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TO STUDY THE EFFECT OF COMBINATION OF METFORMIN, GLIMEPRIDE VOGLIBOSE IN TCF7L2 GENE ASSOCIATED TYPE 2 DIABETES MELLITUS.

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ABSTRACT

Background: The TCF7L2-gene (TCF7L2; Transcription factor 7-like 2) involves in regulation of cellular proliferation and differentiation. It also increased risk for type 2 diabetes (T2D), dose effect were reported for the rs7903146 variant. The risk alleles of TCF7L2 gene involves in progression of impaired glucose tolerance to diabetes prospectively and an increased severity of the disease

Material and Methods: Prospective, randomised study. Combination of Metformin, Glimepride Voglibosehas been prescribed in TCF7L2 gene associated type 2 diabetes mellitus patients s

Results: TCF7L2 gene is associated with Type 2 diabetes mellitus. Genetic investigation was done in all 40 patients three genotypes have been identified 10 patients were on CC, 12 patients were on CT and 18 patients were on TT genotypes.Baseline values are higher in TT genotype when compared with CT & CC genotypes. There were significant improvement in blood glucose levels were as a controlled lipid profile was observed in CC genotype but no significant was observed in CT, TT and in group

Conclusion: Patients HbA1c ranges from <9.0 - 9.5 % prescribed with triple drug combination therapy of metformin, Glimepride, voglibose shows significant improvement in blood glucose levels in all three genotypes but no significant was observed in CT, TT genotypes. As a result combination of triple drug combination therapy of metformin with glimepride, voglibose is the better drug of choice in CC genotype associated type 2 diabetes mellitus after 3 months of treatment.

Keywords:TCF7L2 gene, metformin, Glimepride, voglibose

INTRODUCTION:

T2D is a complicated condition marked by a sustained rise in blood glucose levels (hyperglycemia) caused by inadequate insulin production. According to recent standards, 382 million individuals aged 20 to 79 have diabetes, with that number expected to rise to 592 million by 2035. 1 Diabetes is the fifth biggest cause of death, according to the IDF. 2 Following the initial dietary and lifestyle changes,changes, the most common treatment for T2D is the addition of oral hypoglycaemic agentsOral hypoglycaemic agents (OHAs) are the most prevalent treatment for T2D, with a stepwise increase of agents over time until insulin administration is necessary to maintain glycemia at targetThe TCF7L2 risk alleles rs1225537 and rs7903146 produce an increase in proinsulin synthesis and the proinsulin to insulin ratio, however the T allele causes defective proinsulin. [6] This is a crucial process in the development of type 2 diabetes mellitus. The study's main goal is to see how mono drug therapy affects type 2 diabetes mellitus caused by the TCF7L2 gene.Biguanides, Sulfonylureas (SUs), Meglitinides (glinides), thiazolidinedione (TZDs), -glucosidase inhibitors, and glucagon-like peptide (GLP)-1 receptor agonists inhibitors of the dipeptidyl peptidase-4 enzyme, and inhibitors of the sodium glucose transporter (SGLT-2). Despite the availability of multiple OHAs, only 53% of Diabetes Mellitus patients attain a glycated haemoglobin (HbA1c) target of.7%. 3

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MATERIALS AND METHODS:

A present study is a randomized, prospective; open-label study was conducted in the Department of pharmacology in association with the Department of general medicine& Central research laboratory in Rama Medical College Hospital & Research Centre, Kanpur in 2017. The study was carried out after taking approval from the institutional ethical committee. Patients were enrolled in the study as per inclusion and exclusion criteria. **Inclusion criteria.**

- Newly diagnosed type 2 diabetes mellitus patients.
- Patients of both sexes.
- Age – 30 years to 70 years.
- Glycosylated haemoglobin (HbA1c) more than 9.0 %
- Fasting plasma glucose > 126 mg/dl (7.0 mmol/L)
- 2-hours plasma glucose > 200mg/dl (11.1 mmol/L)
- Patients ready to give an informed consent form**.**

Exclusion Criteria

- Type 1 diabetes mellitus
- Patients already diagnosed with diabetes mellitus and on treatment
- Pregnancy
- Smokers and alcohol.
- Patients who are not ready to give informed consent form.
- Patients having other diseases.

Patient Categorization:

- Patients under inclusion criteria underwent routine investigation of blood glucose levels (HbA1c, fasting blood glucose levels & postprandial blood glucose levels) , Lipid profile (Total Cholesterol, Triglycerides &HDL –C,) for DNA isolation to detect TCF7L2 gene polymorphism. A total of 40 patients were detected as TCF7L2 gene polymorphism was analysed.

Biochemical tests:

Estimation of blood glucose levels is done by glucose oxidase and peroxidase enzymatic methods; estimation of HbA1c was done by ion exchange resin method

Estimation of Lipid profiles, Triglycerides estimation was done by Tinder Methods, HDL – C estimation is done by Phosphotungstic acid methods.

Genomic DNA was extracted from peripheral blood cells by using Qiagen Kit (Procedure and standard protocol was given in Qiagen kit). Genotyping was done by PCR- restriction fragment length polymorphism methods. TCF7L2 gene were analysed for the SNP rs7903146 sequence located on chromosome 10q25.2–q25.

- Forward primer: 5'-GAACAATTAGAGAGCTAAGCACTTTTTAGAAAC-3'
- Reverse Primer: 5'-AGATGAAATGTAGCAGTGAAGTGC-3'.

The PCR involved 38 cycles of 94^{o}C for 30s for 62^{o} C for 30s and 67^{o}C for 30s. Then the PCR products were digested overnight at 67^{o}C with Rsa1 (restriction endonuclease), electrophoreses on 2.5% Agarose gel and strained with ethium bromide.

As per the treatment plan patients were selected according to the range of HbA1c levels more than to 9.0 %. Patients were prescribe with triple drug combination therapy of metformin, glimepride, voglibose and underwent follow up for 3 months.

Follow Up:

All the patients had been briefed about symptoms of hypoglycaemia. Patients underwent follow up for 3 months and routine investigations of HbA1c, fasting blood glucose, postprandial blood glucose, and lipid profile was done and noted down (after treatment). **Statical Analysis:**

The SPSS windows version 21 to analyse the results. The percentage changes were determined after tabulating the value in data, student 't' test were used to analyses the data. Statical significant value less than 0.05.

RESULTS:the present study is to study the effect of monodrug therapy in TCF7L2 gene associated type 2 diabetes mellitus is carried out in department of pharmacology in association with department of medicine and central research laboratory. Total of 40 patients were included in the study underwent route investigation of HbA1c, FBS, PPBS, Triglycerides and HDL levels also genetic testing were conducted. Three genotypes have been identified CC, CT and TT genotypes in both the groups. In all group there is a significant improvement in blood glucose levels were as a controlled lipid profile was observed in CC genotype but no significant was observed in CT, TT genotypes.

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Table 1.Baseline values with 3 months in blood glucose finding in TCF7L2 gene polymorphism associated type 2 diabetes mellitus.

		Baseline	3 Months
HbA1C (%)	CC	9.35±0.10	8.34±0.35
	CT	9.36±0.18	8.45±0.25
	TT	9.42±0.18	8.57±0.23
FBS (mg/dl)	CC	166.33±25.29	147.0±24.72
	CT	172.16±25.17	155.08±25.92
	TT	184.94±30.22	169.88±25.58
PPBS (mg/dl)	CC	240.50±28.17	216.66±27.29
	CT	252.58±23.94	23.083±24.24
	TT	268.72±43.32	249.83±42.77

Figure No: 01 Mean difference after 3 months finding in TCF7L2 gene polymorphism associated type 2 diabetes mellitus patients.

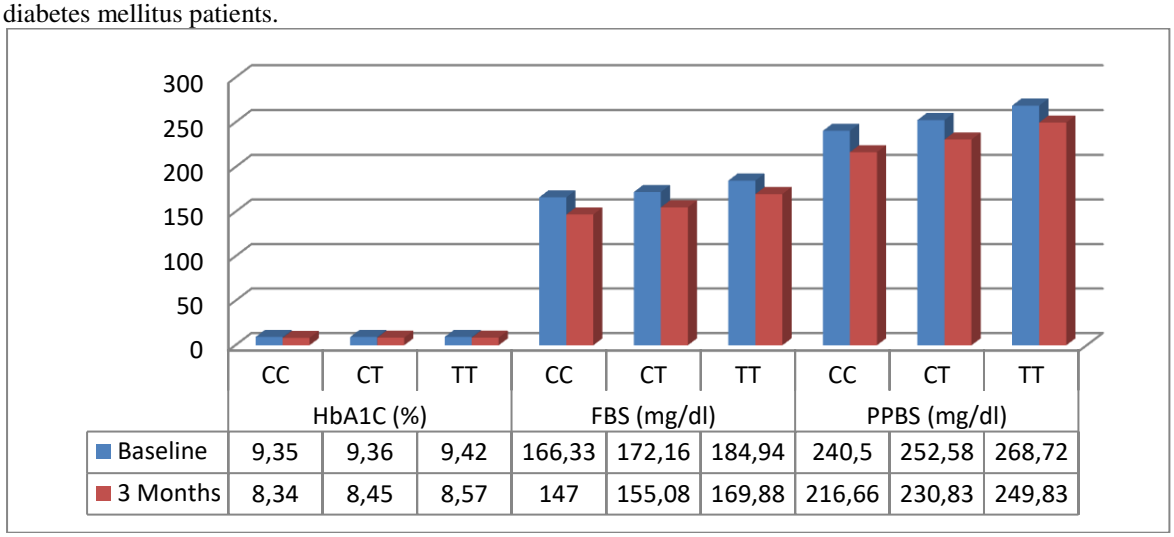

Table 02: Tabular column represents blood glucose Mean difference and p value after 3 months finding in TCF7L2 gene polymorphism associated type 2 diabetes mellitus patients.

		Mean difference	P value
HbA1C (%)	CC	1.11±0.37	0.001
	CT	0.90±0.23	0.002
	TT	0.85±0.23	0.004
FBS (mg/dl)	CC	19.33±3.20	0.001
	CT	17.08±5.19	0.003
	TT	15.05±10.20	0.004
PPBS (mg/dl)	CC	23.83±3.58	0.001
	CT	21.75±3.57	0.002
	TT	18.88±3.30	0.004

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Figure No : 02 Mean difference in blood glucose levels after 3 months finding in TCF7L2 gene polymorphism associated type 2 diabetes mellitus patients

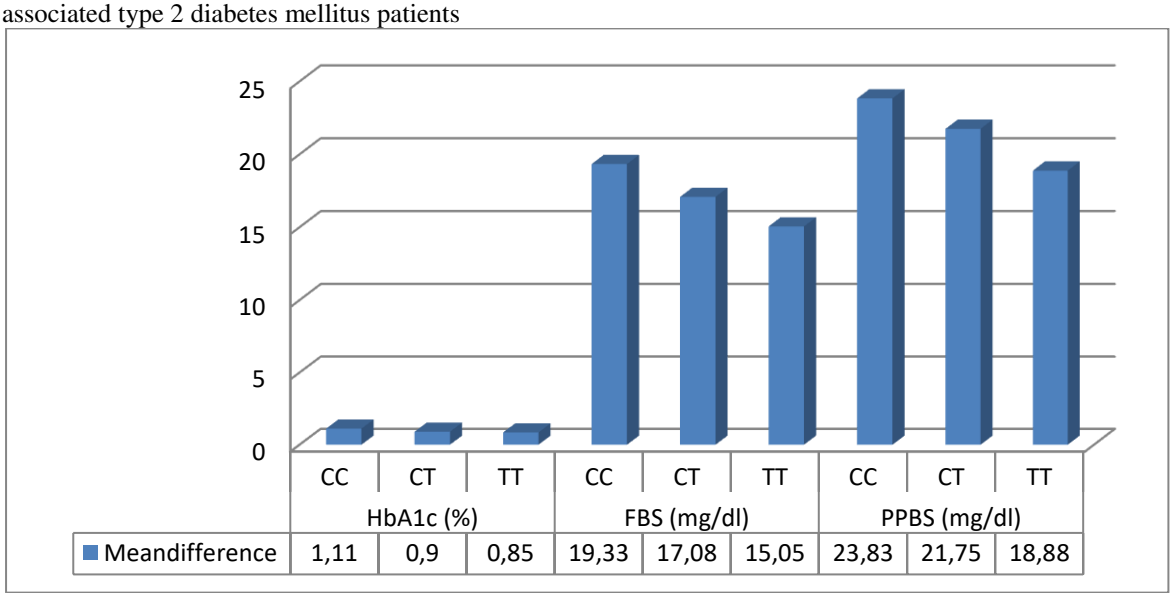

Table No 03.Baseline values with 3 months in lipid profile finding in TCF7L2 gene polymorphism associated type 2 diabetes mellitus

		Baseline	3 Months
TC (mg/dl)	CC	182.60±8.89	173.80±12.80
	CT	173.83±16.69	166.50±13.48
	TT	168.44±9.31	162.44±10.94
TG (mg/dl)	CC	147.20±8.04	137.20±8.01
	CT	152.63±18.58	144.41±17.34
	TT	167.80 ± 9.54	160.44±10.83
HDL (mg/dl)	CC	40.00±5.07	47.100±7.06
	CT	38.58±4.39	43.00±7.24
	TT	37.72±8.98	41.55±6.15

Figure No: 03 Mean difference after 3 months finding in TCF7L2 gene polymorphism associated type 2 diabetes mellitus patients.

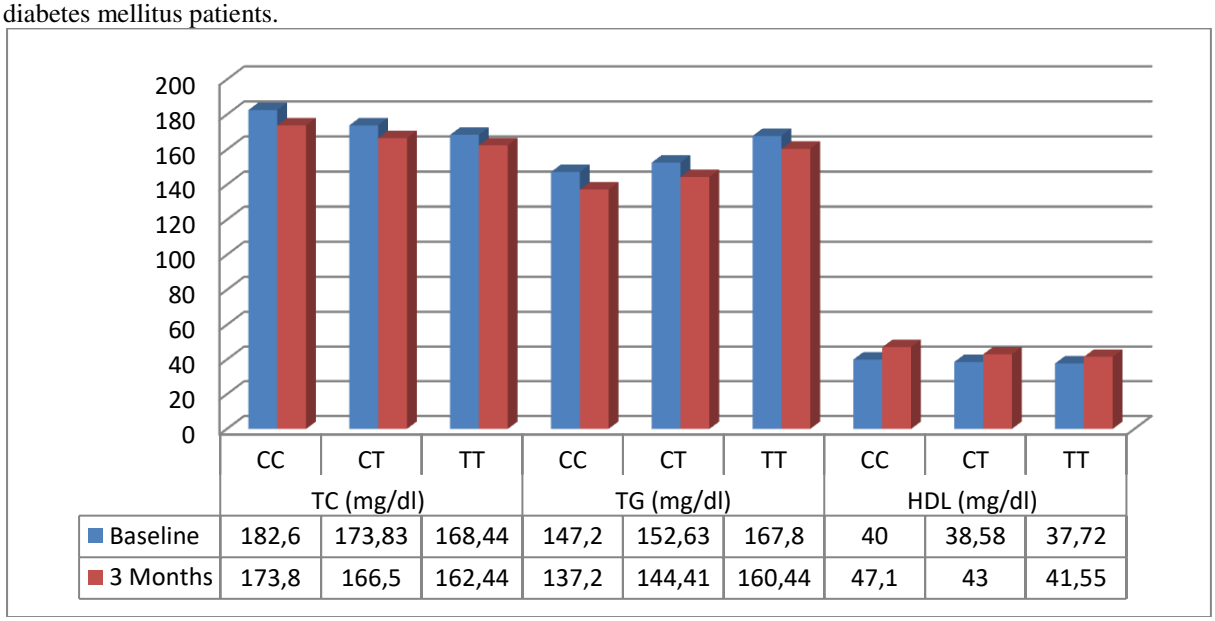

Table No 04: Tabular column represents lipid profile Mean difference and p value after 3 months finding in TCF7L2 gene polymorphism associated type 2 diabetes mellitus patients.

		Mean difference	P value
TC (mg/dl)	CC	8.80±3.91	0.053
	CT	7.00±3.21	0.131

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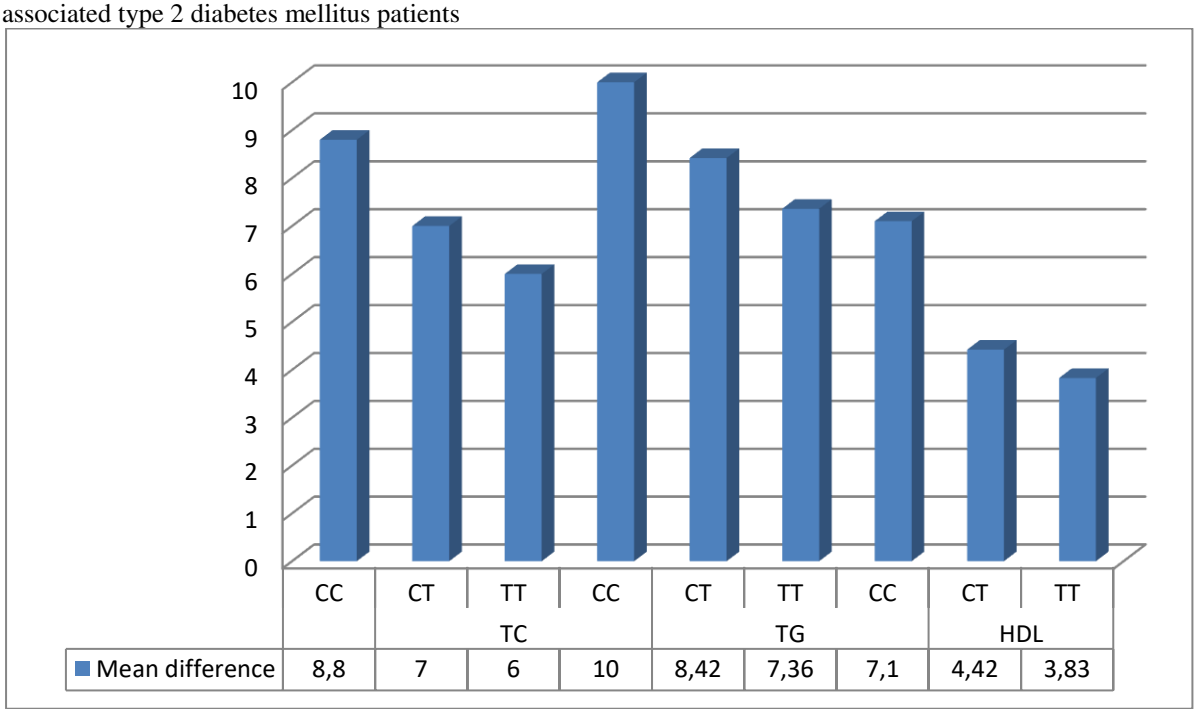
	TT	6.00±1.63	0.140
TG (mg/dl)	CC	10.00±0.003	0.012
	CT	8.42±1.24	0.065
	TT	7.36±1.29	0.118
HDL (mg/dl)	CC	7.1±1.93	0.032
	CT	4.42±2.85	0.172
	TT	3.83±2.83	0.207

Figure No : 04 Mean difference in lipid profile after 3 months finding in TCF7L2 gene polymorphism associated type 2 diabetes mellitus patients



Discussion: The present study was conducted to evaluate the effect of combination of metformin, glimepride voglibose in TCF7L2 gene associated type 2 diabetes mellitus.A study was conducted on 40 type 2 diabetes mellitus patients attending Rama hospital. 10 patients were on CC, 12 patients were on CT and 18 patients were on TT genotypes. In this study patients were treated based on HbA1c levels (more than 9.0 to 9.5%), after 3 months of treatment Statical analysis was done. Genetic testing was also done on all 40 patients three genotypes were observed CC, CT, and TT genotypes. Significant mean difference was observed in HbA1c (CC 1.11%, CT 0.90% & TT 0.85 %), fasting blood glucose levels (CC 19.33 mg/dl (p 0.001), CT 17.08 mg/dl (p 0.002) mg/dl & TT 15.05 mg/dl (p 0.004) mg/dl, Post prandial blood glucose (CC 23.83 mg/dl (p 0.001), CT 21.75 mg/dl (p 0.002) & TT 18.88 mg/dl (p 0.004)), total cholesterol (CC 8.80 mg/dl (p 0.053), CT 7.33 mg/dl (p 0.131) & TT 6.00 mg/dl (p 0.140), total Triglycerides (CC 10.00 mg/dl (p 0.012), CT 8.42 mg/dl (p 0.065) & TT 7.36 mg/dl (p 0.118) & HDL (CC 7.1 mg/dl (p 0.032), CT 4.42 mg/dl (p 0.172) & TT 3.82 mg/dl (p 0.207). Only a few studies have looked at the pharmacogenetics of the TCF7L2 variant's effect on hypoglycemic drug therapeutic response. The T allele has been linked to a higher risk of sulfonylurea treatment failure. Although it had no effect on metformin-treated patients' therapeutic responseTanja Dujic, et al (2019). no as such article available for discussing with our study.

Conclusion: The present study the effect of triple drug therapy in TCF7L2 gene polymorphism associated type 2 diabetes. TCF7L2 gene is associated to causes type 2 diabetes mellitus among them TT geno type is a risk allele. Patients HbA1c ranges from more than to 9.0 % prescribed with triple therapy of metformin, glimepride & voglibose shows significant improvement in blood glucose levels in all three genotypes and on controlling lipid profile significant was observed in CC genotype but no significant was observed in CT and TT genotypes of TCF7L2 gene associated type 2 diabetes mellitus. As a result combination of triple drug combination therapy of metformin with glimepride, voglibose is the better drug of choice in CC genotype associated type 2 diabetes mellitus after 3 months of treatment.

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