperglycemic effect seems to be an extension of its ability to decrease the production of glucose in the liver as well as minimize the toxic effects of glucose on other tissues in the body [9].

Apple cider vinegar, like other vinegar, is produced by the fermentation of apple juice. Recent research has explored a plethora of therapeutic benefits of apple cider vinegar including its potential as an immune-stimulant as well as an anti-oxidant, however the major bulk of research seems to surround its effects on lipids, weight loss and its anti-diabetic activity [10,11] Various studies on animal models suggest the attenuation of lipids as well as improved HbA_{1c} levels by the administration of Apple Cider Vinegar [12,13]. A study carried out in obese Japanese subjects documented weight loss with a subsequent reduction in BMI after the ingestion of apple cider vinegar for 12 weeks [14].

Recently there has been a tilt towards the treatment of both acute and chronic diseases with herbal/organic extracts over conventional allopathic treatment with drugs due to decreased incidence of side effects and better tolerability. Moreover, due to scarcity of evidence, a niche that needs to be explored in more detail is the combination of conventional and natural treatment agents, which is also supported by the notion that the interactions of the two are majorly reported to be relatively harmless and minor [15] Therefore this study aims to explore the activity of a combination of metformin and apple cider vinegar, an agent from each type of category i.e. a conventional drug and herbal therapy respectively and evaluate its effects on the weight and subsequently the Body Mass Index, and parameters of glucose control namely Fasting Blood Sugar and Hemoglobin A_{1c} in newly diagnosed patients of Type 2 Diabetes Mellitus, one of the most common chronic diseases around the world.

MATERIALS AND METHODS

Trial Design and Setting

This open-label randomized controlled trial with a parallel design using the consecutive sampling technique was held from April to August 2019 at a tertiary care hospital and a diabetes clinic in Karachi, Pakistan. The biochemical parameters were assessed at Ziauddin Laboratory, Karachi, Pakistan.

The outcome measures assessed were:

Weight and BMI (Body Mass Index): The anthropometric measurements of weight and height of the participants were measured via standard calibrated scales, and the BMI was calculated as body weight divided by the square of the height for both groups, both at the start of the study and at the end of 12 weeks.

FBS (Fasting Blood Sugar): After 12 hours of fasting and taking appropriate aseptic measures 5cc of venous blood was obtained from each patient and analysed for FBS levels at the start and end of the study period.

HbA_{1c} (Hemoglobin A_{1c}): After appropriate aseptic measures 5cc of venous blood was obtained from each patient and analysed for glycated hemoglobin (HbA_{1c}) levels at the start and end of the study period.

Inclusion Criteria

This study focused on recruiting individuals with the following characteristics:

- Recently diagnosed Type 2 diabetic patients taking metformin 750 mg daily as the oral anti-diabetic agent
- Patients with Hemoglobin A_{1c} in the range of 6.5 to 7.5%

Exclusion Criteria

- All newly diagnosed Diabetic Patients requiring a dosage other than 750 mg per day
- Patients on Insulin Therapy or any drugs for diabetes other than Metformin
- Pregnant and Lactating women
- Patients with food allergies to either apple or any source of vinegar
- Patients unable to communicate efficiently/mentally challenged

- Type 2 Diabetic patients with any of the complications of long-standing uncontrolled diabetes were excluded from the study

Sample Size and Study Groups

With significance level (alpha) 5%, Power (1-beta) 80%, the sample size was calculated to be n=126 using the Continuous Superiority Binary Outcome Trial via the Sealed Envelope Power Calculator.

The total of 126 participants within the age range of 26-65 years was divided into two groups on the basis of treatment: (n=126)

- Group 1: 63 Type 2 Diabetic patients taking 750 mg of Metformin alone per day
- Group 2: 63 Type 2 Diabetic patients taking Metformin 750 mg plus 2 tablespoons of Apple Cider Vinegar per day

Data Collection Procedure

The participants enrolled in the study were explained the methodology in detail. Written informed consent in both English and Urdu was obtained from each participant before the commencement of the study in compliance with the Declaration of Helsinki. They were provided a detailed questionnaire enlisting their biodata, comorbidities, allergies and all factors relevant to ensure patient safety and compliance during the period of the study. The patients were thoroughly examined both at the start and at the end of 12 weeks by the involved clinician and were advised to report any health-related event during the course of the study in order to facilitate the participants. Organic Raw Unfiltered Apple Cider Vinegar was used for the purpose of the study and was provided to the participants free of cost throughout the duration of the study.

The process of randomization whilst allocating groups was ensured via providing the patients opaque envelopes containing the labels of which group they will be allocated to and were chosen by the patient completely dependent on chance. The patients have advised lifestyle modifications of a healthy diet encompassing high fiber and low-fat products and avoidance of processed sugar, along with exercise recommendations of 30 minutes brisk walk daily, preferably in the fresh open air before breakfast.

Ethical Considerations

Ethical approval was taken from the Ethics Review Committee of Ziauddin University. The trial was also registered with https://clinicaltrials.gov under the identifier: NCT04120259.

The process of obtaining informed consent from patients was carried out with due diligence, in order to ensure patient autonomy at all times. In the case of illiterate patients, the procedure was discussed and explained in detail verbally and then a thumbprint was taken in written as a record of consent. The patient's safety, rights, and autonomy were prioritized at all times.

Statistical Analysis

SPSS (Statistical Package for the Social Sciences) version 20 was used for data entry and analysis. For parametric data mean and the standard deviation was calculated. In the case of non-parametric data, the median and interquartile range was calculated. For categorical variables frequencies and percentages were calculated. Paired T-test was applied to compare pre and post interventional changes in both groups for parametric variable whereas for non-parametric variables the Wilcoxon-signed rank test was used. While Pooled t-test and Mann-Whitney U test were applied to compare the parameters for inter-group comparisons of post interventional levels of parametric and non-parametric variables respectively. A p-value of <0.05 was considered significant.

RESULTS

Out of a total of 126 patients enrolled in the study, the demographic profile reflected a majority of males in Group I (Metformin only group) with a slight female predominance in Group II (Metformin+ACV group), with a mean age of 42.66 ± 7.19 years in Group I and 40.98 ± 8.27 years in Group II. The mean height observed was 5.60 ± 0.30 ft in Group I whereas it was 5.56 ± 0.30 ft in Group II, whilst the marital status depicted a predominance of married

individuals in both groups. A majority of the patients were educated in both groups at different stages of schooling as depicted in Table 1.

The mean weight of the patients before treatment in Group I (Metformin Only group) was 88.06 ± 15.14 kg whereas after treatment it showed a significant reduction to 86.82 ± 15.20 kg (p-value<0.05). Group II (Metformin+ACV group) showed a similar pattern, with a pre-treatment mean weight of 86.06 ± 18.66 kg being reduced to 83.25 ± 18.54 kg post-treatment (p-value<0.05). However, in the intergroup comparison between the post-treatment weight of the two groups, no significant difference was observed (p-value=0.119). The BMI of the patients changed significantly after treatment from a mean of 30.61 ± 4.37 kg/m^2 to 30.18 ± 4.41 kg/m^2 in Group I (p-value<0.05) similar to Group II where it reduced significantly from 30.50 ± 6.35 kg/m^2 to 29.48 ± 6.23 kg/m^2 (p-value<0.05). However, when the post-treatment values of both the groups were compared, there was no significant difference (p-value=0.07) (Table 2).

The FBS showed a favorable difference post-treatment for both the groups i.e. in Group I it showed a significant reduction from 128.69 ± 9.94 mg/dl to 126.0 ± 8.98 mg/dl and in Group II from 126.41 ± 13.95 mg/dl to 118.58 ± 10.57 mg/dl. Notably, the post-treatment reduction in FBS was also significant when the two treatment groups were compared (p-value<0.05) (Table 2).

Finally, the Hemoglobin A1c was also significantly reduced after treatment in Group I from 7.05 ± 0.36% to 7.0 ± 0.36% as well as in Group II from 7.12 ± 0.30% to 6.89 ± 0.30% (p-value<0.05). Importantly, the HbA_{1c} also showed a significant difference on the intergroup comparison of the post-treatment values of the two groups (p-value<0.05) (Table 2).

Table 1 Demographic Profile of the patients enrolled in the study

Variable		Group I (Metformin Only) (n=63)	Group II (Metformin+ACV) (n=63)
Age (years)	Mean ± SD	42.66 ± 7.19	40.98 ± 8.27
	Median (IQR)	42.0 (37.0-46.0)	40.0 (34.0-47.0)
Height (Feet)	Mean ± SD	5.60 ± 0.30	5.56 ± 0.30
	Median (IQR)	5.60 (5.4-5.9)	5.50 (5.30-5.80)
Gender n (%)	Male	39 (61.9%)	30 (47.6%)
	Female	24 (38.1%)	33 (52.4%)
Education n (%)	Primary/Middle School	13 (20.6%)	7 (11.1%)
	High School	10 (15.9%)	20 (31.7%)
	Higher Secondary School	13 (20.6%)	11 (17.5%)
	Graduation	18 (28.6%)	16 (25.4%)
	Masters	3 (4.8%)	4 (6.3%)
	Nil	6 (9.5%)	5 (7.9%)
Marital Status n (%)	Married	58 (92.1%)	54 (85.7%)
	Unmarried	5 (7.9%)	9 (14.3%)
	No	32 (50.8%)	34 (54.0%)

Table 2 Intra and Intergroup comparison of weight, BMI and glycemic control of patients in both groups

Variable		Group I (Metformin Only) (n=63)	Group II (Metformin+ACV) (n=63)	p-value
		Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	
Weight (Kg)	Pre	88.06 ± 15.14	86.06 ± 18.66	0.119
	Post	86.82 ± 15.20	83.25 ± 18.54	
	p-value	<0.001*	<0.001*	

Body Mass Index (kg/m^2)	Pre	30.61 ± 4.37 30.0 (27.6-33.2)	30.50 ± 6.35 29.3 (26.5-33.0)	0.07
	Post	30.18 ± 4.41 30.4 (27.2-32.9)	29.48 ± 6.23 28.5 (25.1-32.4)	
	p-value	<0.001*	<0.001*	
Fasting Blood Sugar	Pre	128.69 ± 9.94 128.0 (120.0-136.0)	126.41 ± 13.95 126.0 (117.0-133.0)	<0.001*
	Post	126.0 ± 8.98 127 (118.0-132.0)	118.58 ± 10.57 120.0 (110.0-126.0)	
	p-value	<0.001*	<0.001*	
HbA_{1c}	Pre	7.05 ± 0.36 7.1 (6.8-7.4)	7.12 ± 0.30 7.2 (6.9-7.4)	0.044*
	Post	7.0 ± 0.36 7.1 (6.7-7.3)	6.89 ± 0.30 6.9 (6.6-7.1)	
	p-value	<0.001*	<0.001*	

DISCUSSION

With respect to the demographic data of the patients in our study, the mean age was 42.66 ± 7.19 in Group I and 40.98 ± 8.27 years in Group II which is a reflection of other studies conducted on newly diagnosed diabetics in Pakistan, as well as a male predominance in Group I [16,17] (Table 1).

Our study shows a decrease in the weight, with a subsequent decrease in the BMI, as well as improved glycemic control parameters, FBS and HbA_{1c} in the patients administered Metformin only for treatment (Group I) which goes in line with the recommendation of Metformin as the drug of choice in Type 2 Diabetes [18]. Also, both the parameters of body weight and glycemic control are also improved in Group II which uses ACV in addition to Metformin, further strengthening the claim of multiple studies that document increased weight loss and improved glycemic control in diabetics after treatment with ACV [19,20] (Table 2).

However, in cases of metformin monotherapy failure, perhaps in a state of "clinical inertia", clinical guidelines recommend the addition of combination drugs to achieve better glycemic control [21,22]. As Apple Cider Vinegar is well known for its anti-diabetic properties and rare reports of side effects, our study postulates the use of ACV as a combination agent with Metformin for better glycemic control [23].

Our study observes post-treatment comparisons of weight and BMI in between the two groups to be insignificant at the end of the study period of 12 weeks, however, the post-treatment comparisons of the glycemic control of the two study groups were found to have a significant difference i.e. the FBS and HbA_{1c} both showed better control in the Metformin plus ACV group somewhat highlighting the superiority of the combination versus Metformin monotherapy. The probable mechanisms for improved glycemic control with the addition of vinegar may be attributed to its effects of improving insulin sensitivity, causing a delay in gastric emptying and decreasing the production of glucose by the liver as reported by several studies [24-26].

However, this evidence is preliminary because of the localization of its collection sources and limited sample size, amongst other factors. Therefore we strongly recommend studies to further explore the effects of this combination on larger sample sizes, different populations and even different periods of study duration along with different dosage regimens to help elucidate its properties and explain its anti-diabetic role further.

CONCLUSION

Our study concludes that the effect of combining Apple Cider Vinegar with conventional therapy like metformin improves glycemic control more than metformin treatment alone in the form of FBS and HbA_{1c} in newly diagnosed diabetics. However, no significant difference in weight and BMI was observed when comparing the metformin monotherapy group with the Metformin ACV combination group.

DECLARATIONS

Acknowledgments

The authors would like to express their sincere gratitude to Prof. Dr. Syed Ijlal Haider Rizvi (late) for his guidance and support throughout this project. We would also like to acknowledge Dr. Kausar Ismail, Dr. M. Owais Ismail, Dr. Akhtar Ali, Dr. Dabeeran Zehra and Dr. Urooj Zafar from the Department of Pharmacology at Ziauddin University, Karachi for their valuable input towards this study.

Conflicts of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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