INTRODUCTION:

Prediabetes defined as blood glucose levels above the normal but below thresholds for diagnosis of diabetes, is a risk state that defines a high chance of developing diabetes. According to the World Health Organization (WHO), high risk for developing diabetes relates to two distinct states, impaired fasting glucose (IFG) defined as fasting plasma glucose (FPG) from 100-125mg/dl and impaired glucose tolerance (IGT) defined as post-glucose plasma level from 140-199mg/dl based on 2-hours oral glucose tolerance test (OGTT). In 2019, The American Diabetes Association (ADA) applying the same thresholds for IGT, uses a lower cut-off value for IFG (FPG 100-125 mg/dl) and has additionally introduced Glycosylated haemoglobin (HbA1c) levels of 5.7-6.4% as a new category for high risk diabetes.

The prevalence of IFG is more prevalent among men than women. In 2017, the International Diabetes Federation (IDF) estimates, global prevalence of IGT is 7.3% and number of people with IGT 352.1 million and projected to increase to 532 million in 2045. According to Anjana et al., prevalence of prediabetes in India is 10.3% and in Maharashtra is 10.6% (Urban areas) and 4.5% (Rural area). The greatest absolute rises are expected in South-East Asia and the Western Pacific Region.

Progression from prediabetes to diabetes:
Whereas, around 5-10% of people with prediabetes become diabetic annually although conversion rate varies by population characteristics. In Diabetes Prevention Program (DPP) Outcomes Study states that the annualized incidence of prediabetic to diabetic was 11%. In addition, DDP study also revealed that the risk of diabetes development on the basis of above the normal range of FPG and 2-hour post load glucose is broadly similar to an ADA criteria, up to 70% of individuals with prediabetes will eventually develop diabetes.
The most important factors that may explain the pathophysiology of prediabetes are increased insulin resistance and decreased insulin secretion. Normally, during glucose stimulation, pancreatic insulin secretion occur, physiologically suppresses hepatic glucose production in the liver, and also glucose utilization is promoted in the peripheral tissues, including muscle and adipose tissue.\(^9\) Whereas, insulin resistance refers to a dysfunctional physiological response to insulin secretion. Despite normal or higher insulin levels, hepatic glucose production is not adequately suppressed, or a reduction in glucose utilization in peripheral tissue causes increased plasma glucose concentrations. Compared with Normal Glucose Tolerance subjects, there is a significantly higher tendency of insulin resistance in prediabetes subjects.\(^{10}\)

Obesity is one of the most important risk factor for development of Diabetes Mellitus in Indian context.\(^{11}\) Obesity and overweight are abnormal accumulation of body fat. According to WHO classification as body mass index (BMI) of $\geq 30$ kg/m\(^2\) is considered obesity and $\geq 25$ kg/m\(^2\) is considered as overweight. BMI is calculated as weight in kilograms divided by the square of the height in meters.\(^{12}\) However, according to the Endocrine society of India, Indians population the BMI cut-off value are much lesser for obesity and overweight. BMI $> 25$ kg/m\(^2\) is considered as obesity and 23 to 24.99 kg/m\(^2\) is considered as overweight. In spite of having less obesity rates and overweight, India has the highest diabetes incidence as compared with western countries signifying that diabetes might get at a considerably even in lesser BMI of Indian compared with western country persons.\(^{13}\)

Subsequently, comparatively slim Indian adults with a lesser BMI are same risk as those who are overweight.\(^{14}\) Additionally, Indians are hereditary susceptible for progress of coronary artery disease due to dyslipidaemia and low level of high density lipoproteins; these factors make Indians extra liable to progress of diabetes problems at an early age (20-40 years) equated with Caucasians (>50 years) and point out that diabetes must be cautiously screened and examined irrespective of age of patient in India.\(^{15}\) Obesity and a high fat diet may contribute to the development of both insulin resistance and insulin secretary dysfunction in susceptible individuals, insulin resistance in type 2 diabetes is entirely due to the coexistence of increased adiposity.\(^{16}\)
Moreover, Early-onset of diabetes increases risk of diabetic mellitus, however statistics on the incidence of diabetic problems across the whole India is less.\[17\] According to The Chennai urban rural Epidemiology Study (CURES) done by Mohan et al. revealed that long standing diabetes leads to highest incidence neuropathy (24.6 %) followed by cardiovascular disease (23.6 %), a nephropathy (21.1 %), retinopathy (16.6 %) and foot ulcers (5.5 %).\[18\] As per the Chennai urban rural Epidemiology study (CURES-45) study, In Indian diabetic population there is poor glycaemic control, which is accountable for macro- and microvascular complications with diabetes, and other macrovascular complications like such as infarction and necrosis.\[19\]

The most important in management of prediabetes are prevention of diabetes related complications, glycaemic controls and inhibiting progression of atherosclerosis. The association with the glycaemic control and microvascular complication in prediabetes is well recognized. In addition, adequate control of blood glucose levels decreases the progression of microvascular complication.\[20\] Diet and life style modification form the backbone of treatment for prediabetes.\[21\] Drug therapy is supported when target goals are not achieved with the life style modification.\[22\] Oral anti-hyperglycaemic drugs are main stay in management of the glycaemic control in prediabetes and Type 2 DM. Based upon their mechanism of action, they are divided into drugs that increase insulin secretion like Meglitinides, Sulfonylureas, Glucagon-like peptide-1 (GLP-1) agonists, Dipeptidyl Peptidase-4 (DPP-4) inhibitors, decrease glucose production like Biguanides, increase insulin sensitivity like Thiazolidinediones (TZDs) and decrease carbohydrate absorption like α-Glucosidase inhibitors.\[23\]

Oral antidiabetic drugs are effective clinically as monotherapy in improving glycaemic control however due to progressive nature of loss of β cell function in prediabetes and type 2 DM, monotherapy is insufficient to control glycaemia and loss of efficacy over time. Fixed dose combination (FDC) drugs having different mechanism of action improve glycaemic control, permits use of submaximal doses of the drug, there is better efficacy, thereby reducing the unwanted adverse effects and has complementary benefit on prediabetes and type 2 DM patients.
Metformin, a biguanide class of oral hypoglycaemic drug, is the first line drug for the management of type 2 DM. Metformin is used clinically for the management of prediabetes, diabetes mellitus and obesity, recent studies have recognized activation of AMP dependent protein kinase (AMPK) play a crucial role in mediating the actions of metformin, the key features of which are: (1) Decreases plasma glucose levels by inhibiting gluconeogenesis in liver, (2) Improving insulin sensitivity by increasing peripheral glucose uptake and utilization by up-regulating expression of glucose transporter (GLUT-4) in muscle and skeletal muscle and (3) Decreases intestinal absorption of glucose. Additionally, metformin has pleiotropic effects leading to improved lipid and cholesterol metabolism, reduced inflammation and inhibition of cell growth. (4) Metformin activates AMPK, which primarily and secondarily decreases mammalian target of rapamycin (mTOR) complex levels, playing a main role in governing cell growth, production, and breakdown which act as an anticancer agent. (5) Increases plasma levels of glucagon-like peptide 1 (GLP-1) which is a member of the incretin family of peptide hormones which is released from the gut in response to ingested glucose thereby leading to retardation of gastric emptying, inhibiting glucagon release from α cell, and produces a feeling of satiety.

Voglibose is alpha-glucosidase enzyme inhibitor which acts by decreasing post-prandial blood glucose (PPBG) levels. It decreases intestinal absorption of starch, dextrin, and disaccharides by inhibiting of α-glucosidase which is a final enzyme for the digestion of carbohydrates in the brush border of small intestinal mucosa. Inhibition of this enzyme leads to does not catalyse the breakdown of disaccharides into monosaccharides and decreases absorption and digestion of carbohydrates. α-Glucosidase inhibitor has no pancreatic action and hence does not cause hypoglycaemia. Voglibose is most effective α-glucosidase inhibitor amongst its class.

Pioglitazone, insulin-sensitizing Thiazolidinedione’s (TZDs), is commonly prescribed for the treatment of type 2 diabetes. TZDs are known to activate a peroxisome proliferator-activated Receptor-γ (PPAR-γ) which are ligand-activated transcription factors which belongs to the nuclear receptor superfamily. Among the several antidiabetic drugs, pioglitazone has a decreases insulin resistance.
activation by pioglitazone leads to increased insulin sensitivity in liver, fat and skeletal muscle cells, increases peripheral uptake of blood glucose in tissues.\textsuperscript{32} Pioglitazone is dependent on the presence of insulin to exert its advantageous effects and preserve β-cells of the islets of Langerhans, but does not act same as an insulin secretagogue.\textsuperscript{33} Improved glycaemic control results in lowering of circulating HbA1C and insulin levels in type 2 DM patients.\textsuperscript{34} Through agonistic action of PPAR- α, activation of genes regulating fatty acid metabolism and lipogenesis in adipose tissue, results in Lipolysis and plasma fatty acid levels are reduced.\textsuperscript{35,36}

HOMA-IR is a simple and predominantly helpful laboratory tool in the evaluation of insulin resistance in prevalence studies, including persons with both glucose intolerance, controlled and uncontrolled diabetes, and in other insulin-resistance conditions. HOMA-IR values ≥ 2.4 indicate IR in adults.\textsuperscript{37,38} It is calculated multiplying fasting serum insulin (IRI) mIU/L by fasting Blood glucose (FPG) mg/dl from the same sample then dividing by the constant 405, i.e. HOMA-IR = (FSIxFPG)/405.\textsuperscript{39}

Insulin resistance (IR) is characteristically defined as decreased sensitivity or responsiveness to the metabolic actions of insulin, such as insulin-mediated glucose uptake and inhibit production of hepatic glucose.\textsuperscript{39} Although, impaired beta-cell function is ultimately responsible for Type 2 DM, IR leads to beta-cell dysfunction and thus, plays a key role in the pathogenesis of this chronic disease.\textsuperscript{40} There are numerous tools used for evaluating insulin sensitivity and resistance directly (insulin suppression tests and hyperinsulinemic euglycemic glucose clamping) and indirectly [frequently sampled oral glucose tolerance test, intravenous glucose tolerance test, meal tolerance test, and alternative methods based on alternate markers derived from fasting serum insulin (immunoreactivity insulin (IRI), and glucose, such as homeostasis model assessment-insulin resistance (HOMA-IR)].\textsuperscript{41}

Glycated haemoglobin (GHb) also commonly known as glycosylated haemoglobin, glycohemoglobin, HbA1, HbA1c or A1c is a term used to describe a series of stable minor haemoglobin components formed slowly and non-enzymatically from haemoglobin and glucose.\textsuperscript{42} The glycation of haemoglobin can occur at various
sites present on the polypeptide chains of the haemoglobin molecule with different carbohydrate molecules. The glycohemoglobin is subdivided into subtractions depending on each of the glycation sites and reaction partners involved in glycation. More recently HbA1c is defined as Hb that is irreversibly glycated at one or both N-terminal valines of the β-chain. The remaining GHbs have glucose, glucose-6-phosphate, fructose-1,6-diphosphate, or pyruvic add bound to one of the 44 additional sites occurring at s-amino group of lysine residues or at the NH₂ terminal of the α-chain. [43] Formation of HbA1c is irreversible and the blood levels depend on both of the life span of red blood cell (average 120 days) and blood glucose concentration. The rate of formation of HbAlc is directly proportional to the ambient glucose concentration. The amount of HbAlc therefore represents the integrated values of glucose over the last three months and provides an additional means of assessing glycaemic control. [44]

Maintaining glycaemic levels as close to diabetic range as possible has been demonstrated to have a powerful beneficial impact on diabetes-specific complications, including retinopathy, nephropathy and neuropathy in the setting of type 1 diabetes; in type 2 diabetes, more intensive treatment strategies have likewise been demonstrated to reduce complications. Intensive glycaemic management resulting in lower HbA1c levels has also been shown to have a beneficial effect on cardiovascular disease complications in type 1 diabetes. [45] The measurement of HbA1c in human blood is therefore considered the most important marker for long-term assessment of glycaemic state in patients with diabetes, and goals for therapy are set at specific HbA1c target values. HbA1c level of 5.7–6.5% (39–48 mmol/mol) has been recommended by the American Diabetes Association (ADA) to indicate intermediate Hyperglycaemia and WHO has recommended that individuals with HbA1c between 6.0% and 6.5% (42–48 mmol/mol) should be considered for diabetes prevention interventions. [45, 46]
Study Rationale

This study introduces a conceptual framework for care of prediabetes patients that includes screening and the provision of up-to-date clinical therapies in conjunction with an evidence based health care intervention. Male gender, advanced age persons and obesity were each independently associated with higher prevalence of prediabetes. \[47\] Earlier diseases were common in fourth decade of life but now is frequently seen in adolescents and younger children. The onset is rarely recognized in the early phase of disease (IFG and IGT- Prediabetes). Nearly 50% cases present with one or more complication at diagnosis. \[48\]

Increased prevalence of prediabetes also correlated with the indices of hypercholesterolemia and dyslipidaemia. \[49\] The parallel increase of the two diseases poses some contradiction. Both are associated with increase in body weight, insulin resistance and obesity have a causal role in the pathogenesis of T2DM. \[50\] Prediabetes is a substantial health problem in India that may present a significant challenge to the national healthcare system in the future. \[51\] Measurement of insulin resistance predicts future development of Diabetes and to prevent future development of metabolic syndrome, Diabetes and coronary heart disease. It has been further suggested that investing in treatment for people with prediabetes is much more cost-efficient than providing treatment only after the development of type 2 diabetes. \[52\] We believe that, appropriate therapeutic regimens and adopting healthy lifestyle behaviours, these modalities represent the most effective means for delaying or even preventing the onset of diabetes and its complication in a prediabetes population.

There is a lack of scientific evidence in support of this mechanism of action of FDC of Metformin with Voglibose and FDC of Metformin with Pioglitazone, which improves glycaemic control and prevents development of complications of diabetes from prediabetes. Individuals who have prediabetes or diabetes should receive individualized Pharmacological therapy as needed to achieve treatment goals.

In light of the conflicting results and methodological limitations of this evolving literature, the concern for definitive conclusive role of Metformin, Voglibose, Pioglitazone in prediabetes remains elusive. Moreover, majority of studies were carried out in Caucasian, American and Mexican populations, while Indian population despite
being at higher risk are less investigated. Keeping in view of prevalence and increased risk of cardiovascular disease in diabetes particularly in Indians, it is becoming necessary to diagnose prediabetes individuals and assess their lipid profile and prevent them from developing overt diabetes and hence preventing their further morbidity and mortality.

According to the ADA guideline, Metformin is suggested as the preferred initial agent of DM, is also the drug which is most often used in the management of prediabetes. This probably results from the fact that metformin reduces blood sugar levels. Here, it can be seen that, Alpha glucosidase inhibitors like voglibose was the most favoured second line of management of prediabetes, after metformin. The Thiazolidinedione’s, which include pioglitazone, have been regarded as Third line for prediabetes. In Diabetes Prevention Program (DPP), a 58% relative reduction in the progression to diabetes was observed in the lifestyle group versus a 31% relative reduction in progression for the metformin group after 2.8 years. Participants in the STOP-NIDDM trial, 30 with impaired glucose tolerance randomized to α - Glucosidase inhibitor had a 25% relative risk reduction in progression to diabetes after 3.3 years. In the PROactive has shown that pioglitazone can significantly reduce the risk of secondary macrovascular events in a very high-risk patient population with established macrovascular disease.

The purpose of this study is to evaluate the potential association between FDC of Metformin with Voglibose and FDC of Metformin with Pioglitazone in prediabetes from both pathophysiologic and clinical perspective. Additionally, to assess effect of pharmacotherapy supplementation on glucose homeostasis in terms of glycaemic control in patients of prediabetes not well controlled on a diet/ exercise regimen. Furthermore, FDC of two antidiabetic drugs with different mechanisms of action maintains greater glycaemic control at lower doses than a high dose of an individual drug in prediabetes patients which shows better antihyperglycemic efficacy, offer synergistic effect, reduced side effects, reduce numbers of pill burden and to optimize the therapy for prediabetes, offers increased bioavailability of anti-diabetic drugs in relevant to their simultaneous administration as separated pills, thus reduced the number of pills to take at a time, reduces resistance of insulin and combining provides advantageous in terms of maximizing treatment adherence, well tolerability, dosing
flexibility, submaximal dose, reducing toxicity. It is cheaper to acquire a FDC’s product than to acquire single product individually. This article examines the use of FDC’s therapy for the treatment of prediabetes and it gives ideas to prescribers, payers and patients.

But there was no head to head studies comparing FDC of Metformin and Voglibose versus FDC of Metformin and Pioglitazone. Therefore, this study was undertaken to evaluated the efficacy and safety of FDC of Metformin and Voglibose versus FDC of Metformin and pioglitazone patients with prediabetes – Serum Insulin, HOMA –IR, fasting Blood glucose (FBG) levels, Postprandial blood Glucose (PPBG), HbA1c levels and Lipid Profile.

Therefore, in the present study, we aimed at study safety of efficacy of FDC of Metformin and Voglibose versus FDC of Metformin and Pioglitazone on the impact of insulin resistance on glucose metabolism in prediabetes patients. We used three markers to evaluated metabolism of glucose in prediabetes patients: Serum Insulin, HOMA-IR, FBG, PPBG, HbA1c and Lipid Levels.

The primary end point of the study was to evaluate the efficacy and safety of FDC of (i.e. Metformin and Voglibose Versus Metformin and Pioglitazone,) which group improves glycaemic control compared with each other and its impact on Glucose Triad i.e. HBA1c, Fasting serum Insulin and HOMA-IR.