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Effect of Insulin with Other Hypoglycemic Agents and Multivitamin Consumption on Diabetes Progression

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Abstract: The aim of this study was to assess the long-term effect of insulin administration (3 years) with other hypoglycemic agents (OHA) and multivitamins (MV) on the glycemic index and diabetic progression. An equal number of male and female (n = 11/group) subjects who had diabetes for more than 5 years were selected and enrolled in this study. All subjects were consuming multivitamins with three hypoglycemic drugs (a combination of metformin, Glimepiride and Voglibase) only or with insulin divided into groups. Blood samples were collected, and clinical analyses were performed to determine fasting (FBS), postprandial blood glucose (PPBS), glycosylated hemoglobin (HbA1c), and body mass index (BMI). Each parameter was analyzed for pre and post-study periods to determine the changes during the study period, and a gender-based analysis was also performed to examine the effects on a gender basis. Though we observed an increasing trend in FBS, and HbA1c levels in both groups compared to their basal (pre-study) levels, these changes were not significant. There was no change in PPBS at baseline as well as post-study. BMI was not changed significantly compared to its baseline, BMI was significantly ($P<0.05$) changed in both the groups of female participants only due to the higher dysglycemia risk in South Asian women. From these results, we concluded that long-term insulin administration with MV and OHA has less effect on controlling the glycemic index in subjects with chronic diabetes. However, our results warrant a long-term and large-scale randomized study.

Keywords: Diabetes mellitus, Multi-vitamin, Insulin, HbA1c, Hypoglycemic, Blood glucose

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Introduction

Diabetes is an incurable metabolic disorder (Karamanou *et al*., 2016; Blasi, 2016) and is linked to diminished life expectancy, which stems from significant morbidity arising from diabetes-associated micro/macro-vascular complications (Dregan *et al*., 2014; Viigimaa *et al*., 2020). Brown *et al*. (2016) found that patients with diabetes mellitus have a significantly reduced quality of life (Rubin and Peyrot 1999); moreover, patients require lifelong pharmaceutical management of the disease by taking antidiabetic (antihyperglycemic) medications (Brown *et al*., 2016). Multiple genetic alterations/mutations have also been known to cause diabetes mellitus (Groop and Pociot, 2014; Støy *et al*., 2021; O'Connor *et al*., 2022), however, it is not caused solely by genetic abnormalities. Numerous pathogenesis processes are known to cause pancreatic beta cells' destruction, leading to insulin insufficiency and the prevalence of metabolic dysfunction (Marasco and Linnemann, 2018). This subsequently causes insulin resistance, which ensues for manifold reasons such as lack of insulin, mutations of the insulin gene or the gene coding for the insulin receptor, mutations of the glucose transporter (GLUT) genes responsible for insulin-mediated glucose uptake, or decreased insulin action (Støy *et al*., 2021). Diabetes affects carbohydrate, fatty acid, and protein metabolism because insulin action is impaired.

Oral hypoglycemic agents (OHA) are anti-diabetic medications that address the problem of hyperglycemia. Several types of OHAs are used for the treatment of hyperglycemia, namely biguanides, sulfonylureas, α-glucosidase inhibitors, thiazolidinediones, and incretin analogs/agonists (Song, 2016). Most diabetic patients' hyperglycemic levels are managed with any one of the drugs for a couple of years. However, chronic consumption requires a high concentration or combination of other hypoglycemic drugs or insulin (Cheng and Fantus, 2005). Diabetes mellitus (due to impaired insulin sensitivity) can cause immune system dysfunction in humans (Rahman *et al*., 2021; Sty *et al*., 2021).When the pancreas does not secrete insulin normally and/or insulin levels are low, pharmacological management of hyperglycemia does not work. Exogenous insulin from porcine or humulin is administered to diabetic patients to manage hyperglycemia (Inzucchi *et al*., 2015).

Several decades of research documented that chronic oxidative stress is known to be the cause of diabetic-associated complications, and antioxidant supplementation is thought to compensate for the oxidative stress. Bouayed and Bohn (2010) and Polyak *et al.* (2018) believe that exogenous antioxidant supplementation can compensate for oxidative stress. Supplementation or endogenous activation of antioxidants can suppress the severity of diabetes mellitus (Bouayed and Bohn, 2010; Polyak *et al*., 2018). For several decades, clinical trials of antioxidants have been inconclusive as mixed effects have been observed; a few clinical trials have revealed that antioxidants may also impede normal redoxfunctions of cells and might further complicate diabetes management (Chiabrando *et al.*, 2002; Violi *et al.*, 2004; Steinhubl, 2008; Levy *et al.*, 2009; Davies and Holt, 2018; Ahmad and Leake, 2018).

Although single or multiple oral hypoglycemic agents (OHA) with insulin are effective in managing glycemic control, the effect of OHA with insulin and multivitamins on diabetes progression is unknown. In this study, we aimed to assess the impact of insulin administration on glycemic management in diabetic subjects with other antihyperglycemic and multivitamin drugs for a minimum period of 3 years between 2014 and 2018. Diabetic subjects consumed 3 hypoglycemic drugs (a combination of metformin, Glimepiride, and Voglibase tablet) with multivitamin supplements to determine the basic glycemic index management over the years to find whether insulin supplements had the potential to slow down diabetes progression.

Composition of vitamins/cofactors	Per serving (per tablet)
VITAMINS	
Vitamin A (as Acetate)	2500 IU
Vitamin E (Tocopherol)	10 IU
Vitamin K	10 mcg
Vitamin D3 (Cholecalciferol)	200 IU
Vitamin B1 (Thiamine Mononitrate)	2 mg
Vitamin B2 (Riboflavin)	3mg
Vitamin B6 (Pyridoxie Hydrochloride)	1.5mg
Niacinamide	26mg
Vitamin C (Ascorbic Acid)	50mg
Vitamin B12 (Cyanocobalamin)	1mcg
Folic Acid	0.3mg
Calcium Pantothenate	5mg
Biotin	30mcg
MINERALS:	
Zinc (as zinc sulphate Monohydrate)	15mg
Iodine (as potassium iodide)	0.15mg
Ferrous fumarate equ. To Iron	9mg
Magnesium(as Magnesium oxide)	100mg
Manganese (as Managanese sulphate monohydrate)	2.5mg
Copper (as Cupric Oxide)	2mg
Calcium (as Dibasic calcium Phosphate)	162mg
Phosphorous	125mg
Potassium (as Potassium Chloride)	40mg
Chloride	36.3mg
Chromium (as Chromium Chloride)	100mcg
Selenium (as selenium silicate)	25mcg
Nickel (Nickel sulphate)	5mcg
Silica (as colloidal silicon Dioxide)	10mcg
Vanadium	10mcg
Molybdenum(as Sodium Molybdenum)	100mcg

Table 1: Composition of multivitamin tablets.

Materials and Methods

Diabetic patients (n=50) who had diabetes for more than 5 years and were regularly consuming (prescribed & non-prescribed) multivitamin supplements (Table 1) from 2014 to 2018 in Tamil Nadu, India (South region) were approached to get their informed consent to assess their medical records from Karunya Sugalaya Diabetic Care and Research Centre in Kumbakonam, Tamil Nadu, India. Informed consent was obtained from all the patients, and enrolled patients were notified. Samples were collected, processed, and clinical analyses were performed in Karunya Sugalaya Diabetic Care & Research Centre in Kumbakonam, Tamil Nadu, India. The inclusion and exclusion criteria of the diabetic subjects were followed as described in Figure 1. Only 22 subjects were included in this study, and the age of the patients ranged from 45 to 80. The distribution of subjects was 1:1 for males: females. Body mass index (BMI), fasting (FBG), and postprandial blood glucose (PPBG) levels, and HbA1c, levels were extracted from the database and used for this study. This study was approved by the Bharathidasan University Institution bioethical committee (IEC; DM/2014/101/47).

Statistical Analysis:

Statistical analyses were used for the calculation of mean and SEM. All values are represented as mean ± SEM. The P-value < 0.05 ($P < 0.05$) was considered statistically significant. All statistical analyses were performed using the GraphPad Prism. One-way ANOVA (analysis of variance) was performed to find the difference in statistical significance between the means of two or more groups.The P-values for ANOVA analyses are given in the respective results wherever ANOVA was performed.

Results

Characteristics of the study participants:

At baseline, there was no statistical significance

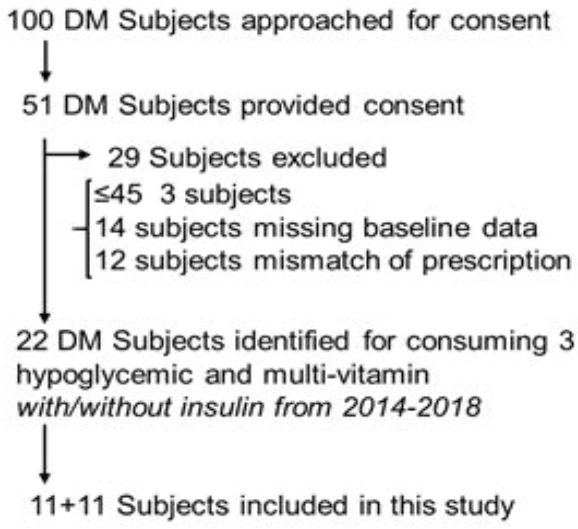

Fig. 1: Criteria for study subject selection.

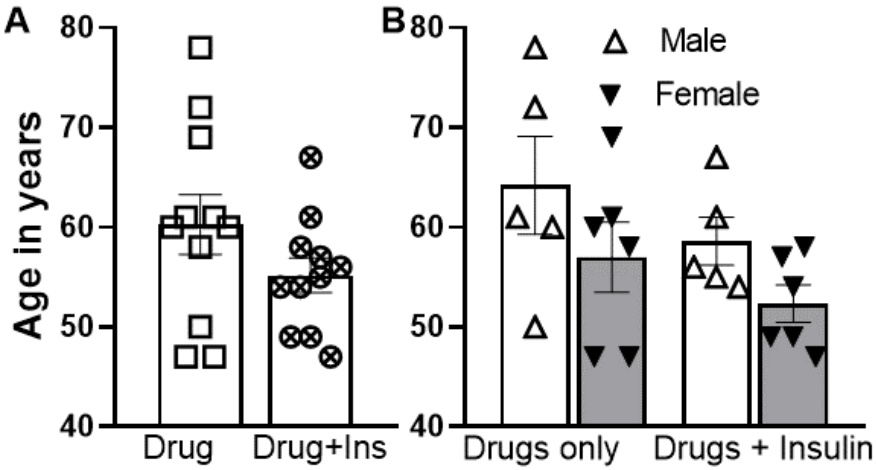

Fig. 2: Ages of the study participants. (A) Comparison of ages between two groups of subjects included. (B) Bar graph illustrating the ages of males and females separately in each group.

observed in blood glucose (FBS and PPBG), age and BMI among the group participants. However, we observed differences in HbA1c levels but they were not statistically significant. We included two patients with higher age in the drug-only group to match the gender association of patients with an equal number and also to achieve the total number of participants per group to a minimum of 10. The mean age of participants for the drug-only group was 60.27±3.0, whereas the drug+Insulin group was 55.18±1.73. In each group, we included 5 males and 6 females. The average age of males and females in the drug-only group was 64.20±4.90 and 57±3.51 and in the drug+Insulin group was 58.60±2.42 and 52.33±1.89, respectively (Figs. 2A, B.)

Fasting and post-prandial blood glucose levels:

First, we analyzed the changes in FBS and PPBS to determine whether prolonged intake of multi-vitamins with hypoglycemic drugs alone and/or insulin preserves blood glucose levels in study subjects. We observed an increasing trend in the FBS levels of participants in the drug-only group. However, this change was not statistically significant within the group as well as the gender (Figs. 3A, B). Next, we analyzed the pre and post-treatment changes in PPBS levels between the

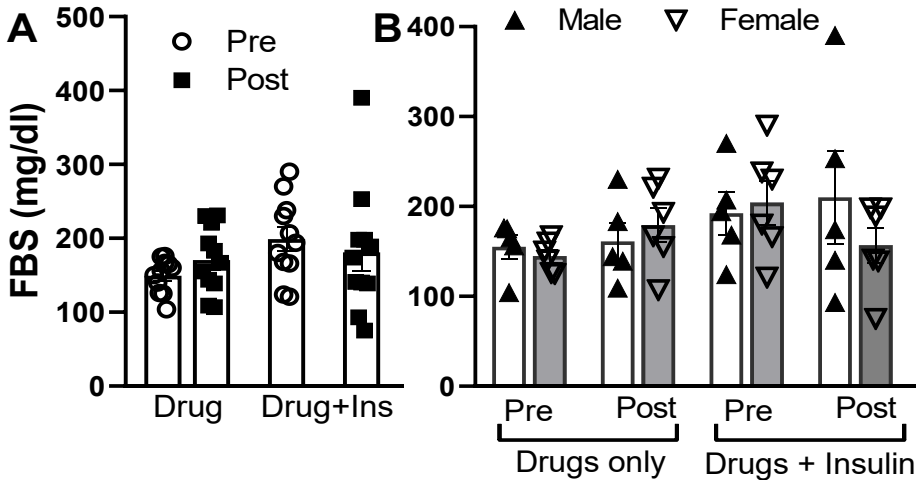

Fig. 3: Change infasting blood sugar (FBS) levelsbefore start (pre) and end of the study (post). (A) Overall changes in FBS levels in both groups between the study periods. (B) Gender associated changes in FBS. Drug, hypoglycemic drugs with MV.

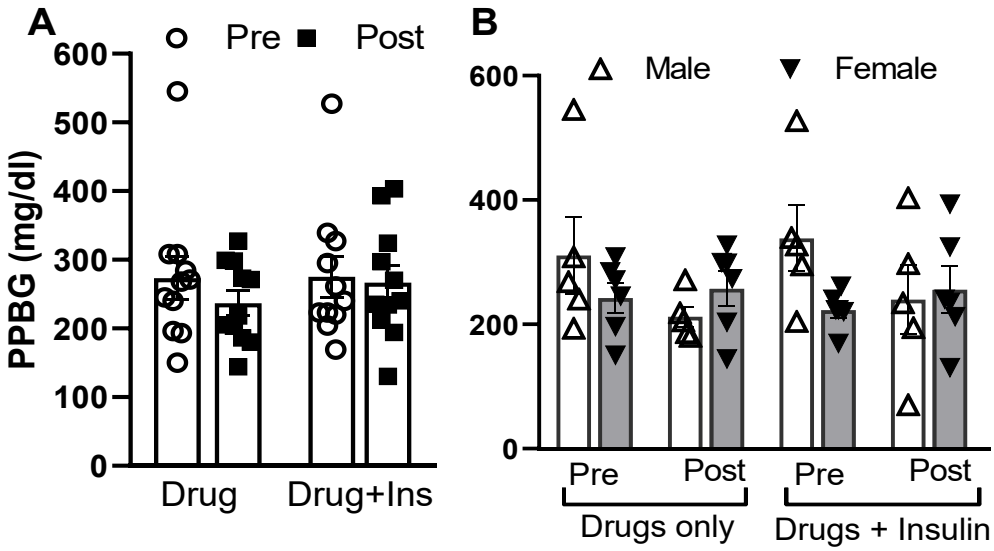

Fig. 4: Post-prandial blood glucose (PPBG) changes in DM subjects treated with drugs or drugs with insulin. (A) Changes observed in PPBG levels overall between the study times in each group. (B) Comparison of changes in PPBG between males (n=5) & females (n=6).

groups and also gender. No significant differences were seen in PPBS levels during pre and post-study times (Fig. 4A). Our gender-based comparison also showed no changes within the groups or between the genders. Although we observed a decrease in the PPBS levels in both groups' males, these changes were not statistically significant (Fig. 4B). Overall, the results suggested that there were no significant changes observed in the blood glucose levelshypoglycemic drugs only or hypoglycemic drugs with the insulin-treated group during the study period.

HbA1C levels:

Although no significant changes were observed in blood glucose levels, next, we assessed the HbA1c levels in study subjects to determine whether

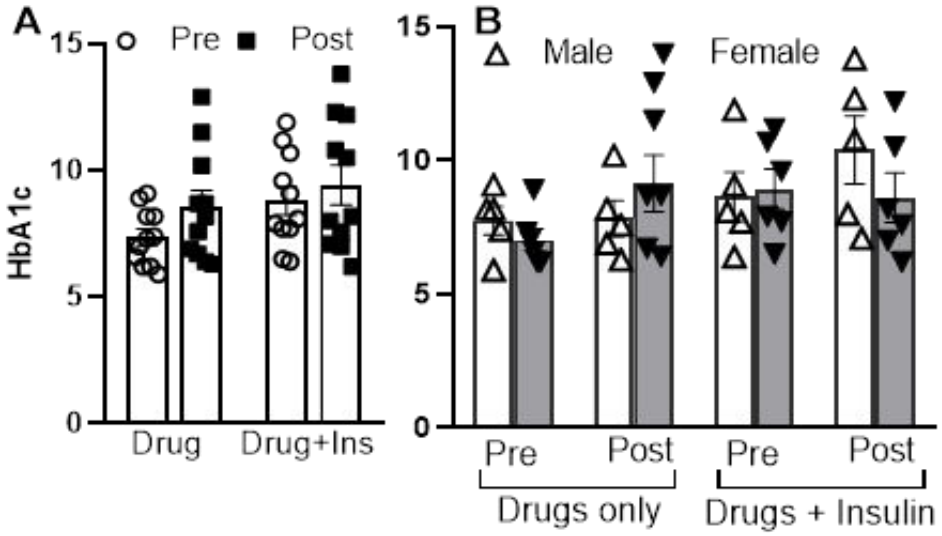

Fig. 5: Changes were observed in the HbA1c levels of participants. (A)Study subject responses to drug vs drug+ insulin (B) Differential changes occurred in HbA1C levelsin male vs female participants.

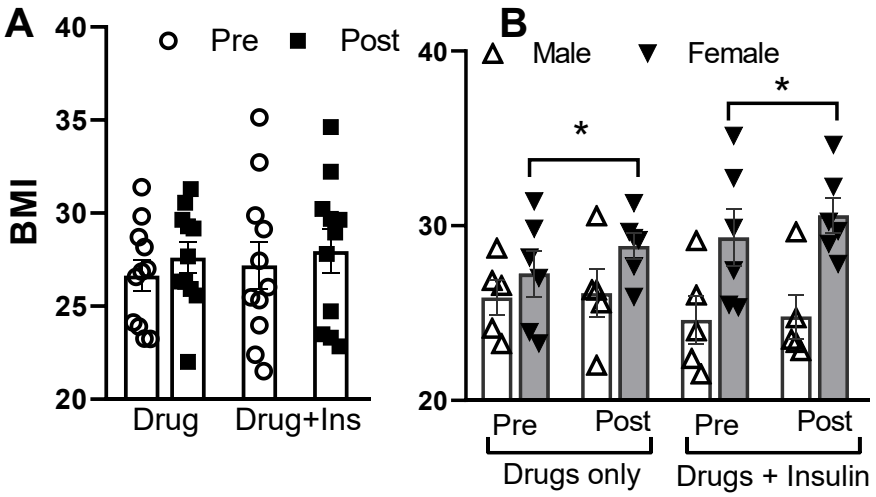

Fig. 6: Mean BMI changesoccurred during the intervention. (A) Comparison of differences in BMI with in groups. (B) Changes in BMI among genders. * indicates $p < 0.05$, which is statistically significant.

chronic multivitamin consumption with hypoglycemic drugs alone or insulin stabilizes HbA1c levels in the study subjects. Interestingly, both groups showed an increasing trend in HbA1c levels during the post-study period compared to baseline (pre) values (Fig. 5A). However, these changes were not statistically significant. Further, our gender-based analysis also revealed that both genders in the drug + insulin receiving group showed an increase in HbA1c levels. However, we did not observe any statistically significant differences within/between the genders (Fig. 5B).

Body mass Index:

As subjects with persistent elevation of blood glucose and HbA1c levels might gain body weight, we next measured the body mass index in both groups. In these subjects, the drug alone or the drug plus insulin administration had no effect on BMI over time (Fig. 6A). Further, our gender-based analysis revealed that both the groups'

~50% of female subjects showed a statistically significant increase in BMI ($p < 0.05$), however, we did not observe any changes in male groups (Fig. 6B).

Discussion

Chronic diabetes mellitus associated with oxidative stress causes microvascular complications such as diabetic neuropathy, nephropathy, and retinopathy as well as macromolecular damages such as protein carbonylation, protein glycation, lipid peroxidation, etc., leading to several macro-vascular complications. Multivitamins have been reported as antioxidants and are assumed to suppress oxidative stress and its associated damage. While multivitamin consumption is not required for healthy subjects, it may be needed for aged individuals (Atkinson, 2011) and patients with diseases like diabetes, myocardial infarction, and other complications (Grodstein *et al*., 2013). Although several decades of preclinical research supported the beneficial effects of antioxidants (Polyak *et al*., 2018); previous clinical trials indicated that prolonged antioxidant consumption is not beneficial, and a few studies reported its harmful effects (Chiabrando *et al*., 2002; Violi *et al*., 2004; Steinhubl 2008; Levy *et al*., 2009; Bouayed and Bohn, 2010; Grodstein *et al*., 2013; Davies and Holt, 2018; Ahmad and Leake, 2018). Regular use of these hypoglycemic drugs or insulin administration has been shown to have a significant hypoglycemic index, and a combination of these drugs alone may be effective in lowering blood glucose levels for a limited time (1 year) (Cheng and Fantus, 2005). However, it is unclear whether chronic use of these hypoglycemic drugs (3 years) in conjunction with multivitamin consumption of diabetic management in this south Indian population. Simultaneous consumption of multivitamins with hypoglycemic drugs alone and with insulin is predicted to decrease blood glucose and HbA1C levels. In this preliminary study, we have focused on the impact of multivitamin intake with a combination of hypoglycemic drugs and/or insulin to determine the basic diabetic profiles of these specific subjects in the South Indian population. Although we observed changes in FBS, PPBS, and HbA1c levels in both drugs alone and drug + insulin groups, these observations were not significant, suggesting that these subjects showed a steady rise in glycemic index (both glucose and HbA1C levels) trend to develop other vulnerable complications (Bennett *et al*., 2007). However, antioxidant intake combined with these hypoglycemic drugs and insulin was not successful in halting the progression of diabetes and its complications.

Diabetes mellitus is caused by both decreased insulin production and insulin sensitivity, leading to hyperlipidemia and resulting in insulin resistance and obesity (Ferris and Kahn, 2016). Persistent increases in HbA1c levels (>7.5) accompanied by elevated BMI (>25) exacerbate insulin resistance and other associated complications. Our study results showed that ~50% of patients with higher HbA1c levels and BMI (>27) were prescribed medium to high doses of insulin to control their glycaemic status. However, their glycemic profiles were also higher, which was not significant.

This study has several limitations, including a small number of subjects with long-duration diabetes. Although gender and age matches were followed for the participation of subjects, the duration of diabetes was not considered in either group. Additionally, while the dosage of three drugs was the same among participants, the insulin dosage for each participant was different, which might be one of the causes of poor blood glucose and HbA1c outcomes. Further study is needed with a controlled age of diabetes and an equal age of participants to determine the impact of insulin administration with multivitamins and other hypoglycemic drugs. Although several studies have determined the long-term effects of hypoglycemic drugs, insulin, and multivitamins separately in diabetic subjects, our study

determined the combined effect on south Indian diabetic subjects.

Conclusion

Our findings indicated that prolonged multivitamin consumption with hypoglycemic drugs and/or insulin had less effect on blood glucose, BMI, and HbA1c levels in both genders with chronic diabetes (>5 years). However, female subjects showed significantly increased BMI, which may be due to higher dysglycemia risk in women in South Asia.

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