EFFICACY AND SAFETY OF EMPAGLIFLOZIN AS AN ADD-ON DRUG THERAPY WITH METFORMIN, TENELIGLIPTIN AND GLIMEPIRIDE IN TYPE 2 DIABETES PATIENTS WITH HYPERTENSION

Thesis Submitted for the Award of the Degree of

DOCTOR OF PHILOSOPHY
in

Pharmacology
By

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DECLARATION

I hereby declare that the work reported in the thesis entitled, **"EFFICACY AND SAFETY OF EMPAGLIFLOZIN AS AN ADD-ON DRUG THERAPY WITH METFORMIN, TENELIGLIPTIN AND GLIMEPIRIDE IN TYPE 2 DIABETES PATIENTS WITH HYPERTENSION''** has been carried out by me under the supervision of Dr. Sazal Patyar, (Department of Pharmacology, LPU, Jalandhar, Punjab, India), co-supervision of Prof. Shariq Rashid Masoodi, (Department of Endocrinology, SKIMS Deemed university, Soura, Srinagar, JK, India) and Dr. Shakeel Ahmad Mir (Department of Clinical Pharmacology, SKIMS Deemed university, Soura, Srinagar, JK, India) during the session 2018- 2022.

The work reported in the thesis has not been submitted for the award of any other degree/diploma/fellowship/associateship or any other similar distinction.

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CERTIFICATE

This is to certify that the work reported in the Ph. D. thesis entitled "**EFFICACY AND SAFETY OF EMPAGLIFLOZIN AS AN ADD-ON DRUG THERAPY WITH METFORMIN, TENELIGLIPTIN AND GLIMEPIRIDE IN TYPE 2 DIABETES PATIENTS WITH HYPERTENSION**" submitted in fulfillment of the requirement for the reward of degree of **Doctor of Philosophy (Ph.D.)** in the Department of Pharmacology, Lovely Professional University, is a research work carried out by **Imtiyaz Ahmed Najar**, (Registration No. 11814996) is bonafide record of his original work carried out under my supervision and that no part of thesis has been submitted for any other degree, diploma or equivalent course.

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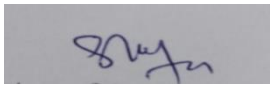

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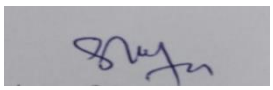
Imtiyaz Ahmed Najar has worked to the best of his capability with sincerity on the study assigned to him and has successfully completed the work. I feel both pleased and satisfied in forwarding his thesis for evaluation as fulfillment for the degree of **Doctor of Philosophy (Pharmacology)** in **Lovely Professional University, Jalandhar, Punjab, India.** The work reported in the thesis has not been submitted for the award of any other degree/diploma/fellowship/associateship or any other similar distinction.



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Imtiyaz Ahmed Najar

LIST OF ABBREVIATIONS

ACE	**Angiotensin- converting enzyme**
ACCORD	**Action to control cardiovascular risk in diabetes study group**
ADA	**American diabetes association**
AGEs	**Advanced glycation end products**
ANOVA	**Analysis of variance**
APD	**Action potential duration**
ARMD	**Age related muscular degeneration**
BMI	**Body mass index**
CAD	**Coronary artery disease**
CAN	**Cardiac autonomic neuropathy**
CaSR	**Calcium sensing receptor**
CHF	**Congestive heart failure**
CK	**Creatine kinase**
CSIR	**Council of scientific and industrial research**
DBP	**Diastolic blood pressure**
DCCT	**Diabetes control and complications trial**
DDP-4	**Dipeptidyl peptidase-4 inhibitor**
DM	**Diabetes mellitus**
DS	**Diet satisfaction**
EDIC	**Epidemiology of diabetes interventions and complications study**
eGFR	**Estimated glomerular filtration rate**
FBG	**Fasting blood glucose**
GADPH	**Glyceraldehyde phosphate dehydrogenase**
GCP	**Good clinical practice**
GDM	**Gestational diabetes mellitus**
GH	**General health**
GSH	**Reduced glutathione**
GLP-1	**Glucagon like peptide-1**

HbA1c	**Glycated hemoglobin**
HDL	**High density lipoprotein**
HER	**Hydroxyethylrutosides**
HF	**Heart failure**
HOPE	**Heart outcomes prevention evaluation**
IEC	**Institutional ethical committee**
ID	**International Dollar**
IDDM	**Insulin dependent diabetes mellitus**
IGF	**Insulin- like growth factor**
I.P	**intraperitonial**
LDH	**Lactate dehydrogenase**
LDL	**Low density lipoprotein**
LV	**Left ventricular**
MAPKs	**Mitogen activated protein kinases**
MDA	**Malondialdehyde**
MET	**Metformin**
MH	**Mental/enotional health**
MI	**Myocardial infarction**
MSCs	**Mesenchymal stem cells**
MT-TG	**Mettallothionein- overexpressing transgenic**
NADH	**Nicotinamide adenine dinucleotide**
NF-KB	**Nuclear factor kappa B**
NIDDM	**Non insulin dependent diabetes mellitus**
NYHA	**New York heart association**
NO	**Nitric oxide**
PARP	**Poly (ADP ribose) polymerase**
PE	**Physical endurance**
PKC	**Protein kinase C**
PPARy	**Peroxisome proliferator activated receptor-gamma**
PPG	**Post prandial glucose**

RAR	**Retinoic acid receptor**
RAS	**Renin angiotensin system**
RL	**Role of limitation to physical health**
ROS	**Reactive oxygen species**
RXR	**Retinoid X receptor**
SBP	**Systolic blood pressure**
SB	**Symptom botherness**
SEM	**Standard error of mean**
SGLT-2i	**Sodium glucose co-transporter-2 inhibitor**
SMC	**Smooth muscle cell**
SOD	**Superoxide dimutase**
SR	**Sarcoplasmic reticulum**
TC	**Total cholesterol**
TNF-α	**Tumour necrosis factor- alpha**
TS	**Treatment satisfaction**
T2D	**Type 2 diabetes**
UKPDS	**The United Nations prospective diabetes study**
VEGF	**Vascular endothelial growth factor**
WHO	**World Health Organization**

ABSTRACT

Background: Empagliflozin is a competitive SGLT2 inhibitor that reduces hyperglycemia in Type 2 Diabetic (T2D) patients by lowering kidney glucose reabsorption and increasing urinary excretion of sugar. It has been found effective and safe in T2D patients who showed inadequate glycemic control with triple-drug treatment (Glimepiride + Metformin + Teneligliptin). It has been reported that Empagliflozin alone effectively lowered blood pressure in people with T2D and hypertension. However, there is a dearth of data regarding the effectiveness and safety of empagliflozin as an add-on to triple therapy in patients having uncontrolled T2D along with hypertension. Diabetes has a detrimental effect on quality of life (QoL). Comorbidities and polypharmacy worsen diabetes patients' QoL. Thus along with glycemic control, assessment of QoL is progressively gaining significance. So the current study was designed to assess the efficacy, safety, tolerance, QoL, and pharmacoeconomics of Empagliflozin as add-on medication in T2D patients who do not improve from triple therapy (Metformin, Glimepiride, and Teneligliptin) and acquire hypertension as comorbidity.

Methods: In this prospective, observational trial, 200 T2D-hypertensive patients were prescribed Empagliflozin (25mg) as an additional therapy to metformin, teneligliptin, and glimepiride for three months. Clinical and biochemical parameters including blood glucose levels, HbA1C, blood pressure, heart rate, kidney function tests, liver function tests, complete blood count, fasting serum insulin, and fasting C-peptide levels were measured at intervention and after 3 months of follow up. Any adverse effect observed during the period was noted. QoL and management of treatment cost in addition to direct and indirect cost parameters were assessed before and after addition of empagliflozin. In addition, the incremental cost-effectiveness ratio (ICER) was computed.

Results: The mean age of the study cohort was 49.83 years. After 3 months of addition of empagliflozin treatment, significant decrease was observed in blood glucose levels, HbA1C, blood pressure and heart rate where as significant increase was noted in fasting

C-peptide levels, fasting serum insulin, HOMA-β and hemoglobin levels. No significant change was observed in body mass index, serum creatinine, eGFR and HOMA-IR after three months of treatment. Two cases of genital infections were reported. According to ICER, empagliflozin required an extra USD 68.05. All the patients tolerated the drug. Empagliflozin as an add-on therapy significantly improved various aspects of QoL domains (i.e. role limitations due to physical health, physical endurance, general health, treatment satisfaction, symptom botherness, financial worries, mental health and diet satisfaction.

Conclusion: Empagliflozin therapy was effective and safe in uncontrolled T2D diabetic hypertensive patients as an add-on therapy. Its addition exerted favorable effects on QoL in T2D patients with hypertension. However the increased cost per unit improvement in QOLID score for Empagliflozin as a new antidiabetic agent compared to conventional antidiabetics is USD 1.89.

Chapter 1

INTRODUCTION

1. Introduction

Diabetes mellitus (DM) is an endocrine condition characterized by irregularities in insulin secretion and/or activity. Lack of insulin or less insulin raises glucose levels and results in hyperglycemia. In diabetic individuals, high blood glucose levels may cause impaired vision, polydipsia, weariness, polyuria, hyperphagia, and weight loss. It has been found to damage a few bodily frameworks, most notably veins, eyes, kidneys, heart, and nerves. The perils of cardiovascular or peripheral vascular problems, which can lead to 'neuropathy, retinopathy, vision loss, renal failure, and stroke', are increased by diabetes (Deepthi et al., 2017). Insulin-dependent diabetes mellitus (IDDM, Type 1) and non-insulin-dependent diabetes mellitus (IDDM, Type 2) are two types of DM. T-cell-mediated autoimmune illness characterized by the destruction of pancreatic β cells is called as Type 1 Diabetes (T1D). Its clinical signs include hyperglycemia and insulinopenia, which necessitate long-term insulin administration (Kelly et al., 2001; Olokoba et al., 2012). As per an estimate, in 2019, 77 million people in India suffered from DM, and the figures are expected to rise beyond 134 million by 2045 (Pradeepa & Mohan, 2021). Type 2 Diabetes (T2D) is very common (representing over 90% of DM patients) than T1D or gestational diabetes (DeFronzo et al., 2015). The burden of T2D is dramatically increasing worldwide, particularly in developing countries such as India, owing to an increase in the incidence of obesity and sedentary lifestyles.

It has been observed that there is a high prevalence of hypertension among T2D patients (Mubarak et al., 2008). T2D and hypertension generally co-exist and have a bidirectional link (Sun et al., 2019). The menace of cardiovascular or end-stage renal disease, and even death is increased when T2D causes hypertension (Ferrannini et al., 2012). Controlling hypertension in T2D patients can slow the course of cardiovascular diseases (Gaede et al., 2008). This highlights the need for monitoring and controlling blood pressure in T2D patients, along with the maintenance of an optimal glycemic profile (Sun et al., 2019). Generally, oral anti-diabetic drugs (OAD) are used for the treatment of T2D. American Diabetes Association (ADA) recommends that if monotherapy fails to achieve

the glycated hemoglobin (HbA1c) goal, dual or triple drug therapy with oral medications such as ‘sulfonylureas (SU), thiazolidinediones (TZD), dipeptidyl peptidase-4 inhibitors (DPP-4), and sodium-glucose cotransporter-2 inhibitors (SGLT-2i) can be given to the patient (Inzucchi et al., 2015). Nevertheless, there are no specific recommendations regarding the management of T2D patients who don't observe enough improvement with triple-drug therapy and also develop hypertension. So nowadays, SGLT2 inhibitors are being investigated for their add-on potential to triple therapy (Jeon et al., 2018; Ku et al., 2019a; Ku et al., 2019b).

Empagliflozin is a competitive SGLT-2i that lowers hyperglycemia in T2D patients by decreasing renal glucose reabsorption and increasing urine glucose excretion. It provides a substantial improvement in HbA1c levels whether used alone or in combination with metformin and possesses a favorable safety profile. Its effectiveness and safety in diabetic patients as an additional medicine to triple treatment i.e. ‘glimepiride, metformin and teneligliptin’ have been studied. It was proven to be efficacious and safe in T2D patients who responded poorly to triple-drug therapy (Pattanaik, 2018). In addition to anti-diabetic action, Empagliflozin has demonstrated an anti-hypertensive effect also. It has been reported that Empagliflozin effectively lowered blood pressure in people with T2D and hypertension (Mancia et al., 2016). Various other studies have reported that Empagliflozin significantly reduces the incidence of cardiovascular diseases in T2D patients (Zinman et al., 2015; Aronow &, Shamliyan, 2017). However, to date, the efficacy and safety of Empagliflozin as an add-on drug to triple-drug in T2D patients having hypertension has not been investigated. As Empagliflozin reduces blood pressure and is also used as an add-on to triple therapy, it was suggested that it might be effective in controlling hypertension in T2D patients who are not responding to triple therapy.

DM affects QoL in general, and when comorbidities emerge, patients' QoL deteriorates further (Trikkalinou et al., 2017). The coexistence of T2D and hypertension impacts treatment results, increases the risk of cardiovascular disease, and reduces QoL. It has been reported that Empagliflozin improved health-related QoL in heart failure patients

with preserved ejection fraction (Butler et al., 2022). There is presently insufficient data to support Empagliflozin's impact on QoL in T2D patients with hypertension. So, this study analyzed the effect of aforementioned treatment regimen on QoL in Indian patients before and after therapy.

As T2D is a chronic progressive condition, cost-benefit analysis of anti-diabetic drugs is critical because higher overall healthcare costs are associated with medication non-compliance. Furthermore, anti-diabetic drugs vary greatly in efficacy, impact, and cost profiles. It is difficult for a physician or endocrinologist to provide optimal patient treatment at the lowest feasible cost. Due to the scarcity of studies comparing the cost-effectiveness of various newer antidiabetics as an add-on therapy to conventional antidiabetics, it is difficult to determine if the additional cost of Empagliflozin as an add-on medicine is worth the increased efficacy and safety. The current study's cost-effective analysis data may help in customized or case-by-case decision-making in the Indian healthcare system, depending on socioeconomic status and comorbidity.

Thus, the current study was designed to assess the efficacy, safety, tolerance, QoL, and pharmacoeconomics of Empagliflozin as an add-on drug treatment in T2D participants who became resistant to triple treatment- (Metformin, Glimepiride, & Teneligliptin) and acquire hypertension as comorbidity.

Chapter 2

REVIEW

OF

LITERATURE

2.1 T2D

T2D or adult-onset diabetes, accounts for 90–95 % of all the diabetes cases. Cell dysfunction and insulin resistance are the two main insulin-related problems in this kind of diabetes (Leahy, 2005; Defronzo, 2004; Muoio & Newgard, 2008). Reduced sensitivity to insulin in peripheral tissues, especially the muscle, liver, and adipose tissue, is a result of insulin resistance. In the early stages of the condition, decreased insulin sensitivity causes cells to hyperfunction, which leads to a compensatory increase in insulin production to maintain normoglycemia. Hyperinsulinemia, or having too much insulin in the bloodstream, avoids hyperglycemia. However, cells' greater ability to produce insulin is insufficient to make up for the loss of insulin sensitivity that occurs with time. Additionally, cell function starts to decline, and insulin deficiency results from cell dysfunction. As a result, hyperglycemia develops since normoglycemia is no longer achievable (Muoio & Newgard, 2008).

2.1.1 Epidemiology of T2D

DM affects around 415 million people globally, with a projected increase to 642 million by 2040 (International Diabetes Federation IDF, 2021). It has been estimated that Asia alone will have more than 60% of the world's diabetic population. In India, more than 65.1 million people have been diagnosed with the condition. As per an estimate, this number might reach 89 million by 2030, with metropolitan areas accounting for around 56% of patients (Ramachandran, 2014; IDMRO, 2015). According to reports, T1D accounts for around 10% of all DM cases, impacting over 20 million individuals globally while 90-95 % of all cases account for T2D, resulting in approx. 5 million fatalities every year (International Diabetes Federation IDF, 2021).

2.1.2 Etiology of T2D

T2D has a complicated etiology that includes both inherited and environmental factors, such as obesity connected to higher living standards, lifestyle changes, and

persistent urban migration (Unnikrishnan et al., 2007; Kaveeshwar & Cornwall, 2014). The complex interaction of genetic, metabolic, and environmental risk factors for T2D results in a higher prevalence of the condition. Although ethnicity and family history/genetic predisposition, which are non-modifiable risk factors for T2D, have a strong genetic basis, epidemiological evidence indicates that many cases of T2D can be prevented by addressing the major modifiable risk factors (obesity, lack of physical activity, and a poor diet) (Hu et al., 2001).

2.1.2.1 Ethnicity and genetic predisposition

The risk of T2D varies widely by ethnicity and region around the world, with Japanese, Hispanics, and Native Americans having the highest rates (Chan et al., 1993; Dabelea et al., 2009; Liu et al., 2009). According to studies (Karter et al., 2013; Sattar et al., 2015), Asians have higher incidence rates than white Americans and white Britons (UK) (McKeigue et al., 1991), with black persons at the greatest risk (Haines et al., 2007). Despite the lack of a clear explanation, major factors have been discovered, including modern lifestyle factors (which increase obesity), socioeconomic factors, direct genetic susceptibility, and gene-environment interactions. Genetic susceptibility has a significant influence on the risk of having T2D. The complex polygenic nature of T2D has been highlighted by a number of genome-wide association studies, with most of these loci increasing T2D risk via main impacts on insulin production and a small number acting through reducing insulin action (Fuchsberger et al., 2016; McCarthy, 2010). The effects on insulin release pattern, insulin secretion with fasting hyperglycemia, insulin secretion with normal fasting glycemia, and insulin processing were all used by Dimas et al. to classify these variations in relation to probable intermediary pathways in T2D pathogenesis (Dimas et al., 2014). These results show that T2D has a highly polygenic genetic architecture, and more association studies are needed to identify the majority of T2D loci (Flannick & Florez, 2016). The lack of heritability of T2D may be explained by interactions between susceptibility loci and environmental factors, which suggests that the impact

of a particular genetic variation may be affected by environmental factors (and vice versa) (Franks et al., 2013).

2.1.2.2 Life style based factors

The most important risk factor for T2D is obesity (BMI 30 kg/m^2), which is linked to metabolic abnormalities that lead to insulin resistance (Bellou et al., 2018; Carey et al., 1997). (Sinha et al., 2002). Although the exact mechanisms by which obesity results in T2D and insulin resistance are unknown, a number of factors, including both cell-autonomous mechanisms and inter-organ linkages, have been implicated in the development of this disease process. Another risk factor for T2D is a sedentary lifestyle, as shown by the Women's Health Study and the Kuipio Ischemic Heart Disease Risk Factor Study, which indicated that people who walked for at least 40 minutes a day or 2-3 hours a week had a 34% and 56% lower risk of getting T2D, respectively (Weinstein et al., 2004; Lynch et al., 1996). There are three main advantages of physical activity that help to delay the onset of T2D. In the beginning, skeletal muscle cell contraction boosts blood flow into the muscle, enhancing plasma glucose absorption (Venkatasamy et al., 2013). Second, exercise reduces the dreaded intra-abdominal fat, a known risk factor for developing insulin resistance (Strasser, 2013). Last but not least, moderate exercise has been shown to boost glucose absorption by 40%. Exercise improves insulin sensitivity and glucose uptake, but it can also reduce or even eliminate inflammation and oxidative stress, both of which are risk factors for T2D (Venkatasamy et al., 2013).

2.1.3 Pathogenesis of T2D

Preserving cellular integrity and tightly regulating the processes and pathways involved in cell physiology are necessary to ensure optimal cell activity (Cerf, 2013). Beta cells are responsible of producing pre-proinsulin, which is the precursor to insulin. With the help of several proteins in the endoplasmic reticulum (ER), pre-proinsulin undergoes a structural change during maturation to produce proinsulin (Bunney et al., 2017). Then,

proinsulin is moved from the ER to the Golgi apparatus (GA), where it enters immature secretory vesicles and is converted into C-peptide and insulin (Halban, 1994). Until insulin release is triggered, insulin is created and held in granules. High glucose concentrations are the main reason for insulin release. It is important to note that several factors, including hormones, fatty acids, and amino acids, can also cause the release of insulin (Boland et al., 2017). The glucose transporter 2 (GLUT2), a solute carrier protein that simultaneously serves as a glucose sensor in cells, is the main mechanism by which cells absorb glucose when blood glucose levels rise. When glucose enters the cell, glucose catabolism begins. This increases the intracellular ATP/ADP ratio and causes the plasma membrane's ATP-dependent potassium channels to close. As a result, the membrane depolarizes and voltage-dependent Ca^{2+} channels open, allowing Ca^{2+} to enter the cell. Insulin exocytosis occurs as a result of the secretory insulin-containing granules being primed and fused to the plasma membrane when the intracellular Ca^{2+} concentration increases (Fu et al., 2013; Boland et al., 2017; Rorsman & Ashcroft, 2018; Seino et al., 2011). Additionally, RY receptors (RYR), which may be crucial in the coupling of the stimulus and insulin production because of their strategic locations within the cell and ability to mediate Ca^{2+} driven Ca^{2+} release, can augment Ca^{2+} signals. When messenger molecules sensitise the channel, RYRs enhance Ca^{2+} signals and consequently insulin secretion (Islam, 2002).

However, other cell signals can support or increase the release of insulin from cells. The most crucial messenger for boosting insulin release may be cyclic AMP (cAMP). The study found that cAMP increases mobilisation of secretory vesicles carrying insulin by reducing intracellular Ca^{2+} reservoirs and increasing intracellular Ca^{2+} concentrations (Cuinas et al., 2016). Moreover, there is compelling evidence that extracellular ATP plays a crucial role in controlling cell activity. Cells release ATP in response to glucose stimulation by the exocytosis of insulin granules. Independent of glucose, purinergic transmission stimulates Ca^{2+} mobilisation and controls insulin exocytosis. It has been discovered that P2Y purinoreceptors and G-proteins interact (Lustig et al., 1993; Simon et al., 1995). P2X-type receptors are non-cation-selective ATP-activated ligand-gated ion

channels (Valera et al., 1994). It has been proposed that intracellular Ca2+ mobilisation in response to inositol-1,4,5-triphosphate (IP3) synthesis, which promotes Ca2+ release from ER storage and amplifies the exocytosis-triggering Ca2+ signal, mediates insulin release in the case of P2Y receptors (Blachier et al., 1988; Li et al., 1991).

Cell death and malfunction have long been connected (Christensen & Gannon, 2019). However, recent studies suggest that T2D cell dysfunction may be brought on by a more intricate web of interactions between the environment and numerous cell biology-related biochemical processes (Halban et al., 2014). Insulin resistance and ongoing inflammation are encouraged by hyperglycemia and hyperlipidemia. Cells are exposed to toxic stimuli like inflammation, ER stress, metabolic/oxidative stress, and amyloid stress as a result of genetic susceptibility variations, which can result in islet integrity loss (Christensen & Gannon, 2019).

Through the apoptotic unfolded protein response (UPR) pathways, excess free fatty acids (FFAs) and hyperglycemia cause cell death (Yamamoto et al., 2019). In fact, metabolic and oxidative stress brought on by obesity-related lipotoxicity, glucotoxicity, and glucolipotoxicity result in cell death (Halban et al., 2014). High saturated FFA stress can activate the UPR pathway in a number of ways, such as by directly disrupting ER homeostasis, activating IP3 receptors, or inhibiting the ER-Ca^{2+}-ATPase, which is responsible for ER-Ca^{2+} mobilisation. Additionally, proinsulin biosynthesis and the production of islet amyloid polypeptides (IAAP) are both stimulated by persistently high glucose levels, which leads to the accumulation of misfolded insulin and IAAP as well as an increase in the production of reactive oxygen species (ROS) mediated by oxidative protein folding (Yamamoto et al., 2019). These ejects alter the usual mobilisation of ER Ca^{2+}, favouring pro-apoptotic signals and the destruction of proinsulin mRNA. They also encourage the release of interleukin (IL)-1, which draws macrophages and intensifies local islet inflammation (Halban et al., 2014). As was previously mentioned, adequate regulation of insulin secretion is necessary to meet metabolic demand. In order for cells to respond to metabolic demands, appropriate islet integrity must be kept. The mechanism outlined

above can eventually result in islet integrity/organization disruption under pathogenic conditions, impairing optimal cell-to-cell communication within pancreatic islets, lowering the ability to control insulin and glucagon release, and ultimately worsening hyperglycemia. Insulin secretory dysfunction, the primary cause of cell failure and the underlying cause of T2D, can be brought on by errors in the synthesis of either insulin precursors or insulin itself, as well as by interruptions in the secretion process. The following elements have been linked to the emergence of T2D:

2.1.3.1 Nutritional-factors

The high-calorie western diet comprises a lot of fats and carbohydrates, which raise blood glucose and increase the quantity of circulating very-low-density lipoproteins (VLDLs), chylomicrons (CMs), and their remnants (CMRs) that are high in triglycerides (TG). This causes an increase in reactive oxygen species (ROS) concentrations, which causes an aberrant production of inflammatory chemicals. Given that inflammation is a known inducer of oxidative stress, a synergistic combination between the two processes occurs after a large meal, resulting in an increase in damaging postprandial ejects. The persistent and considerable rise in steady-state ROS levels contributes greatly to the pathophysiology of T2D and insulin release. As a result, a pro-oxidant environment causes mitochondrial malfunction, ER stress, NADPH oxidase (NOX) activation, and superoxide ($O^{-2\cdot}$) generation. Increased $O^{-2\cdot}$ production activates the five major pathways involved in the pathogenesis of diabetes complications: polyol pathway enhancement, increased formation of advanced glycation end products (AGEs), increased expression of AGEs receptor and its activating ligands, activation of protein kinase C (PKC) isoforms, and overactivity of the hexosamine pathway (Dali-Youcef et al., 2013; Hummasti, 2010). Increased intracellular ROS induces poor angiogenesis in response to ischemia, activates a variety of pro-inflammatory pathways, and generates long-lasting epigenetic alterations that drive pro-inflammatory gene expression even when glycemia is corrected (Giacco & Brownlee, 2010). Furthermore, high FFA levels in the blood causes mitochondrial dysfunction via two separate mechanisms: FFA metabolism by-products disrupt electron

flow across the mitochondrial respiratory chain, and FFA incorporation into the mitochondrial membranes favours electron leakage (Graciano et al., 2011).

2.1.3.2 Life style based factors

Obesity and T2D are linked by decreased physical activity and exercise training, as well as increased sedentary habits, which are related with elevated indicators of chronic low-grade systemic inflammation (Esser et al., 2014; Pradhan et al., 2001). In this situation, pro-inflammatory molecules such as interleukin 6 (IL-6) and CRP, tumour necrosis factor-alpha (TNF-alpha), or IL-1 are released into the circulation, causing metabolic inflammation (Bunney et al., 2017). Indeed, IL-1 is implicated in the pancreatic autoimmune response, decreasing β cell activity and activating the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) transcription factor, therefore limiting β cell function and encouraging death (Venkatasamy et al., 2013). Preclinical animal findings demonstrate that elimination of the macromolecular complex NLRP3 inflammasome, which is responsible for the generation of IL-1 and IL-18, results in increased insulin sensitivity, implying that inflammation resolution might prevent the development of T2D in obesity and prediabetes (Vandanmagsar et al., 2011).

2.1.3.3 Mitochondrial dysfunction

There is a growing body of data linking mitochondrial dysfunction to T2D development, age-related insulin resistance and T2D comorbidities (Kim et al., 2008). Indeed, oxidative stress, poor mitochondrial biogenesis, genetic changes affecting mitochondrial integrity, and ageing all enhance mitochondrial dysfunction and are linked to the development of T2D (Stump et al., 2003; Petersen et al., 2003). The primary function of mitochondria is to produce ATP via oxidative phosphorylation in response to metabolic demand (Sazanov, 2015). Mitochondria also contribute to the formation of several metabolites that serve as precursors to a variety of macromolecules (lipids, proteins, and DNA). Furthermore, mitochondria play a key role in ion homeostasis, ROS clearance,

stress response, and the integration of numerous signalling pathways (Spinelli & Haigis, 2018). Unbalanced energy intake and expenditure in the mitochondria results in mitochondrial dysfunction, which is defined by a decreased ratio of energy generation to respiration (Petersen et al., 2003). Under these conditions, nutrient oxidation efficiency decreases, resulting in a lower ratio of ATP synthesis/oxygen consumption, which increases $O2^{\cdot-}$ generation (Shigenaga et al., 1994). Indeed, one hypothesised mechanism connecting mitochondrial dysfunction to insulin resistance is the buildup of ROS in the mitochondria (Sergi et al., 2019). Studies indicating lower mitochondrial oxidative capacity in skeletal muscle and poor lipid metabolism in obese and insulin-resistant patients compared to healthy controls substantiated this association (Kelley et al., 1999; Simoneau, et al., 1999; Kim et al., 2000). Furthermore, individuals with T2D have been discovered to have decreased phosphocreatine re-synthesis rate and down regulation of genes involved in oxidative metabolism that are controlled by the peroxisome proliferator-activated receptor co-activator (Mootha et al., 2003; Patti et al., 2003; Schrauwen-Hinderling et al., 2007). Furthermore, certain relatives of T2D patients were shown to have lower mitochondrial respiration, indicating that mitochondrial dysfunction may preceed T2D development. It has also been postulated that T2D may be caused by abnormalities in the oxidative phosphorylation system and the electron transport chain (ETC), rather than a reduction in mitochondrial content (Phielix et al., 2008).

2.1.3.4 Insulin resistance

Insulin resistance is defined as a reduction in the metabolic response of insulin-responsive cells to insulin or, on a systemic level, an impaired/lower response to circulating insulin by blood glucose levels (Czech, 2017). There are three broad types of insulin resistance or insulin-deficient conditions: decreased insulin secretion by β cells; insulin antagonists in the plasma caused by either counter-regulatory hormones or non-hormonal bodies that impair insulin receptors or signaling; and impaired insulin response in target tissues (Pearson et al., 2016). Interactions of other substances such as growth hormone and Insulin- like growth factor-1 (IGF-1) influences insulin function. To avoid insulin-induced

hypoglycemia, glucagon, glucocorticoids, and catecholamines suppress the insulin response when fasting. The insulin/glucagon ratio is important in this regulation because it regulates the degree of phosphorylation of downstream enzymes in regulatory signaling pathways. Glucocorticoids stimulate muscle catabolism, gluconeogenesis, and lipolysis while catecholamines enhance lipolysis and glycogenolysis. As a result, increased release of these hormones may be implicated for triggering insulin resistance (Wilcox, 2005; Nussey, 2001). In terms of the last category, there are three primary extra-pancreatic insulin-sensitive organs that play important roles in the aforementioned processes: skeletal muscle, adipose tissue, and the liver. A deficiency in insulin action in these organs frequently precedes the development of systemic insulin resistance, ultimately leading to T2D.

2.1.4 Management of T2D

Comprehensive diabetes care necessitates an initial assessment of the risk factors, the existence or absence of diabetic complications and an initial review of prior treatment/s. This allows healthcare practitioners to manage individuals with pre-diabetes or diabetes in a better manner. Management of T2D is focused around lifestyle changes, pharmacotherapy and regular blood glucose control.

2.1.4.1 Glycemic control

Glucose monitoring and glycemic control are very significant for many diabetics in order to meet their glycemic goals. ADA, European Association for the Study of Diabetes (EASD), American College of Endocrinology (ACE) and American Association of Clinical Endocrinologists (AACE) have issued recommendation regarding glycemic management. Assessment of glycemic control is typically done by the HbA1c test. Self-monitoring of blood glucose has been incorporated in major clinical studies of insulin-treated patients as part of multifactorial treatments to establish the efficacy of rigorous glycemic control on diabetic complications (DCCTR group, 1993). The ACE/AACE

standards are stricter, recommending HbA1c values of fewer than 6.5 %, whereas the ADA/EASD guidelines prescribe a target of less than 7.0%. Suboptimal HbA1c management is linked to poor T2D outcomes (Standards of medical care, 2012; Rodbard et al., 2009). The risk of microvascular problems is lowered by 33% to 37% for every 1% drop in HbA1c (UKPDS group, 1998; DCCTR group, 1993).

2.1.4.2 Lifestyle changes

Life style related factors like physical exercise, diet control and weight reduction are integrated with pharmacotherapy for achievement of glycemic goals in diabetic patients.

2.1.4.3 Pharmacotherapy

Oral anti-diabetics are generally prescribed to T2D patients when lifestyle changes are ineffective. There are several classes of anti-diabetic medications available (Table 1).

Table 1: Anti-diabetic drugs.

Class of anti-diabetic drug (route of administration)	Name of anti-diabetic drug	Mechanism of action	HbA1c reduction (%)	Cardiovascular (CV) benefit and risks	Other adverse effects
Biguanide (oral)	Metformin	Insulin sensitizer, numerous effects on inhibition of hepatic glucose production	1–2	Reduce MI by 39% and coronary deaths by 50% (UKPDS)	Vitamin B_{12} deficiency, which may cause anemia and neuropathy (risk in elderly). Very safe drug, but stopped metformin if creatinine >1.5 mg/dL in males and >1.4 mg/dL in females
Dipeptidyl peptidase 4 Inhibitor-DPP4i (oral)	Linagliptin Alogliptin Sitagliptin Saxagliptin Vidagliptin	Inhibition of degradation of GLP	0.5–0.8	Decreases postprandial lipemia, however, may cause CHF by degradation of BNP	Pancreatitis
Sodium-glucose cotransporter inhibitor (oral)	Canagliflozin Dapagliflozin Empagliflozin	Glucosuria due to inhibition (90%) of glucose reabsorption in renal PCT; insulin independent mechanism of action	--	Positive CV effect due to reduction of sodium and uric acid absorption and reduction of BP	Ketoacidosis (rare), vaginal mycosis, increased low density lipoproteins, and bone fractures
Insulin (parenteral)	Short-acting regular (R) (Humulin R, Novolin R) Intermediate NPH (N) Long-acting	Activation of insulin receptors and downstream signaling in	1–2.5	Heart failure if used in combination with thiazolidinediones (TZD)	Lipoatrophy and lipohypertrophy at sites of injection, allergy to injection components

	Insulin glargine (Lantus) Insulin detemir (Levemir) Insulin degludec (Tresiba) Rapid-acting Humalog (Lispro), Novolog (Aspart) Glulisine (Apidra) Pre-mixed 75% insulin lispro protamine/25 % insulin lispro (Humalog Mix 75/25) 50% insulin lispro protamine/50 % insulin lispro (Humalog Mix 50/50) 70% insulin lispro protamine/30 % insulin aspart (Novolog 70/30) 70% NPH insulin/30% Regular	multiple sensitive tissues			

Glucagon-like peptide-1 agonists (parenteral)	Liraglutide Exenatide Dulaglutide	Activation of GLP1 receptor, increased insulin secretion, decreased glucagon, delayed gastric emptying, increased satiety	0.5–1.5	Reduce CV risk	Nausea, vomiting, pancreatitis
Sulfonylureas (oral)	Glimepiride Glipizide Glyburide	Insulin secretion	1–2	Increased cardiovascular disease risk, mainly due to hypoglycemia	β-blockers to be used with caution
Thiazolidinediones (oral)	Rosiglitazone Pioglitazone	True insulin sensitizer	0.5–1.4	Cardiac failure	Bladder cancer; fractures

Metformin is commonly used as a first-line therapy. If metformin is no longer effective after three months, a second oral medication of a different type or insulin may be administered. Additional classes of medications include: SU, TZD, DPP-4 inhibitors, SGLT-2 inhibitors and glucagon-like peptide-1 (GLP-1) analogs. If a single therapy fails to provide satisfactory glycemic control, a second and subsequently a third therapy may be added to the treatment, while reiterating the importance of changing one's lifestyle. Different drugs are added to metformin and SU for the management of T2D (Fig. 1).

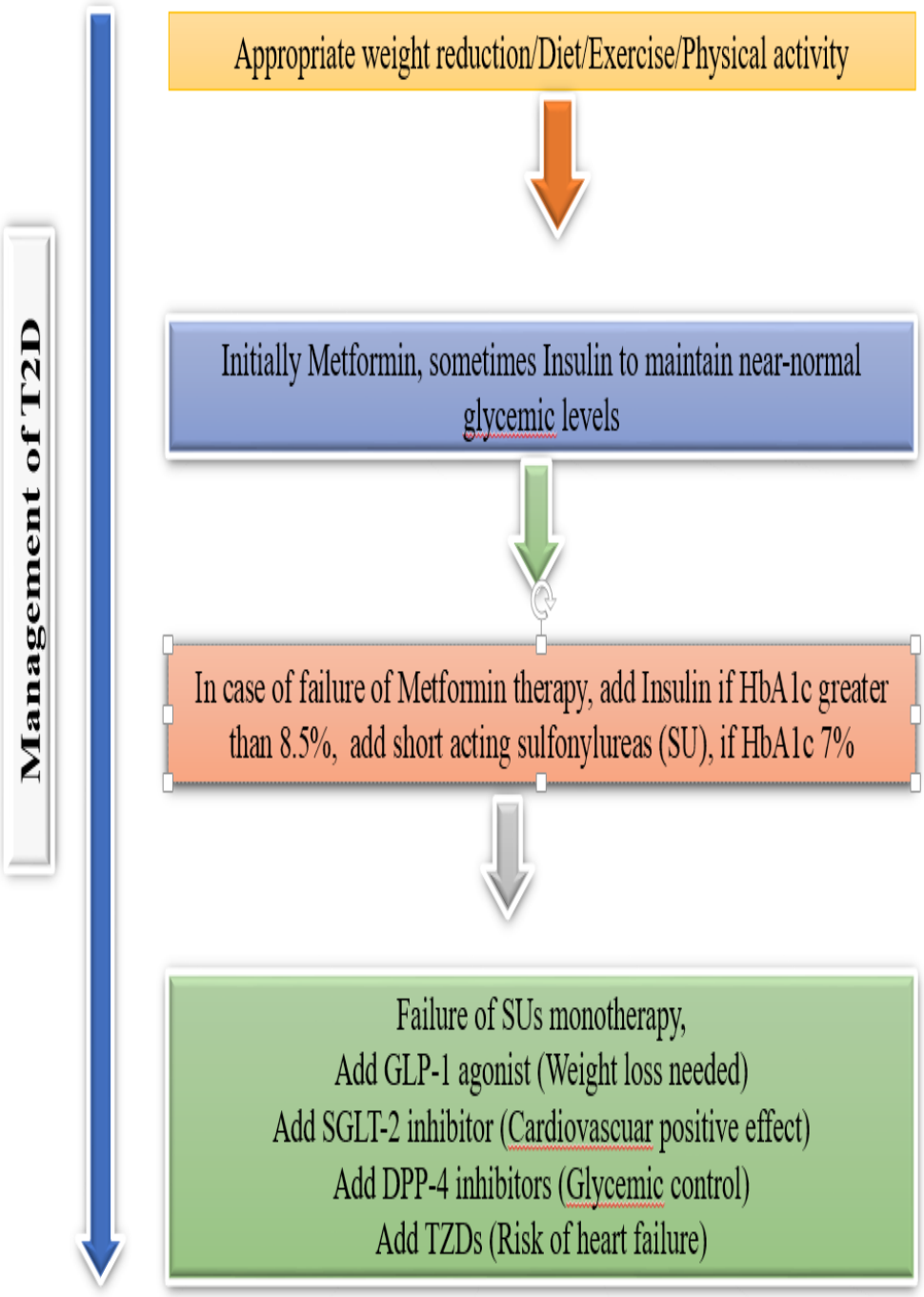

Figure 1. Management of diabetes

A third drug is usually added to the existing dual therapy for better glycemic control. Triple therapy combinations (Metformin/SU/DPP-4 inhibitors) and (Metformin/DPP-4 inhibitors/Insulin) are being increasingly used and may result in greater reduction in HbA1c.

2.1.5 Challenges for T2D management

The use of multidrug combination treatment in T2D patients may enhance health outcomes, but it may also result in extra problems that must be carefully considered. Furthermore, attention must be paid to the comorbidities linked with diabetes. The diabetic environment promotes the synthesis of AGEs, which can lead to the development of diabetic problems and even cancer in diabetic individuals.

2.1.6 Comorbidities of T2D

Diabetics are at an increased risk of developing cardiovascular, peripheral vascular, and cerebrovascular disorders. T2D increases the mortality rate of adults from heart disease and stroke by a factor of two to four, and it is associated with both micro- and macro-vascular complications, the latter of which includes accelerated atherosclerosis leading to severe peripheral vascular disease, premature coronary artery disease (CAD), and an increased risk of cerebrovascular diseases (Haffner et al., 1998; Beckman et al., 2002; Nesto, 2004). T2D is considered a substantial risk factor for CVD due to the involvement of various molecular processes and pathophysiological pathways (NCEP, 2002). These comorbidities are attributed to a number of pathologic mechanisms like abnormalities in glucose, lipid, and protein metabolism owing to a lack of insulin action on target tissues. The involvement of insulin resistance in atherosclerosis, vascular function, oxidative stress, hypertension, macrophage buildup, and inflammation are among them (Reaven, 2012; Bornfeldt & Tabas, 2011; Davidson & Parkin, 2009; Laakso, 2014).

2.1.6.1 Macrovascular complications

Macrovascular complications of diabetes may progress to myocardial infarction, stroke, and peripheral artery disease. Atherosclerosis is the fundamental pathologic process associated with macrovascular disease, which is exacerbated in due to vascular lesions (Kattoor et al. 2017). T2D causes a roughly 2-fold increase in CVD risk (Haffner et al., 1998; Juutilainen et al., 2005). As a result, people with T2D have worse outcomes following an acute coronary syndrome and increased risks of re-infarction or heart failure (Abbott et al., 1988).

2.1.6.2 Microvascular complications

Microvascular diseases promote the development of retinopathy, nephropathy, and neuropathy, all of which are important causes of morbidity and mortality in diabetic patients. In the United States alone, diabetic retinopathy affects around 28% of adults with primary illness of established T2D (Zhang et al., 2010). Diabetes retinopathy is causing 12,000 to 24,000 new cases of visual loss each year. As a result, the coexistence of hypertensive retinopathy with diabetic retinopathy increases the risk of vision loss (Congdon et al., 2003). Within 5 years of diabetes diagnosis, 14 % of patients with type 1 diabetes and 33 % of patients with T2D developed diabetic retinopathy, according to the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) (Varma et al., 2008). Diabetic retinopathy may be split into two types: proliferative and non-proliferative. Non-proliferative diabetic retinopathy causes increased capillary permeability, bleeding, and retinal edoema, and can proceed to proliferative retinopathy as a result of neovascularization on the retina's vitreous surface, the vitreous cavity, and the iris. The coexistence of scarring and fibrosis over time causes traction of the retina, which can progress to retinal detachment and vision loss.

Studies show that diabetic nephropathy occurs in up to 40% of diabetic patients,

and hypertension increases the risk of this microvascular complication (Sowers & Epstein, 1995; NHBP report, 1994). As a result, diabetic nephropathy was shown to be histopathologically distinct from other causes of renal disease. Thickening of the glomerular basement membrane causes a rise in the quantity of mesangial matrix, which can develop to progressively severe diffuse or nodular glomerulosclerosis in some individuals (Sowers & Epstein, 1995). Diabetic neuropathy affects around 70% of diabetic individuals and is the leading cause of foot amputation. Etiology of peripheral neuropathy is poorly understood, but is thought to be connected to their causes, namely, reduced blood flow, nerve demylelinization, and inflammation. Peripheral neuropathy develops in chronic hyperglycemia and is linked with metabolic derangements such as increased polyol flow, accumulation of advanced glycosylation end products, lipid derangements, and oxidative stress (Tesfaye et al., 2010). Thus each organ-specific microvascular complication has its own unique or integral clinical and histologic features, but all are related to chronic hyperglycemia and are driven by downstream cellular effects, such as polyol accumulation (due to hexokinase pathway saturation and consequent increased activity of aldose reductase), AGE-induced injury, increased vascular permeability, and oxidative stress (Brownlee, 2005). According to the findings of the Action in Diabetes and Vascular Disease: Preterax and Diamicron Controlled Evaluation (ADVANCE) trial cohort, the existence of microvascular problems increase the frequency of cardiovascular issues in individuals with T2D (Mohammedi et al., 2017).

2.1.7 T2D and hypertension

Hypertension is one such ailment that is highly common in diabetic people. T2D and hypertension, two key components of the global disease burden, frequently co-occur (Ferrannini et al., 2012; Zhou et al., 2017). . T2D patients have a hypertension prevalence of 60-70% (Mubarak et al., 2008). According to the literature, Diabetics have double the rate of hypertension as in non-diabetics. Furthermore, hypertension individuals usually have insulin resistance-(IR) and were more susceptible to acquire

diabetes than normo-tensive people. The cardiovascular effects of diabetes and hypertension, which are mostly caused by microvascular and macrovascular problems, also overlap significantly. T2D and hypertension raise the incidence of CVS disease, kidney diseases, & death (two to four times that of non-diabetic and normotensive adults) (Ferrannini et al., 2012). Individuals with hypertension and concurrent diabetes were found to have higher risks of cardiovascular mortality, myocardial infarction, angina pectoris, and stroke in the Hypertension in Diabetic study-(HDS) when compared to non-hypertensive diabetics (Turner et al., 1993).

2.1.7.1 Pathophysiology

Diabetes and hypertension are inextricably connected due to shared risk factors such as endothelial dysfunction, vascular inflammation, arterial remodelling, atherosclerosis, dyslipidemia, and obesity. Diabetes and hypertension are frequent risk factors for vascular problems, which are associated with atherosclerosis, inflammation, endothelial dysfunction, and structural remodelling, resulting in macrovascular and microvascular complications (Fig. 2). There is also significant overlap in the cardiovascular consequences of diabetes and hypertension (Fig. 3). Thus common pathological events such as renin-angiotensin-aldosterone system upregulation, oxidative stress, inflammation, and immune system activation are likely to associate diabetes with hypertension.

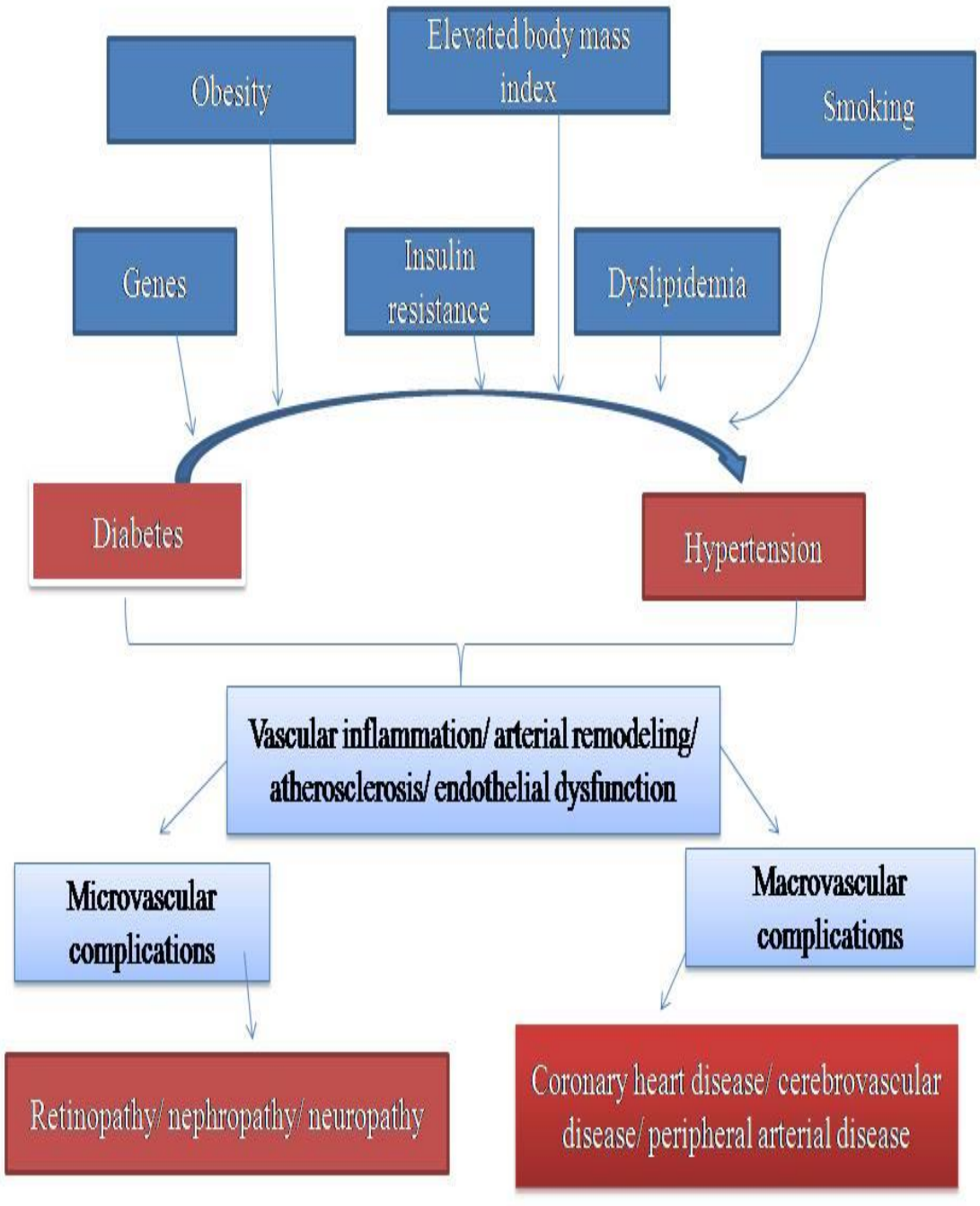

Figure 2. Association between diabetes and hypertension.

Diabetes-related circulating AGEs may act with endothelial RAGEs, resulting in changes in cellular-properties i.e. expression of the transcription-factor (NF-kB) (Bierhaus et al., 1997). As a result, AGE activation of RAGEs transduces or activates various signals, including NAD(P)H oxidase, p21ras, the mitogen-activated protein kinases (MAPKs), extracellular signal-regulated kinase 1/2 and p38, and the GTPases, culminating in nuclear transcription factor activation and translocation (Huttunen et al., 1999; Taguchi et al., 2000; Schiekofer et al., 2003). Endothelin 1, VCAM 1, ICAM 1, E selectin, tissue-factors, thrombo-modulin, VEGF, and proinflammatory cytokines such as interleukin-1, interleukin-6 & tumor necrosis factor-alpha are examples (Basta et al., 2004). AGEs stimulate monocytes to generate and release cyto-kines such TNF-alpha & IL 6 (Vlassara et al., 1988). Enhanced oxidative-stress hastens athero-sclerosis development & elevates the menance of CVs events via triggering inflammatory-responses (Giugliano et al., 1996).

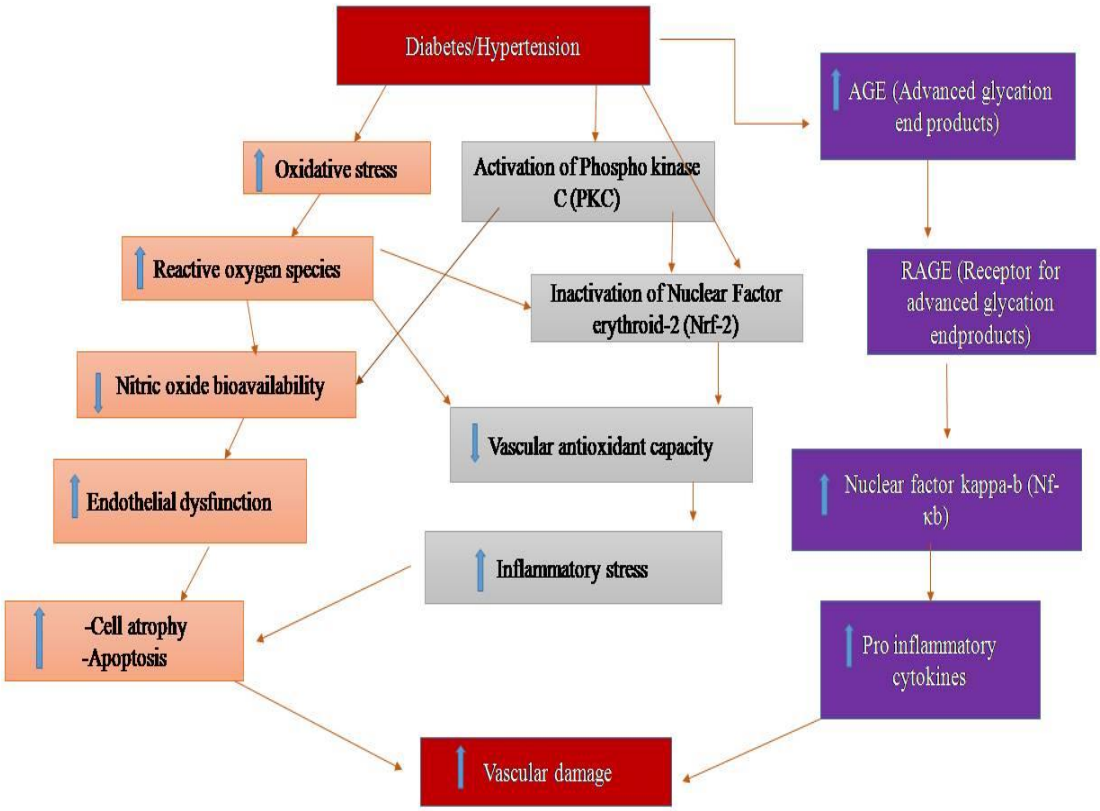

Figure 3. Overlapping consequences of diabetes and hypertension.

2.1.7.2 Management of T2D with hypertension

Management of patients with T2D should not only aim to control glycemia but also hypertension. As control of blood pressure is difficult to achieve in patients with diabetes, combination therapy is often required. In an ideal scenario, a drug used in combination should be able to reverse the pathology with an improved overall health status of the patient and ensure that no new complications arise due to the existing management strategies. The use of multidrug combination therapy in diabetes has improved health outcomes in T2D patients. Lowering blood pressure has been shown to reduce cardiovascular events in patients with diabetes and to exert a renoprotective

effect. There are no clear guidelines on how to handle individuals who do not exhibit satisfactory control with triple medication therapy or who develop hypertension as a consequence of diabetes. As per ADA guidelines, the main objective of treatment is to attain blood pressure less than 130/80 mm Hg and a low-density lipoprotein–cholesterol (LDL–C) less than 100 mg/dL (below 70 mg/dL in high-risk patients) (Standards of medical care, 2012).

2.1.8 Empagliflozin

Empagliflozin (Jardiance/Gibtulio) is a highly selective SGLT2-i used for the treatment of T2D patients. Because it is SGLT2-i, it reduces reabsorption of filtered glucose in the kidney's proximal tubules, lowers the renal threshold for glucose, increases urine glucose excretion and lowers blood glucose levels. Empagliflozin has shown a greater selectivity for SGLT2 than for SGLT1. Furthermore, its selectivity is significantly greater than that of other SGLT2 inhibitors, such as dapagliflozin and canagliflozin. SGLT1 absorbs glucose and galactose predominantly in the small intestine, but it also functions in the distal section of the proximal tubule to reabsorb leftover glucose not taken up by SGLT2. It is approved for glycemic control in T2D patients. It has been reported to demonstrate reduction in the incidence of CVDs in T2D patients. It has gained US FDA to reduce T2DM associated cardiovascular risk in adult patients. It is a well-tolerated drug and has demonstrated good safety profile in T2D patients. It has been investigated in a number of clinical studies (Table 2).

Table 2: Reported therapeutic outcomes of Empagliflozin.

S.No.	Therapeutic outcomes in clinical trials	References
1.	The trial demonstrated that Empagliflozin lowered HbA1c and was well tolerated in individuals with T2D and stage 2 or 3 CKD. However, the findings may not be relevant to the overall population of individuals with T2D and renal impairment.	Barnett et al., 2014
2.	In this trial, Empagliflozin, was shown to be an effective and well-tolerated 2nd step drug choice to T2D-participants who hadn't maintained satisfactory glycemic-control on metformin.	Ridderstrale et al., 2014
3.	In this clinical study, Empagliflozin reduced blood pressure while improving indices of arterial inflexibility and vascular resistance.	Chilton et al., 2015
4.	In this study, Empagliflozin was associated with significant and clinically important reductions in blood pressure and HbA1c as compared to placebos, and it proved well-tolerated in those with T2D and hypertension.	Tikkanen et al., 2015

5.	Empagliflozin was well tolerated in this trial and resulted in lasting decrease in HbA1c and weight in individuals with T2D when administered as an add-on therapy to pioglitazone with or without metformin for 76 weeks compared to placebo.	Kovacs et al., 2015
6.	The study revealed that combining linagliptin with Empagliflozin and Metformin for 24 weeks improved glucose control comparison to placebo and was adequately tolerated.	Merker et al., 2015
7.	This study reported that Empagliflozin 10 and 25 mg as an addition to another diabetic oral-medication for 52-weeks was highly tolerated & linked to clinically considerable-reduction of HbA1c in Japanese T2D-participants.	Araki et al., 2015
8.	It has been reported that Empagliflozin reduces the risk of death and hospitalization in patients suffering from cardiovascular disease, heart failure, low ejection fraction or T2D.	Zinman et al., 2015
8.	In this study, Empagliflozin-effectively lowered weight & adiposity-indices, potentially improving cardio-metabolic menace in T2D patients.	Neeland et al., 2016

9.	The study reported that use of Empagliflozin in T2D hypertensive individuals for twelve weeks lowered BP, regardless of the use of other drugs like diuretics, or ACE-inhibitors/angiotensin receptor-blockers.	Mancia et al., 2016
10.	According to this specific investigation, Empagliflozin, 10 mg and empagliflozin 25 mg were generally tolerated in patients with T2D.	Kohler et al., 2016
11.	According to this clinical research study, despite age/degree of obesity, Empagliflozin was well-tolerated. It decreased HbA1c, FPG, overall body weight in all BMI and age sub-groups in Japanese-patients suffering from T2D. This study reported that Empagliflozin is very safe & effective in the management of T2D.	Shiba et al., 2017
12.	This study reported that adding Linagliptin to Empagliflozin plus Metformin during 24-weeks maintained glycemic-control relative to placebo & was well-tolerated.	Tinahones et al., 2017
13.	The study revealed that adding Empagliflozin/Linagliptin tablet to metformin may be explored in patients with inadequate glycemic control, or as an alternative to first-line therapy with empagliflozin or linagliptin when metformin is not acceptable,	Jain, 2017

	particularly in patients with extremely poor glycemic control or those who need to attain goal more rapidly.	
14.	Empagliflozin may be better cost-effective than standard medication in T2D patients with high cardiovascular risk.	Nguyen et al., 2017
15.	In this trial, Empagliflozin, was shown to be an effective and well-tolerated 2nd drug treatment choice to T2D-participants, who hadn't achieved satisfactory glycemic-control on metformin.	Scheen, 2017
16.	The study reported that Empagliflozin reduced all-cause and cardiovascular mortality in patients with established cardiovascular disease and T2D. Direct evidence suggested no difference in mortality between empagliflozin and metformin, glimepiride, linagliptin, or sitagliptin. However long-term comparative safety needs to be established.	Aronow &, Shamliyan, 2017
17.	This study reported that Empagliflozin can provide significant clinical benefits for T2D patients, showing inadequate control to triple drug treatment of metformin, glimepiride and teneligliptin.	Pattanaik, 2018

18.	This study demonstrated that SGLT2 inhibitors can be effectively used as add on oral anti diabetic drugs in T2D patients who are treated with three other oral anti diabetic drugs. More specifically, empagliflozin was found more effective in reducing HbA1c and improving other cardiometabolic parameters than dapagliflozin.	Ku et al., 2019a
19.	This study demonstrated that a regimen comprising four different orally active antidiabetic agents, including empagliflozin, was effective and safe as a therapeutic strategy for treating T2D patients for glycaemic control and improvement of other cardiovascular and metabolic indices.	Ku et al., 2019b
20.	In patients with heart failure with preserved ejection fraction, empagliflozin reduced the risk for major heart failure outcomes across the range of baseline Kansas City Cardiomyopathy Questionnaire (KCCQ) scores. Empagliflozin improved health-related QoL, an effect that appeared early and was sustained for at least 1 year.	Butler et al., 2022

Chapter 3

Rationale of the study

3.1 Hypothesis

In clinical practice, anti-diabetic drugs are prescribed when lifestyle modification is not effective in the management of T2D. If a single drug fails to achieve adequate glycaemic control then a dual or triple therapy with oral agents such as SUs, TZDs, DPP-4 inhibitors and SGLT-2 inhibitors is prescribed (Inzucchi et al., 2015). But for patients not showing adequate control with triple drug therapy, insulin administration is recommended. But reluctance of patients for injectable insulin therapy has ushered the need to investigate other drugs as add-ons to triple therapy. The recently approved SGLT-2 inhibitors are being explored for their add-on potential (Jeon et al., 2018; Ku et al., 2019a; Ku et al., 2019b).

Empagliflozin is a competitive SGLT2 inhibitor that reduces hyperglycemia in T2D patients by lowering renal glucose reabsorption and increasing urinary excretion of glucose. It provides a substantial improvement in HbA1c levels whether used alone or in combination with metformin and possesses a favorable safety profile. Its efficacy and safety as an add-on drug in T2D patients demonstrating inadequate glycemic control to triple therapy (Glimepiride + Metformin + Teneligliptin) in diabetic patients has been investigated. It was found effective and safe in T2D patients who showed inadequate glycemic control with triple-drug treatment. Other studies have reported that Empagliflozin reduces the risk of death and hospitalization in patients suffering from cardiovascular disease, heart failure, low ejection fraction or T2D (Zinman et al., 2015; Aronow & Shamliyan, 2017). It also causes moderate reductions in blood pressure and body weight. It has been reported that Empagliflozin effectively lowered blood pressure in people with T2D and hypertension. However, there is a dearth of data regarding the effectiveness and safety of empagliflozin as an add-on to triple drug treatment (glimepiride, metformin and teneligliptin) in patients having uncontrolled T2D along with hypertension. Thus the present study was conducted to evaluate the efficacy and safety of addition of Empagliflozin in T2D patients who do not respond to triple therapy and develop hypertension as comorbidity.

Diabetes affects the QoL in general and when comorbidities emerge, patients' QoL deteriorates further (Trikkalinou et al., 2017). The coexistence of T2D and hypertension affects treatment outcomes, increases the risk of CVD and deteriorates QoL. So it was proposed that addition of Empagliflozin would imprve the QoL. There is currently a dearth of evidence regarding the effect of Empagliflozin on QoL in T2D patients with hypertension. So, this study investigated the impact of Emplagliflozin addition on the QoL in Indian patients.

Furthermore, due to chronic progressive nature of T2D, cost-benefit analysis of anti-diabetic drugs is considered very crucial because higher overall healthcare costs may affect the medication compliance. As anti-diabetic drugs vary greatly in efficacy, safety and cost profiles, it is difficult for a physician or endocrinologist to provide optimal patient treatment at the lowest feasible cost. Due to the scarcity of studies comparing the cost-effectiveness of various newer anti-diabetic drugs as an add-on therapy to conventional anti-diabetic drugs, it is difficult to determine whether the additional cost of Empagliflozin as an add-on therapy is worth paying in terms of greater efficacy and safety when the efficacy target is not met. The current study aimed to carry out cost-effective analysis of Empagliflozin add-on with the hypothesis that such data may help in customized or case-by-case decision-making in the Indian healthcare system, depending on socioeconomic status and comorbidity.

Hence the current study was conducted to evaluate the efficacy, safety, tolerance, QoL, and pharmacoeconomics of Empagliflozin as add-on therapy in T2D patients who do not respond to triple therapy (Metformin, Glimepiride and Teneligliptin) and develop hypertension as comorbidity.

Chapter 4

AIMS

&

OBJECTIVES

4.1 Aim

To study the efficacy and safety of Empagliflozin as an add-on drug therapy to Metformin, Teneligliptin and Glimepiride in T2D patients with hypertension.

4.2 Objectives

- To assess the efficacy of Empagliflozin as an add-on drug therapy to Metformin, Teneligliptin and Glimepiride in T2D patients with hypertension.
- To assess the safety and tolerablity of Empagliflozin as an add-on drug therapy with Metformin, Teneligliptin and Glimepiride in T2D patients with hypertension.
- To study the impact of Empagliflozin addition on QoL in T2D patients with hypertension.
- To carry out Cost-effectiveness analysis of Empagliflozin as an add-on drug in T2D patients with hypertension.

Chapter 5

MATERIALS

&

METHODS

5.1 Study design

The current study was undertaken as one-year prospective, open label research in the Department of Endocrinology, SKIMS deemed university, a tertiary care facility in Srinagar. This was carried out by studying a total of 200 patients of T2D with hypertension as comorbidity. All patients were consecutive patients at the Department of Endocrinology. The patients were enrolled in October, 2020 and the study was completed in October, 2021.

5.2 Study population

Both male and female patients of T2D with hypertension without any other co-morbid conditions were included in the study as per inclusion criteria. The study was carried out in SKIMS Deemed university, Srinagar, a tertiary care hospital in North India. The study was uni-centric and patients visiting the hospital were recruited. All patients were Kashmiri.

5.3 Inclusion and exclusion criteria

Inclusion criteria: The study included patients with poorly controlled hypertension (systolic blood pressure ≤130 mm Hg and diastolic blood pressure≤80 mm Hg), HbA1c≤6.5 per cent and blood glucose (fasting ≤ 126 mg/dl and post prandial (PP) 200 mg/dl).

Exclusion criteria: Patients with severe comorbidities that have a significant impact on blood glucose levels, such as allergy, intolerance, bypass surgery, pregnancy/lactation, liver illness, and renal disease, were excluded from the current research. In addition, the opinion of an endocrinologist was taken into account.

5.4 Study ethics

The Ethics Committee of the Institute approved the study [RP 29/2020 (IEC-SKIMS/2020-591)] in compliance with the ICH-GCP ethical criteria established by the

Indian Council of Medical Research (ICMR). In this investigation, good clinical practice (GCP) standards and a revised version of the Helsinki Declaration were followed. Participants in the study provided their informed written consent before the conduct of study. Each and every participant was guaranteed confidentiality and the anonymity of their identity.

5.5 Sample size

The sample size was estimated using the formula [n = t2. p (1- p) / m2] (where n = needed sample size, t=confidence interval at 95 % (1.96), p = prevalence in population, and m= margin of error with a standard value of 0.05) (Suresh & Chandrashekara, 2012). Diabetes is predicted to affect 6% of our population (Zargar et al., 2000), hence the sample size needed was around 200 people.

5.6 Methodology

All the visiting T2D patients were screened as per inclusion criteria. Recruited patients were screened for baseline data. They were treated with Empagliflozin (25 mg, once in a day after breakfast) as an add-on therapy with Metformin (2g/day), Teneligliptin (20 mg/day), and Glimepiride (8 mg/day) for three months. After 3 months, followup data (efficacy, safety, tolerance, QoL and cost effective parameters) were collected (Fig.4). Medication adherence was measured using the pill count.

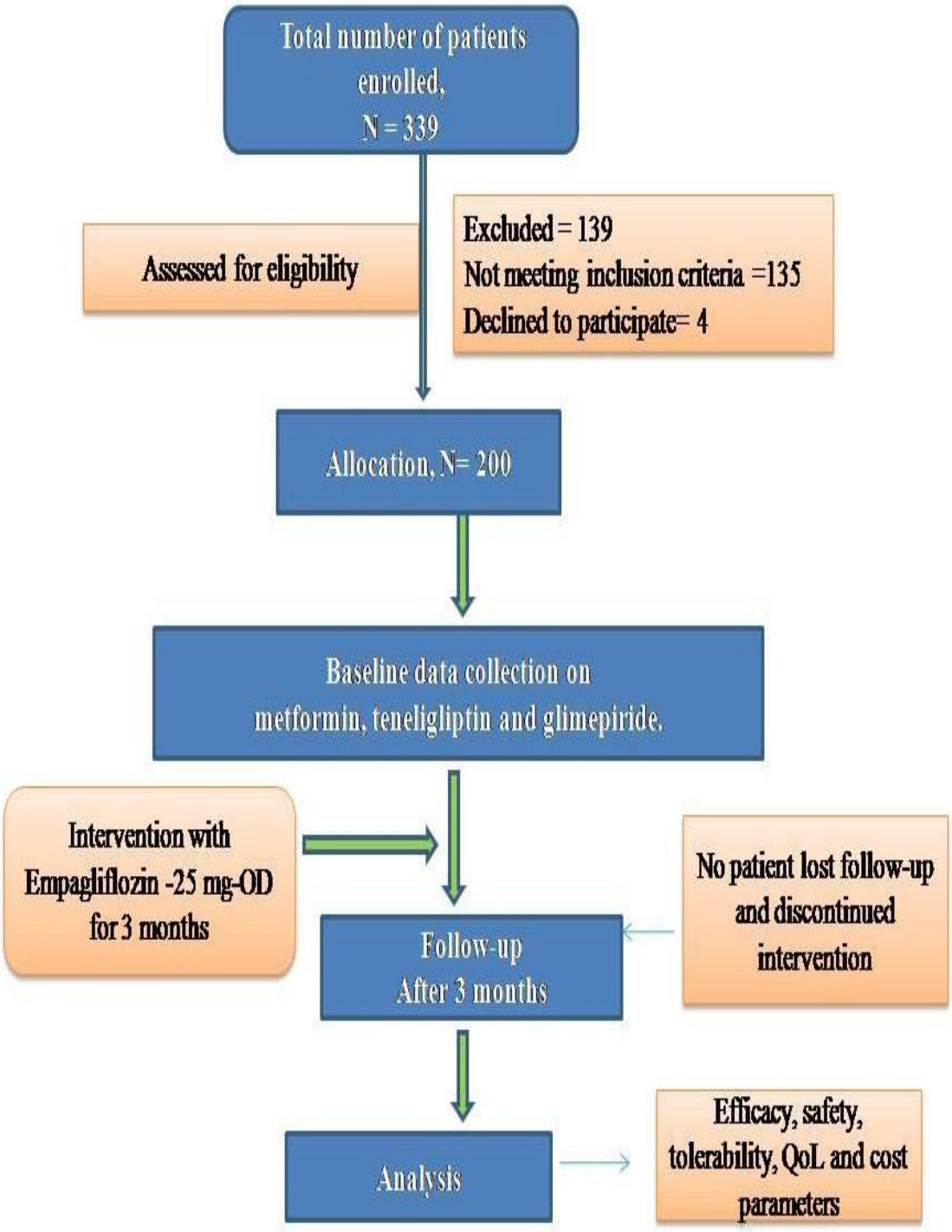

Figure 4. Methodology or study outline.

5.7 Demographic and anthropometric characteristics of the study participants

Relevant demographic and anthropometric information was recorded in the case report form (CRF) at baseline. Unique patient identification number, date of enrollment in study, age, domicile, gender, educational background, monthly income, life style, smoking status, family history, duration of diabetes, height, weight and waist/hip circumference etc. were recorded in CRF. Height was measured barefoot, and weight was measured with the subject dressed in light clothing. Height and weight were computed to the closest 0.1 cm and 0.01 kg. Digital weighing scale (Beurer GmbH, Sofinger Ulm, Germany) was used for weight measurement. With arms rested at the sides, the waist circumference was calculated with a flexible ruler halfway across the inferior costal border and the greatest point of the hip bone above the mid-axillary line. BMI was calculated using formula: Weight/height^2 (kg/m^2). BP and HR were measured using a mercury-free LCD sphygmomanometer (Omron, Japan automatic blood pressure monitor, HEM-7156) and the three readings were taken at 10 min intervals after subjects had been seated for at least 10 min. The average value of the three readings was taken.

5.8 Assessment of efficacy

Effectiveness was assessed by comparing primary as well as secondary end-points at baseline and three-month follow-up following empagliflozin add on. The primary efficacy end-point was the change in HbA1c from baseline to 3 month follow-up. Secondary efficacy end-points included pre and post changes in FBG, PPG, HR, SBP and DBP. Other end-points included the assessment of changes in fasting insulin, fasting C-peptide, homeostasis model assessment of insulin resistance (HOMA-IR), homeostasis model assessment of β -cell function (HOMA- β) and lipid profile.

5.8.1 Primary end-points

5.8.1.1 HbA1c measurement

Blood samples were analyzed for HbA1c measurement. The HPLC Assay Kit was used for measuring HbA1c levels in whole blood. After an 8-hour fast, 4 ml of blood was drawn through venous puncture. In a purple-colored tube, 2 ml blood was extracted for HbA1c measurement, and high performance liquid chromatography (HPLC) was done.

5.8.2 Secondary end-points

5.8.2.1 FBG and PPG

2 ml blood was placed in a grey top (Na fluoride/K oxalate) tube, spun for around 10 minutes at 1100–2000 rpm. Glucose levels were determined using the hexokinase technique for fasting plasma glucose measurement**.** Ortho-toluidine method was used for the evaluation of FBG and PPG (Praful & Darshan, 2003).

5.8.2.2 BP and HR

BP and HR were measured using a mercury-free LCD sphygmomanometer (Omron, Japan automatic blood pressure monitor, HEM-7156) and after individuals had been seated for at least 10 minutes, three readings were obtained at 10-minute intervals. The average result of the three readings was taken.

5.8.3 Other end-points

5.8.3.1 Lipid profile test

All lipids (triglycerides, cholesterol, LDL and HDL) were analyzed by the laboratory at the hospital of SKIMS (clinical biochemistry) using colorimetric technique (Praful & Darshan, 2003). Results were presented in mg/dl.

5.8.3.2 Fasting C-peptide and insulin

Fasting C-peptide concentrations in human serum were analyzed using chemiluminescence immunoassay (Meites, 1986; Gerbitz et al., 1980; Boehm & Lebovitz,

1979; NCCL standards, 1998; Turkington et al., 1982; Sacks, 1994; Kahn & Rosenthal, 1979). Results were presented in ng/ml.

5.8.3.3 HOMA-IR and HOMA-β

HOMA-IR and HOMA-β were determined by the formula: [(fasting glucose in mg/dL)-(fasting insulin)/405] and [(360-fastinginsulin)/(fasting glucose in mg/dL)-63] (Matthews et al., 1985).

5.9 Assessment of safety

Patients were monitored for three months before and after the treatment. Adverse medication responses that occurred during the trial period were documented. During each follow-up, the adverse drug reactions were evaluated to see if they were unchanged, determined, or worsened. A researcher used "Naranjo's method", it is defined as meticulous "causality's evaluation technique" meant for assumed adverse reactions, to examine all suspected adverse drug reactions. This method was formerly used in ADR surveillance investigations (Aurich-Barrera et al., 2011; Bansal et al., 2013; Anderson et al., 2015).

5.9.1 Causality assessment (Naranjo algorithm)

Questions	**Yes**	**No**	**NA**	**Score**
Is there any major prior study on this reactions?	1	Zero	zero	
Were the adverse events caused by the implicated medicine?	2	-1	Zero	

Is the adverse events reduced once the medication is withdrawn or a specified antagonist's is administered?	1	Zero	Zero	
Does the terrible occurrence happen again when the drug was restarted?	2	-1	Zero	
Were there any other conditions that might have caused the reactions'?	-1	2	Zero	
Was the effect recurring after a "placebo" was administered?	-1	1	Zero	
Did this substance identified at hazardous amounts in blood or other body's fluid?	1	Zero	Zero	
Did this response more severe when the dosing was increased or less severe when the dose was decreased?	1	Zero	Zero	
Do the patients already have a similar reaction with the identical or comparable drugs?	1	Zero	Zero	
Was there any factual evidence to back up the negative event?	1	Zero	Zero	
TOTAL				

- **Definite**

  A clinical event or unexpected lab test results connected to the therapy that can't be explained by disease or a concomitant drug. There is typically a favorable recovery to medication withdrawal and recur upon rechallenge. This ADR will be Naranjo rated 9 or above.

- **Probable**

  A clinical event or an aberrant lab result that has a realistic timing period relationship to the administered medicine and is not caused by other medicines or concurrent disease. A withdrawal has a moderately good response. This will be rated 5-8 by Naranjo.

- **Possibile**

  A clinical event or abnormal lab finding that has a credible time course relationship to the medicine but might also be accounted by a concurrent substance or disease. This will receive a 1-4 Naranjo rating.

- **Unrelated**

  There is no logical association (the sequential connection between therapy intake and the onset/course of the negative event is unlikely; or a causal relationship to study treatment is unlikely). Naranjo would give this a 1. ADRs deemed unconnected to treatment will not be considered in the analysis of incidence rates or when analyzing toxicity. All extra adverse drug reactions (i.e. definite, probable, and prospective) will be pooled for assessing toxicity.

5.9.2 Severity assessment (Hartwig's severity assessment scale)

The severity of adverse reactions was determined using Hartwig's Severity Evaluation Score and a previously established approach (Marson et al., 2007; Biton et al., 2001).

Level-1	There was ADRs, but no alterations in treatments with the likely medicine were required.
Level-2	The ADRs required that the implicated drug therapy be “halted, terminated, or altered” in some other way. There were no demands for a cure or any other form of treatment. The average length of stay had not increased.
Level-3	The ADRs required that the implicated drug's therapy be “halted, terminated, or modified in some other way”. In addition/or It was a demand for a cure or other form of treatment. The LOS did not rise.
Level-4	Every Level-3 ADR that adds at least “one day to the LOS”. Otherwise The admission was granted due to the ADRs.
Level-5	Any Levels-4 ADR requiring intensive medical care.
Level-6	The patient suffered irreversible injury as a result of the unfavorable response.
Level-7	The patient died as a result of the bad response, possibly directly or indirectly.

Mild = Levels1 and 2; Moderate =Levels 3 and 4; Severe = Levels 5 -7

Severe: perilous or possibly lethal; Moderate: needing treatment or lengthening the length of hospital admission; Mild: There is no need for therapy, and there is no influence on the length of stay in the hospital.

5.9.3 Preventability assessment (Modified Schumock and Thornton scale)

To examine the preventability of ADR, the "Schumock and Thornton scale" was employed (Schumock and Thornton, 1992). These questions pertain to the

"appropriateness of the medication, the dosing, route, and period of administration, ‘therapy drug monitorings’ and blood amounts (if pertinent), allergies, pharmaceutical interactions, and adherence". Adverse medication responses were classified as certainly avoidable, perhaps preventable, or unpreventable.

Evaluation questions on preventability
Absolutely preventable
Is generally a background of allergies or previous pharmacological reactions?
Did the medicine used unsuitable for the patient's clinical conditions?
Did the dosing, approach, or frequency of management appropriate for the patient's age, heaviness, or state of illness?
Is there documentation of a dangerous blood medication concentration (or laboratory monitoring test)?
Is there a proven medication for Adverse Drug Reactions?
Probably preventable
Did therapy drug monitoring or other necessary laboratory tests omitted?

Be the ADR caused by a medication interaction?
Is low compliance considered ADRs?
Did precautionary measures recommended or provided to the patients?
Not preventable
Whenever any one these above prerequisites are not satisfied,

5.10 Assessment of tolerance

5.10.1 Renal function tests

Diacetylmonoxime method was used to determine serum urea levels. Alkaline-picrate method was used to determine serum creatinine levels and creatinine clearance. Total blood protein levels were measured by Biuret method. Bromocresol green method was used for serum albumin analysis (Praful & Darshan, 2003).

5.10.2 Liver function tests

Analysis of serum bilirubin levels, SGOT, SGPT and alkaline phosphatase was carried out by autoanalyzer (Praful & Darshan, 2003).

5.10.3 Hematological tests

Using sterile disposable syringes, 5 mL of intravenous blood was drawn from

the selected patients in a simple vacuum container. The samples were kept at room temperature for 15-30 minutes before being centrifuged at 2000X for 10 minutes in refrigerated conditions to separate serum and plasma. The plasma was used for complete blood count.

5.11 Impact on QoL

Socio-demographic information was collected from CRF. QOLID was used to compare the quality of health outcomes before and after therapy. It is a collection of 34 questions encompassing eight categories (including role of limitation owing to physical health, financial-concerns, physical-endurance, mental-health, general-health, treatment-satisfaction, symptom-botherness, & food-satisfaction) (Nagpal et al., 2010). Patient responses were gathered via face-to-face interviews at baseline and follow-up, and scores were recorded in the case report form. To assess the internal consistency of the QOLID instrument in the Urdu version, the Cronbach's alpha was calculated using baseline QOLID score data. Cronbach's alpha was found to be 0.89.

5.12 Pharmacoeconomic analysis

Diabetes medication has significant economic ramifications for patients, particularly in developing nations such as India. Only effectiveness may not justify a therapeutic choice for long-term therapy because cost is uniformly substantial. Similarly, an apparently more expensive pharmaceutical or therapy regimen may turn out to be a great choice when efficacy and tolerance are considered. As a result, comprehensive analyses of the cost-effectiveness of combination medicines and add-on medications in the management of T2D with hypertension are crucial.

A few researches have been conducted in other countries to investigate the “cost-effectiveness” on various combination therapies in T2D with hypertension, but to the best of our knowledge and literature searched, no such study has been conducted in Indian patients. The current research was conducted to evaluate the "costeffectiveness" of

additional therapy in the management of T2D patients with hypertension in the north Indian population. The study's goals were (a) to assess the cost-effectiveness of 'empagliflozin' addition treatment to "metformin, glimepride, & teneligliptin" T2D hypertensive patients.

A case report was utilized to collect data on demographics, diabetes history, and anti-diabetic medication information, as well as treatment efficacy metrics and treatment cost. Patients who were registered were followed up on for three months, after which the following data was collected. Patients were reached via phone to get further study-related information.

5.12.1 Treatment cost

The costs of patients' therapy were separated into direct and indirect charges. Direct expenses covered both "direct-medical and direct-non medical cost". Direct and indirect expenditures are clearly quantifiable in economic terms. To capture the cost-related factors, the patients were given a well-designed case report form to fill out. Because the cost of each parameter (medication, tests, meals, and so on) might vary depending on location, point in times, and a participant's monetary state, case report form were employed at given research to ensure consistency in costs computation. (The cost was determined using 1 US dollar and 75.385 INR as of October 13, 2021.)

5.12.2 Direct cost

5.12.2.1 Direct-medical expenses

During the three months follow-up period, direct medical costs were related with medical therapy and comprised the cost of anti-diabetic medication and diagnostic testing. The medications' prices were derived employing the Current Index of Medical Specialties. (CIMS, 2020-21) and total number of doses of medicine used during a three-month time. It is similarly carried out for medications covered by their insurance/ reimbursement plan. The difference in antidiabetic dosage during the research period was also taken into account when evaluating the overall expense of therapies. Hence, results from examinations

undertaken at our institution during the course of the research were computed using the Revised Rates of SKIMS Investigation Charges, SIMS 138/68/2019, dated March 15, 2019. The cost of medication for three months equals to one day multiply by thirty days and then multiply by three (3 months).

5.12.2.2 Direct non-medical costs

Transportation fees are one example of a direct non-medical expenditure (excluding expenses for attendants). Northern trains were used to calculate the patient's route to our hospital in Srinagar (Fares Tables, 2020-2021). Patients were informed how much days they remained for treatment (including stays at relatives' houses) throughout the research period, and lodging expenses were computed using the every day payment offered used for the lowly wage level in the "pay level" of the Seventh Pay Commission's Travelling Allowance Rules, which amounted USD 5.96 (INR 450) per day (Travel Allowance Rules, 2018). Food expenditures were tallied during their journey and stay; if they were not as much as "United States-Dollar-6.680 (Indian Rupees-500)/days", they were deemed actual. If patients indicated it as greater than "United States-Dollar 6.630 (INR 500) per day, "United States-Dollar-6.630 (Indian Rupees-500)/days were regarded minimal compensation paid in meals in the pay matrices.

5.12.3 Indirect-costs

Expense suffered by patients (without the attendant's wages-losses) as a result of lost efficiency or absence as of employment owing to an appointment is referred to as an indirect cost. The patients were advised of their salary loss due to their hospitalization. The cost was computed by using the minimum wage set under the Office of Labours Commission of the Labor Departments (Skill Labour Department Notification, 2017).

- Un-skilled- INR 225, USD 2.98 per day
- Skilled- INR 350, USD 4.64 per day

- Highly skilled- INR 400, USD 5.30 per da
- Administrative/ministerial/account staff- INR 325, USD 4.3 per day

To determine the additional cost per unit of outcome incurred, ICER was utilized. ICER was computed as follows: ICER = (Cost of triple combination medication for three months - Cost of triple combined therapy)/ (Effectiveness of triple combination treatment for three months - Effectiveness of triple combination therapy) (Azimi & Welch, 1998).

5.13 Statistical analysis

Description statistics were used to highlight demographic features. To determine the significance of mean differences, the sample T-test was performed. The improvement in QoL score at follow-up was measured using the Wilcoxon matched-pairs sign ranked tests. Statistical significance was considered when "p was less than 0.05". For all statistical analysis, 'Graph Pad Prism 6' was utilized.

Chapter 6

RESULTS

6.1 Sociodemographic characteristics

For a period of 1 year, 339 patients were enrolled, 139 were excluded for not meeting inclusion criteria and 200 T2D patients with hypertension were recruited. The patients were recruited in October, 2020 and study was compiled in October, 2021. Table 3, represents sociodemographic characteristics of T2D patients. The recruited patients in our investigation were 49.83 years old on average. There were 37.5% men and 62.5% females. The majority of the respondents were graduates or undergraduates, 40%, and 14.5% were illiterate. 96.5% of them were married, 60.5% were from rural regions; and 64% and 36% were from "weaker or middle-income families", respectively. 59.5% individuals had diabetes for 5 years or less, and 24% had a family history of diabetes. 32% had a smoking-history. Also, 36% of patients had a habit of exercising after the onset of diabetes. Angiotensin II receptor blockers (64%) were most used class of antihypertensive agents followed by Calcium channel blockers (19%) and beta blockers (17%). At baseline, mean weight of patients was 76.60 ± 8.191 and at follow-up the weight gets decreased to 74.47 ± 7.787 significantly ($p=0.0081$). Waist circumference, hip circumference (only in male patients), WHR, and WHtR indicate a significant decrease ($p<0.05$). The BMI was reduced, although only little ($p=0.0518$). At baseline, mean waist circumference of female patients was 92.24 ± 4.140 and at follow-up decreased to 87.94 ± 4.138 significantly ($p<0.0001$).

Table 3. Sociodemographic profile and concomitant medication of the study participants

Characteristics	N (%)
Age (year)	
<50	83 (41.5)
50-60	73 (36.5)
>60	44 (22)
Gender	
Male	75 (37.5)
Female	125 (62.5)
Educational status	
Illiterate	29 (14.5)
Primary education	74 (37)
Higher secondary	17 (8.5)
Under Graduation/ Graduation	80 (40)
Smoking history	
Yes	64 (32)
No	136 (68)
Residential status	
Urban	79 (39.5)
Rural	121 (60.5)
Monthly income	
Less than 15000 INR= 202.07 USD	128 (64)
More than 15000 INR= 202.07 USD	72 (36)
Diabetes family history	
Yes	48 (24)
No	152 (76)
Duration of diabetes (year)	
≤ 5	119 (59.5)
6-10	69 (34.5)
11-15	11 (5.5)
>15	1 (0.5)
Habit of exercise after onset of diabetes	
Yes	72 (36)
No	128 (64)
Concurrent hypertension therapy	
Angiotensin-2 receptor antagonist	128 (64)
B-blocker	34 (17)
Ca^{+2} channel inhibitor	38 (19)
Marital status	
Single	2 (0.5)
Married	193 (96.5)
Widow/Divorce	5 (2.5)

Data presented in numbers and percentage.

6.1 Efficacy parameters

Table 4 shows the impact of empagliflozin on efficacy parameters in T2D hypertensive patients after three months of medication.

6.1.1 Primary end point

6.1.1.1 HbA1c

The most important endpoint of efficacy parameters was HbA1c. HbA1c was 9.046 at baseline and reduced significantly to 8.424 after three months of treatment of empagliflozin (Table 4).

6.1.2 Secondary end point

6.1.2.1 FBG and PPG

FBG was decreased from 193.5 ± 42.02 to 151.1 ± 14.49 significantly and PPG was also improved significantly from 253.2 ± 35.71 to 180.2 ± 21.78 (Table 4).

6.1.2.2 SBP, DBP and HR

SBP and DBP was 137.4 and 83.65, it gets decreased significantly after 3 months to 130.9 and 82.09 respectively. The HR was decreased significantly ($p<0.0001$) from 86.29 to 81.40 after 3 months of empagliflozin treatment (Table 4).

6.1.3 Other end points

6.1.3.1 Lipid profile

Table 4 also shows that the lipid parameters (TC, TG, LDL, and VLDL) decreased significantly after three months of follow-up ($p<0.0001$). TC, TG, LDL, and VLDL means

values gets improved from 182.5 ± 15.23, 149.8 ± 11.26, 89.51 ± 11.76, 26.11 ± 2.342 and 42.61 ± 2.007 to 154.8 ± 15.39, 128.3 ± 10.28, 72.76 ± 10.78, 23.07 ± 2.262 and 45.69 ± 2.551.

6.1.3.2 Pancreatic beta cell function

When compared to the baseline, fasting insulin in serum and C-peptide level improved considerably after 3 months ($p<0.0001$). The fasting insulin in serum and C-peptide gets increased from 7.716 ± 1.107 and 1.762 ± 0.3294 to 9.752 ± 1.057 and 3.162 ± 0.7977 respectively. The beta cell homeostasis model assessment (HOMA-β) improved significantly ($p<0.0001$), although insulin resistance (HOMA-IR) improved non-significantly ($p=0.6927$) given in Table 4.

Table 4. Efficacy outcome variables of the study participants at baseline and follow up

Anthropometric measurements			
Variables	**Baseline**	**Follow-up (3 months)**	**P value**
Weight (kg)	76.60 ±8.19	74.47 ± 7.78*	0.0081
BMI (kg/m^2)	30.55 ± 4.45	29.70 ± 4.25ns	0.051
Female			
Waist circumference (cm)	92.24 ± 4.14	87.94 ± 4.13*	<0.0001
Hip circumference (cm)	101.0 ± 5.85	99.53 ± 5.89 ns	0.0542
WHR	0.91 ± 0.04	0.88 ± 0.04*	<0.0001
WHtR	0.60 ± 0.03	0.57 ± 0.02*	<0.0001
Male			
Waist circumference (cm)	103.9 ± 6.27	99.47 ± 6.30*	<0.0001
Hip circumference (cm)	89.70 ± 2.33	88.73 ± 2.38*	0.0129
WHR	1.15 ± 0.07	1.12 ± 0.06*	0.0014
WHtR	0.61 ± 0.04	0.58 ± 0.04*	0.0001
Primary end point			
Variables	**Baseline**	**Follow-up (3 months)**	**P value**
HbA1C (%)	9.046 ± 0.95	8.424 ± 0.88*	<0.0001
Secondary end points			

FBG (mg/dl	193.5 ± 42.02	151.1 ± 14.49*	<0.0001
PPG (mg/dl)	253.2 ± 35.71	180.2 ± 21.78*	<0.0001
Heart Rate (bpm)	86.29 ± 6.84	81.40 ± 4.65*	<0.0001
SBP (mmHg)	137.4 ± 3.60	130.9 ± 3.81*	<0.0001
DBP (mmHg)	83.65 ± 2.76	82.09 ± 2.07*	<0.0001
Other end points			
Variables	**Baseline**	**Follow-up (3 months)**	**P value**
Fasting Insulin (mIU/L)	7.71 ± 1.10	9.752 ± 1.05*	<0.0001
Fasting C-peptide (ng/mL)	1.76 ± 0.32	3.162 ± 0.79*	<0.0001
HOMA-IR	3.67 ± 0.88	3.641 ± 0.54 ns	0.6927
HOMA-β	23.35 ± 7.50	40.83 ±7.44*	<0.0001
Total cholesterol (mg/dl)	182.5 ± 15.23	154.8 ± 15.39*	<0.0001
Triglycerides (mg/dl)	149.8 ± 11.26	128.3 ± 10.28*	<0.0001
LDL (mg/dl)	89.51 ± 11.76	72.76 ± 10.78*	<0.0001
VLDL (mg/dl)	26.11 ± 2.34	23.07 ± 2.26*	<0.0001
HDL (mg/dl)	42.61 ± 2.07	45.69 ± 2.55*	<0.0001

The sample T test was used, and "$p<0.05$ is deemed significant"; "significant and non-significant values" are represented by "*" and "ns," respectively.

The data is displayed as mean and standard deviation. WHR denotes for waist hip ratio; and WHtR refers as waist height ratio. BMI is for body mass index; SBP is for systolic blood pressure; DBP indicates meaning of diastolic blood pressure; FBG represents for fasting blood glucose; PPG is for postprandial blood glucose; and HbA1c refers to glycated haemoglobin.

HOMA-IR stands for Insulin resistance homeostasis model assessment; Homeostasis model evaluation of beta cell function is denoted by (HOMA-β); VLDL refers to very low density lipoprotein; LDL represents meaning of low density lipoprotein; and HDL indicates with high density lipoprotein.

6.2 Tolerance parameters

Table 5, represents the impact of empagliflozin on tolerance parameters in T2D with comorbid hypertension after 3 months of treatment with empagliflozin (where $p<0.05$ is significant). It also shows the changes in tolerance parameters after follow-up.

6.2.1 Kidney function tests

The most important parameter in kidney function test was creatinine and eGFR. Their mean values were at baseline and follow up were changed slightly from 0.72 ± 0.07, 97.92 ± 16.01 to 0.73 ± 0.06, 95.90 ± 15.05 respectively. After three months, there was no statistical significant difference in creatinine (p=0.1157) or eGFR (p=0.1940). The significant decrease was observed in serum urea from 32.29 ± 4.630 to 27.44 ± 4.727 after 3 months of treatment with empagliflozin.

6.2.2 Liver function tests

The most important parameter in liver function test was serum bilirubin, AST, ALT, Alkaline phosphate and total serum proteins. The mean values of serum bilirubin, AST, ALT, Alkaline phosphate and total serum proteins were decreased from 0.6949 ± 0.1559, 30.99 ± 5.530, 33.14 ± 5.464, 93.98 ± 10.94 and 5.791 ±0.5679 to 0.5474 ± 0.1351, 27.57 ± 4.496, 28.48 ± 3.841, 80.50 ± 9.654 and 5.182 ± 0.5805 respectively. The statistically significant differences were observed after the 3 months of treatment with empagliflozin.

6.2.3 Complete blood count

In complete blood count, the mean values of WBC (10^9/L), RBC (10^{12}/L), platelets (10^9/L) and haemoglobin (g/dl) were observed at baseline was 5.075 ± 0.6499, 4.571 ±

0.3102, 221.8 ± 45.96 and 12.43 ± 0.7527 and after follow up after 3 months of treatment the mean values were 5.069 ± 0.6283, 4.849 ± 0.3308, 240.1 ± 43.86 and 12.58 ± 0.7832. RBC and platelets were increased; also significant difference was also observed ($p < 0.0001$). But in WBC, the value decreased slightly but not significantly ($p=0.9302$). In

hemoglobin levels, after 3 months of follow-up significant difference were observed (p=0.0464).

Table 5. Tolerance parameters at baseline and follow up

Kidney function test			
Variables	**Baseline**	**Follow-up (3 months)**	**P value**
Serum urea (mg/dl)	32.29 ± 4.63	27.44 ± 4.72*	<0.0001
Serum creatinine (mg/dl)	0.7220 ± 0.07	0.7336 ± 0.06 ns	0.1157
eGFR (ml/min/1.73m^2)	97.92 ± 16.01	95.90 ± 15.05 ns	0.1940
Liver function test			
Variables	**Baseline**	**Follow-up (3 months)**	**P value**
Total serum bilirubin (mg/dl),	0.6949 ± 0.15	0.5474 ± 0.13*	< 0.0001
AST (IU/L)	30.99 ± 5.53	27.57 ± 4.49*	<0.0001
ALT (IU/L)	33.14 ± 5.46	28.48 ± 3.84*	<0.0001
Alkaline phosphatase (IU/L)	93.98 ± 10.94	80.50 ± 9.65*	<0.0001
Total serum proteins (g/dl)	5.791 ± 0.56	5.182 ± 0.58*	<0.0001
Complete blood count			
Variables	**Baseline**	**Follow-up (3 months)**	**P value**
WBC (10^9/L)	5.075 ± 0.64	5.069 ± 0.62ns	0.9302
RBC (10^{12}/L)	4.571 ± 0.31	4.849 ± 0.33*	<0.0001
Platelets (10^9/L)	221.8 ± 45.96	240.1 ± 43.86*	<0.0001

Haemoglobin (g/dl)	12.43 ± 0.75	12.58 ± 0.78*	0.0464

The sample T test was used, and p0.05 is deemed significant; significant and nonsignificant are represented by "*" and "ns," respectively. The data were presented as mean and standard deviation. eGFR stands for glomerular filtration rate; ALT stands for Alanine aminotransaminase; AST stands for Aspartate aminotransaminase; ALP stands for Alkaline phosphatase; WBC stands for white blood cells; RBC stands for red blood cells.

6.3 Assessment of safety profile

The influence of empagliflozin on the safety profile in T2D hypertensive patients after three months is shown in Table 6.

Patients were monitored for the incidence of suspected adverse events following empagliflozin add-on therapy. The reported adverse events were genital infection in two patients, but they continued the study. After a week, they recovered from genital infection. No hypoglycaemia, weight gain, tremors, palpitation and keto acidosis were observed. When major cardiovascular events were assessed, no patients were observed with myocardial or cerebral infarction. No patient died during the study. No patient left the study.

Table 6. Suspected adverse events following empagliflozin add-on therapy

Adverse event	**Baseline**	**Follow up (after 3 months)**
Hypoglycemia	0	0
Weight gain	0	0
Genital infection	0	2
Keto acidosis	0	0
Myocardial infarction	0	0
Cerebral infarction	0	0
Death	0	0

Data were shown as numbers.

6.3.1 Assessment of observed adverse events

Evaluation of two patients' adverse medication responses for 'causality, severity, and preventability' is as follows:

6.3.1.1 Causality assessment

Naranjo scale was used to assess the causality of adverse drug reaction (ADR).

Naranjo algorithm

	Questions	**Yes**	**No**	**NA**	**Score**
1.	Is there any major prior study on this reaction?	1	Zero	Zero	1
2.	Were the adverse events caused by the implicated medicine?	2	-1	Zero	2
3.	Is the adverse event reduced once the medication is withdrawn or a specified antagonist is administered?	1	Zero	Zero	1
4.	Does the terrible occurrence happen again when the drug was restarted?	2	-1	Zero	-1
5.	Were there any other conditions that might have caused the reactions?	-1	2	Zero	0
6.	Was the effect recurring after a "placebo" was administered?	-1	1	Zero	0
7.	Did this substance identified at hazardous amounts in blood or other body's fluid?	1	Zero	Zero	0
8.	Did this response more severe when the dosing was increased or less severe when the dose was decreased?	1	Zero	Zero	0
9.	Do the patients already have a similar reaction with the identical or comparable drugs?	1	Zero	Zero	1

10	Was there any factual evidence to back up the negative event?	1	Zero	Zero	1
	TOTAL				5

- **Definite**
  - A clinical event or unexpected lab test results connected to the therapy that can't be explained by disease or a concomitant drug. There is typically a favorable recovery to medication withdrawal and recur upon rechallenge. This ADR will be rated 9 or above.
- **Probable**
  - A clinical event or an aberrant lab result that has a realistic timing period relationship to the administered medicine and is not caused by other medicines or concurrent disease. A withdrawal has a moderately good response. This will be rated 5-8.
- **Possibility**
  - A clinical event or abnormal lab finding that has a credible time course relationship to the medicine but might also be accounted by a concurrent substance or disease. This will receive a 1-4 Naranjo rating.
- **Unrelated**
  - There is no logical association (i.e, the sequential connection between therapy intake and the onset/course of the negative event is unlikely; or a causal relationship to study treatment is unlikely). Naranjo rating will be 1. ADRs unrelated to treatment will not be considered in the analysis of incidence rates or when analyzing toxicity. All extra adverse drug reactions (i.e. definite, probable, and prospective) will be pooled for assessing toxicity.

6.3.1.2 Severity assessment

The severity of adverse reactions was determined using Hartwig's Severity Evaluation Score and a previously established approach (Marson et al., 2007; Biton et al., 2001).

The Hartwig Severity Level

Level-1	There were ADRs, but no alterations in treatments with the likely medicine were required.
Level-2	The ADRs required that the implicated drug therapy be halted, terminated, or altered in some other way. There were no demands for a cure or any other form of treatment. The average length of stay had not increased.
Level-3	The ADRs required that the implicated drug's therapy be halted, terminated, or modified in some other way. In addition/or It was a demand for a cure or other form of treatment. The LOS did not rise.
Level-4	Every Level-3 ADR that adds at least one day to the LOS. Otherwise The admission was granted due to the ADRs.
Level-5	Any Levels-4 ADR requiring intensive medical care.
Level-6	The patient suffered irreversible injury as a result of the unfavorable response.

Level-7	The patient died as a result of the bad response, possibly directly or indirectly.

Mild = Level 1-2; Moderate = Level 3-4; Severe = Level 5-7 [Severe: perilous or possibly lethal; Moderate: needing treatment or lengthening the length of hospital admission; Mild: There is no need for therapy, and there is no influence on the length of stay in the hospital]

Severity of adverse drug reactions was found to be moderate.

6.3.1.3 Preventability assessment

To examine the preventability of ADR, Schumock and Thornton scale was employed (Schumock and Thornton, 1992). These questions pertain to the appropriateness of the medication, the dosing, and route, period of administration, clinical drug monitoring (TDM), blood amounts (if pertinent), allergies, pharmaceutical interactions, and adherence. Adverse medication responses were classified as certainly avoidable, perhaps preventable, or unpreventable.

Schumock and Thornton Modified Scale

Evaluation questions on preventability
Absolutely preventable
Is generally a background of allergies or previous pharmacological reactions?
Did the medicine used unsuitable for the patient's clinical conditions?
Did the dosing, approach, or frequency of management appropriate for the patient's age, heaviness, or state of illness?

Is there documentation of a dangerous blood medication concentration (or laboratory monitoring test)?
Is there a proven medication for Adverse Drug Reactions?
Probably preventable
Did therapy drug monitoring or other necessary laboratory tests omitted?
Be the ADR caused by a medication interaction?
Is low compliance considered ADRs?
Did precautionary measures recommended or provided to the patients?
Not preventable
Whenever any one these above prerequisites are not satisfied.

As there is a known medication for adverse drug reaction which was observed in this study, reported adverse reactions were considered definitely preventable**.**

6.4 QoL parameters

Table 7 represents the impact of empagliflozin on safety parameters in T2D hypertensive patients after three months therapy with empagliflozin where $p<0.05$ is significant. QoL analysis showed improvement as compared to the baseline. Follow-up QoL data revealed significant differences in different QoL parameters i.e. symptom botherness (SB), role of limitations due to physical health (RL), physical endurance (PE), general health (GH), financial worries (FW), emotional health (EH), and diet satisfaction between baseline and followup data scores. Overall, scores were also found to be significantly improved in follow up (empagliflozin as an add-on therapy).

Table 7. Change in QoL scores in baseline and follow-up during treatment

Domains	**Items**	**Baseline (Mean ± SD)**	**Follow-up (Mean ± SD)**	**P value**	**Minimum**	**Maximum**
RL	6	14.27 ± 2.81	20.95 ± 1.39*	<0.0001	6	30
PE	6	11.64 ± 5.75	19.29 ± 2.11*	<0.0001	6	30
GH	3	6.74 ± 1.07	10.53 ± 1.62*	<0.0001	3	15
TS	4	10.28 ± 0.76	17.09 ± 0.99*	<0.0001	4	20
SB	3	7.805 ± 1.01	12.29 ± 0.95*	<0.0001	3	15
FW	4	10.90 ± 0.99	11.60 ± 1.43*	<0.0001	4	19

EH	5	14.54 ± 1.86	19.18 ± 1.99*	<0.0001	5	25
DS	3	8.63 ± 1.49	9.780 ± 1.67*	<0.0001	3	15

The data were presented in the form of Mean ± SD. The improvement in QoL score at follow-up was measured using the Wilcoxon matched-pairs sign ranked tests. P<0.05 was regarded as significant. Significant and non-significant are represented by "*" and "ns," respectively. Scores in the role of limitation in physical health and physical endurance domain ranged from 6 to 30. The score was 3-15 in the overall health category and 4-20 in the treatment satisfaction domain. The ranges for symptom botherness, financial concerns, emotional/mental health, and diet satisfaction were 3-15, 4-19, 5-25, and 3-15, respectively.

6.4.1 Comparison of independent variables with QOLID parameters

As summarized in Table 8, statistically significant differences were observed at the end of the study:

- Smoking history versus RL (P = 0.0038), PE (P = 0.0057), GH (P = 0.0030), TS (P= 0.0095), EH (P = 0.0095), and DS (P = 0.0464).
- Exercise versus RL (p = 0.0038), PE (P < 0.0001), GH (P < 0 .0001), TS (P < 0 .0001), SB (P < 0.0001), FW (P = 0.0016), EH (P < 0.0001) and DS (P < 0.0001).
- Monthly income versus RL (P < 0.0001), PE (P < 0.0001), GH (P < 0 .0001), T S (P < 0 .0001), S B (P < 0.0001), FW (P = 0.0022), EH (P < 0.0001), and DS (P < 0.0001).
- Age versus RL (P = 0.0038), PE (P < 0 .0001), GH (P < 0 .0001), TS (P < 0 .0001), SB (P < 0.0001), EH (P < 0.0001), and DS (P < 0 .0001). Body mass index (BMI) versus FW (P = 0.0068) (Table 9).
- Educational status versus RL (P = 0.0038), PE (P < 0.0001), GH (P < 0.0001), TS (P < 0.0001), SB (P < 0.0001), EH (P < 0.0001), and DS (P < 0.0001).

- Duration of diabetes versus RL ($P < 0.0001$), PE ($P < 0.0001$), GH ($P = 0.0001$), TS ($P < 0.0001$), SB ($P = 0.0031$), FW ($P = 0.0424$), EH ($P < 0.0001$), and DS ($P = 0.0001$).

Table 8. Comparison of independent variables with QOLID parameters.

Parameters/ variables	N	RL	PH	GH	TS	SB	FW	EH	DS
Gender									
Male	75	93.20	94.02	92.48	95.33	98.67	102.7	95.33	110.5
Female	12	104.9	104.4	105.3	103.6	101.6	99.16	103.6	94.49
P*	5	0.1490	0.20	0.10	0.30	0.76	0.65	0.30	0.05
Residential status									
Urban	79	99.80	103.3	95.60	101.7	98.03	92.89	101.7	99.65
Rural	12	101.0	98.70	103.7	99.72	102.1	105.5	99.72	101.1
P*	1	0.88	0.57	0.29	0.88	0.65	0.11	0.88	0.85
Family history									
Yes	48	108.7	108.6	105.1	108.5	106.8	94.99	108.5	93.96
No	15	97.90	97.95	99.05	97.97	98.50	102.2	97.97	102.6
P*	2	0.23	0.25	0.50	0.24	0.30	0.42	0.24	0.34
Smoking history									
Yes	64	84.05	84.70	84.05	86.63	92.25	110.7	86.63	112.1
No	13	108.2	107.9	108.2	107.0	104.4	95.70	107.0	95.05
P*	6	0.003*	0.005*	0.003*	0.009*	0.11	0.07	0.009*	0.04*

Exercise Yes No P*	72 12 8	135.3 80.93 < 0.0001*	136.9 80.01 <0.0001*	132.3 82.62 <0.0001*	130.7 83.50 <0.0001*	120.7 89.13 <0.0001*	84.17 109.7 0.001*	130.7 83.50 < 0.0001*	72.03 116.5 < 0.0001*
Monthly income >15000=1 <15000=2	71 12 9	135.6 81.16 < 0.0001*	137.1 80.34 < 0.0001*	132.7 82.79 <0.0001*	130.5 83.98 <0.0001*	120.5 89.49 < 0.0001*	84.42 109.3 0.002*	130.5 83.98 < 0.0001*	72.20 116.1 < 0.0001*

A p value less than 0.05 "Mann-Whitney U-test" is deemed significant. The symbol "" stands for significant.

Table 9. Comparison of independent variables with QOLID parameters (Mean rank).

Independent variables	**n**	**RL**	**PH**	**GH**	**TS**	**SB**	**FW**	**EH**	**DS**
Age (years)									
<50	97	127.3	129.7	126.5	126.4	118.5	90.79	126.4	78.01
50-60	75	73.20	72.09	74.97	72.67	81.33	109.8	72.67	127.4
>60	28	80.91	75.43	78.98	85.29	89.57	109.2	85.29	106.3
P*		**<0.0001***	**<0.0001***	**<0.0001***	**<0.0001***	**<0.0001***	0.0549	**<0.0001***	**<0.0001***
BMI									
UW (<18.5)	2	84.50	70.75	103.5	96.75	86.75	146.5	96.75	122.5
N (18.5-23)	8	68.38	61.13	69.38	71.63	86.75	157.1	71.63	138.5
OW (>23.5)	19	102.5	103.0	102.3	102.3	101.7	98.17	102.3	99.20
P*	1	0.2148	0.0871	0.2482	0.2372	0.6326	**0.0068***	0.2372	0.1393
Education status									
Illiterate									
Primary	29	78.81	138.6	77.41	83.93	87.72	107.7	83.93	104.7
Middle	74	73.92	59.69	75.53	73.03	81.95	110.4	73.03	128.3
Undergraduate	17	126.6	113.1	128.6	146.0	136.0	99.74	146.0	111.2
P*	80	127.4	121.8	126.0	122.3	114.8	88.89	122.3	70.94
		<0.0001*	**<0.0001***	**<0.0001***	**<0.0001***	**<0.0001***	0.0941	**< 0.0001***	**< 0.0001***

Marital status Single Married Widow/divorced P*	 2 19 3 5	 175.5 100.3 76.60 0.0996	 178.0 100.3 77.50 0.0941	 172.0 99.67 104.1 0.1720	 146.0 100.4 86.00 0.3528	 136.0 100.8 76.00 0.3004	 66.50 102.0 57.40 0.1402	 146.0 100.4 86.00 0.3528	 19.50 101.9 77.10 0.0796
Duration of diabetes 1-5 6-10 10-20 P*	 11 9 69 12	 114.7 81.54 68.50 **<0.0001***	 117.1 78.90 59.75 **<0.0001***	 113.5 84.53 63.29 **0.0001***	 114.1 80.78 79.33 **< 0.0001***	 109.1 91.07 69.33 **0.0031***	 93.39 107.8 128.8 **0.0424***	 114.1 80.78 79.33 **< 0.0001***	 86.52 121.4 118.8 **0.0001***

*p<0.05 is considered significant by the Kruskal-Walis test. Significant is represented by the symbol *.

Table 10 shows the mean values and the standard deviation for each domain. It shows the comparison of independent variables (Family history, BMI, Education status, Marital status, Monthly income, Gender, Duration of diabetes, Exercise, Age (years) and smoking history with various domains (Mean rank) at end of treatment.

Table 10. Mean QoL score and standard deviation of independent parameters in different domains.

Independent parameters	N	RL	PH	GH	TS	SB	FW	EH	DS
Family history									
Yes	48	21.15 ± 1.38	19.56 ± 2.22	10.65 ± 1.65	17.25 ± 0.97	12.42 ± 0.91	11.48 ± 0.39	19.50 ± 1.95	9.58 ± 1.77
No	152	20.88 ± 1.40	19.20 ± 2.08	10.49 ± 1.61	17.04 ± 1.00	12.25 ± 0.97	11.64 ± 0 .44	19.08 ± 2.00	9.84 ± 1.64
BMI									
UW (<18.5)	2	20.50 ± 0.70	18.00 ± 1.41	11.00 ± 2.82	17.00 ± 1.41	12.00 ± 1.41	12.50 ± 0.70	19.00 ± 2.82	10.50 ± 2.12
N (18.5-23)	8	20.13 ± 0.83	17.88 ± 0.83	9.750 ± 1.38	16.50 ± 0.92	12.00 ± 1.06	12.88 ± 0.83	18.00 ± 1.85	10.88 ± 1.12
OW (>23.5)	191	20.98 ± 1.41	19.35 ± 2.13	10.54 ± 1.62	17.11 ± 0.99	12.30 ± 0.95	11.54 ± 1.42	19.22 ± 1.99	9.723 ± 1.68
Education status									
Illiterate	29	20.41 ± 1.18	20.41 ±1.18	9.82 ±1.19	16.76 ±0.98	12.03 ±1.01	11.79 ±1.37	18.52 ±1.97	10.07 ± .92
Primary	74	20.24 ± 1.04	18.24 ±1.18	9.81 ±1.21	16.54 ± 0.89	11.92 ±1.00	11.86 ±1.35	18.08 ±1.78	10.64 ±1.18
Middle	17	21.47 ±0.87	19.47 ±1.328	11.06 ±1.478	18.00 ± 0.0	13.00 ± 0.0	11.47 ±1.73	21.00 ±0.0	10.12 ±1.69

Undergraduate	80	21.68 ±1.44	20.55 ±2.41	11.33 ±1.71	17.53 ± 0.85	12.58 ± .8233	11.31 ±1.42	20.05 ±1.71	8.813 ±1.79
Marital status									
Single	2	23.00 ± 0.0	23.00 ± 0.0	13.00 ± 0.0	18.00 ± 0.0	13.00 ± 0.0	11.00 ± 0.0	21.00 ± 0.0	7.000 ± 0.0
Married	193	20.94 ± 1.38	19.27 ± 2.11	10.50± 1.61	17.09 ± 0.99	12.30 ± 0.95	11.63 ± 1.44	19.18 ± 1.99	9.819 ± 1.67
Widow/divorced	5	20.40 ± 1.67	18.20 ± 0.83	10.40 ± 1.51	16.80 ± 1.09	11.80 ± 1.09	10.80 ± 0.44	18.60 ± 2.19	9.400 ± 0.89
Monthly income									
>15000=1	71	21.87 ± 1.29	20.77 ± 2.34	11.55 ± 1.68	17.69 ± 0.72	12.69 ± 0.72	11.18 ± 1.33	20.38 ± 1.45	8.817 ± 1.90
<15000=2	129	20.43 ± 1.17	18.47 ± 1.43	9.961 ± 1.27	16.76 ± 0.97	12.07 ± 1.00	11.83 ± 1.43	18.52 ± 1.94	10.31 ± 1.26
Gender									
Male	75	20.76 ± 1.36	19.05 ± 2.02	10.32 ± 1.57	10.32 ± 0.18	12.25 ± 0.97	11.55 ± 1.62	18.97 ± 2.01	10.09 ± 1.54
Female	125	21.06 ± 1.41	19.42 ± 2.16	10.65 ± 1.64	10.65 ± 0.14	12.31 ± 0.95	11.63 ± 1.31	19.30 ± 1.98	9.592 ± 1.73
Duration of diabetes									
1-5	119	21.31 ± 1.44	19.89 ± 2.26	10.90 ± 1.68	17.36 ± 0.93	12.46 ± 0.89	11.42 ± 1.40	19.72 ± 1.87	9.32 ± 1.80

6-10	69	20.45 ± 1.19	18.49 ± 1.55	10.07 ± 1.42	16.70 ± 0.95	12.10 ± 1.00	11.80 ± 1.49	18.39 ± 1.91	10.45 ± 1.20
10-20	12	20.17 ± 0.71	17.83 ± 0.93	9.417 ± 0.51	16.67 ± 0.98	11.67 ± 0.98	12.25 ± 1.05	18.33 ± 1.96	10.42 ±1.16
Exercise									
Yes	72	21.86 ± 1.29	20.75 ± 2.336	11.53 ± 1.68	17.69 ± 0.72	12.69 ± 0.72	11.18 ± 1.32	20.39 ± 1.44	8.819 ± 1.88
No	128	20.43 ± 1.17	18.46 ± 1.436	9.961 ± 1.28	16.75 ± 0.97	12.06 ± 1.0	11.84 ± 1.44	18.50 ± 1.94	10.32 ± 1.26
Age (years)									
<50	97	21.64 ± 1.36	20.36 ± 2.29	11.28 ± 1.67	17.61 ± 0.79	12.65 ± 0.76	11.34 ± 1.47	20.22 ± 1.59	9.041 ± 1.83
50-60	75	20.23 ± 1.04	18.24 ± 1.17	9.800 ± 1.20	16.53 ± 0.89	11.91 ± 1.00	11.85 ± 1.35	18.07 ± 1.78	10.61 ± 1.1
>60	28	20.46 ± 1.17	18.36 ± 1.54	9.857 ± 1.20	16.79 ± 0.99	12.07 ± 1.01	11.82 ± 1.38	18.57 ± 1.98	10.11 ± 0.91
Smoking history									
Yes	64	20.53 ± 1.28	18.75 ± 1.86	10.09 ± 1.47	16.81 ± 0.99	12.13 ± 1.00	11.78 ± 1.49	18.63 ± 1.98	10.16 ± 1.42
No	136	21.14 ± 1.41	19.54 ± 2.18	10.73 ± 1.65	17.22 ± 0.97	12.37 ± 0.93	11.51 ± 1.39	19.44 ± 1.95	9.603 ± 1.76

Data were presented as mean and SD. The range of score in RL and PE domain was 6-30. In GH domain the range was 3-15, whereas, in TS domain the range was 4-20. In SB, FW, EH and DS domain the range was 3-15, 4-19, 5-25 and 3-15 respectively. P value <0.05 was considered as significant.

Table 11: Change in QoL scores: baseline and follow-up.

Domains	**Items[a]**	**Baseline (Mean score)**	**Follow-up (Mean score)**	**P value**	**Minimum**	**Maximum**
Total QOLID score	**34**	84.81 ± 9.593	120.7 ± 6.815	< 0.0001	**34**	**169**

The data were presented in the form of mean±SD. To quantify the improvements in QoL score at follow-up, the "Wilcoxan matched-pairs signed ranked tests" was utilized. *P<0.05 was considered significant. The assessment was done by QOLID scale. The patients were asked to evaluate their perception. The patient's perception was evaluated on baseline and followup (after 3 months of empagliflozin as an add-on therapy).

6.5 Pharmacoeconomics analysis

Table 12 represents the impact of empagliflozin addition on cost-incurred in T2D hypertensive patients ($p<0.05$ is significant). The direct medical cost after empagliflozin addition to the standard antidiabetics [Metformin (2g/day), Teneligliptin (20 mg/day), and Glimepiride (8 mg/day)] was high [USD 68.05 (difference 106.61-38.56)]. Among the various components, expenditures for adverse drug management were not reported. Despite the fact that these components were incorporated in the computation of direct medical costs, the direct medical costs were exclusively determined by the cost of drugs.

Table 12. Cost incurred after empagliflozin addition.

Characteristics	**Triple therapy**	**Empagliflozin add-on to Triple therapy**	**#Difference in cost**
Direct Medical Cost • Cost of Medicines • Cost of Investigations	 38.56 2.52	 106.61 2.52	68.05
Direct non medical Cost • Transportation and Cost of Food	6.63	6.63	
Indirect Cost	5.3	5.3	
Total cost of treatments (Direct medical + Direct non-medical + Indirect)	53.01	121.06	68.05

#additional cost for empagliflozin to improve the parameter as an add-on therapy to standard diabetes therapy

6.6 Incremental cost-effectiveness ratio (ICER)

Table 13 represents the impact of empagliflozin addition on ICER in T2D hypertensive patients. Additional cost per unit improvement in QOLID score with empagliflozin add-on was USD 1.89 as compared to conventional triple combination.

Table 13. Assessment of ICER.

Parameters	**Baseline (Conventional triple combination for last 3 months)**	**Follow-up (After 3 months of empagliflozin 25 mg-OD add-on)**	**Difference**	**ICER**
Overall cost of treatment	53.01 USD (INR 3996.1)	121.06 USD (INR 9126.1)	68.05 USD (INR 5129.9)	
Change in QOLID mean score	84.81	120.7	35.89	1.89[#]
HbA1c	9.046	8.424	0.6220	109.40[#]
FBG	193.5	151.1	42.38	1.60[#]
PPG	253.2	180.2	73.00	0.93[#]
SBP	137.4	130.9	6.470	10.51[#]
DBP	83.65	82.09	1.560	43.62[#]

[#]when compared to conventional antidiabetics or standard therapy, empagliflozin has an additional cost per unit improvement.

Chapter 7

DISCUSSION

Empagliflozin is a competitive SGLT2i that reduces hyperglycemia in T2D patients by lowering renal glucose reabsorption and increasing urinary excretion of glucose. It provides a substantial improvement in HbA1c levels whether used alone or in combination with metformin and possesses a favorable safety profile. Its efficacy and safety as an add-on drug in T2D patients demonstrating inadequate glycemic control to triple therapy (Glimepiride + Metformin + Teneligliptin) in diabetic patients has been investigated. It was found effective and safe in T2D patients who showed inadequate glycemic control with triple-drug treatment. Other studies have reported that Empagliflozin reduces the risk of death and hospitalization in patients suffering from cardiovascular disease, heart failure, low ejection fraction or T2D (Zinman et al., 2015; Aronow & Shamliyan, 2017). It also causes moderate reductions in blood pressure and body weight. It has been reported that Empagliflozin effectively lowered blood pressure in people with T2D and hypertension. However, there is a dearth of data regarding the effectiveness and safety of empagliflozin as an add-on to triple drug treatment (glimepiride, metformin and teneligliptin) in patients having uncontrolled T2D along with hypertension. Thus the present study was conducted to evaluate the efficacy and safety of addition of Empagliflozin in T2D patients who do not respond to triple therapy and develop hypertension as comorbidity.

Over the last decade, T2D care has become more patient-oriented. After three months of therapy, weight, waist circumference, hip circumference (only male patients), WHR, and WHtR showed a substantial reduction ($p<0.0001$). BMI was decreased but not significantly ($p=0.0518$). Findings of the present study indicate that Empagliflozin add-on therapy substantially reduces weight and adiposity indices. HOMA-beta improved considerably whereas HOMA-IR improvement was not significant. Fasting serum insulin and C-peptide enhanced substantially after three months as compared to the baseline. Lipid profile parameters like TC, TG, LDL, and VLDL were significantly improved after three months of follow-up ($p< 0.0001$). HDL levels increased significantly after three-month follow-up when compared with the

baseline.

This prospective observational cohort study confirmed that addition of Empagliflozin to triple drug combination (metformin, teneligliptin and glimepiride) significantly decreased FBG, PPG, HbA1c, SBP, DBP and pulse rate in T2D patients having comorbid hypertension after three months. Earlier Sone et al. have reported enhanced glycemic management with Empagliflozin addition to insulin treatment in Japanese patients with insufficiently controlled T2D (Sone et al., 2020). In another study, Ozcelik et al. have reported improvement in glycemic control after Empagliflozin addition to metformin and gliclazide in T2D patients (Ozcelik et al., 2019). Results of both the studies were consistent with the present study.

The coexistence of T2D with hypertension results in arteriosclerosis-related macrovascular diseases. Reduction in blood pressure in people with diabetes reduces the risk of stroke. Present study observed a considerable change in SBP, DBP and HR ($p<0.0001$) with Empagliflozin addition to triple drug combination after three months. Results were consistent with earlier studies which showed a significant reduction in SBP with Empagliflozin (Chilton et al., 2015). Empagliflozin add-on to triple therapy showed good efficacy in T2D patients with comorbid hypertension.

Empagliflozin has showed potential for lowering HbA1c% even in T2D patients with second- or third-stage chronic renal disease. EMPA-REG OUTCOME® study has linked empagliflozin to lower rates of clinically relevant kidney outcomes as well as a slower decline in the eGFR (Barnett et al., 2014). Kadawoki *et al*. reported that Empagliflozin improved renal outcomes, decreased eGFR decline, and reduced albuminuria when compared to placebo (Kadowaki et al., 2019). Current study showed a slight decrease in eGFR, but a significant difference was not observed.

Empagliflozin has been reported to raise the risk of hypoglycemia, vaginal infection, and urinary tract infection when taken either as monotherapy or as add-on

therapy (MacIsaac et al., 2016). In the present investigation, two cases of genital infection were observed as adverse reactions. A slight increase in Hb was observed after three months of follow-up, with a significant difference of ($p=0.0464$). The present study observations are in line with earlier reports which suggested that Hb and hematocrit were increased by Empagliflozin (Budzianowski et al., 2021).

Preclinical studies showed that SGLT-2i can ameliorate fatty liver by lowering lipid synthesis, increasing insulin resistance and reducing endoplasmic reticulum stress (Petito-da-silva et al., 2019). Insulin resistance is the most common pathogenic condition in individuals with nonalcoholic fatty liver disease (NAFLD) (Marchesini et al., 1999). High insulin levels increase lipogenesis, resulting in liver steatosis. SGLT-2 inhibitors decrease blood glucose levels thereby improving hyperinsulinemia as well as insulin resistance (Qiang et al., 2015) and reduce hepatic lipogenesis. Other responsible mediators contributing to NAFLD development include oxidative stress, mitochondrial dysfunction, and endoplasmic reticulum homeostasis. SGLT-2i have been reported to directly increase DPP peptidase-4 expression in the liver (Aso et al., 2019), decrease plasma PGF21, and improve mitochondrial activity as well as endoplasmic reticulum stress in the hepatic tissue (Aso et al., 2019; Jiang et al., 2014; Koliaki et al., 2015). This prospective research demonstrated that Empagliflozin add-on therapy significantly reduced liver enzymes-AST, ALT and Alkaline phosphate in diabetic hypertensive patients ($p<0.0001$). Our study was supported by Sattar *et al.* that observed that Empagliflozin decreased liver enzymes in T2D patients (Sattar et al., 2018). Another study showed that liver function parameters were improved by SGLT-2i (canagliflozin) (Lee et al., 2021). Our study showed a significant decrease in bilirubin after three months of treatment ($p<0.0001$). However, Wong *et al.* have concluded earlier that total bilirubin remains unchanged with the SGLT-2i (Wong et al., 2021).

Previous research has shown that the severity of T2D has a negative impact on QoL. According to the American Diabetes Association's new guidelines, T2D treatment must be patient-centered with an emphasis on improving patients' QoL and glucose levels. As a result, QoL is becoming increasingly important (ADA, 2015). There is, however, limited

research available in the Indian setting. To the best of our knowledge, this is one of the few studies related to the effect of pharmacotherapeutic agents on QoL in Indian diabetic patients. Most importantly, this is the first study to use the Urdu translated QOLID instrument to the best of our knowledge. This study showed a positive relationship between glycemic parameters and QoL. A significant improvement in QoL in patients of T2D with hypertension with Empagliflozin as an additional drug to the triple management, i.e. Metformin + Teneligliptin + Glimepiride, was observed. Furthermore, an improvement in QoL proportional to improvement in glycemic parameters like a decrease in FBG, PPG and HbA1c levels, was observed as reported earlier by Somappa *et al.* (Somapa et al., 2014). Hlatky et al. noted that except for the diet satisfaction domain, lifestyle variables (e.g. smoking) were significant predictors of QoL in diabetic-hypertensive patients (Hlatky et al., 2010). Another study reported a strong correlation with QOLID parameters, except for financial worries and diet satisfaction (Jin et al., 2018). This study also found a substantial association with QOLID characteristics except financial concerns and diet satisfaction. Overweight (BMI = 23–27.5 kg/m^2) and underweight (BMI = 18.5 kg/m^2) individuals exhibited significantly lower QOLID scores than normal patients. Anthropometric evaluation of patients revealed a strong connection with financial concerns ($p < 0.0068$). Complications associated with increasing BMI may worsen physical well-being and add to increased financial concerns. Increased BMI may have a detrimental influence on the QoL of patients (Akinci et al., 2008). No significant differences were detected in this study regarding gender, marital status, residential status and family-history variables in all eight QOLID domains.

In this cost-effectiveness analysis, Empagliflozin, was found to be more expensive but with better outcomes. Current study estimated an additional cost of USD 68.05 for Empagliflozin 25 mg as an add-on therapy with standard antidiabetic medication for three months. Furthermore additional investigation is required to establish the likely cost-effectiveness amongst contemporary and conventional antidiabetics. As per ICER calculation, the increased cost per unit improvement in QOLID score for empagliflozin as a new antidiabetic agent compared to conventional antidiabetics is USD 1.89. However,

whether the increased price is large or small is determined by the country's ICER value. In India, sufficient data related to cost-effectiveness analysis needs to be maintained as based on this data, customized or case-by-case decision-making considering the socioeconomic status of patients may be implemented while prescribing medicines.

The current study is extremely important and unique in its field as in published literature, no studies on the addition of empagliflozin to current triple drugs in T2D patients with comorbid hypertension were found. The study does, however, have certain limitations.

Limitations of the study

1. It was a single-arm observational study, lacking a control group. Future prospects include two-armed, double-blinded study.
2. The present study was conducted on a limited sample size. Thus, future studies are needed on a significant sample size.
3. The present study was limited to the Kashmir region only, so assessment in larger population is recommended.

Chapter 8

SUMMARY

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CONCLUSION

1. Empagliflozin add-on to triple therapy showed good efficacy in T2D patients with comorbid hypertension. This prospective observational cohort study confirmed that addition of Empagliflozin to triple drug combination (metformin, teneligliptin and glimepiride) significantly decreased FBG, PPG, HbA1c, SBP, DBP and pulse rate in T2D patients having comorbid hypertension after three months.

2. Lipid profile parameters like TC, TG, LDL, and VLDL were significantly improved after three months of follow-up suggesting its cardioprotective role.

3. The combination was found safe and tolerable as except only two cases of genital infection, no major adverse reactions were observed.

4. A significant improvement in QoL was observed in patients of T2D with comorbid hypertension.

5. Cost-effectiveness analysis indicated an additional cost of USD 68.05 for Empagliflozin 25 mg as an add-on therapy with standard antidiabetic medication for three months but with better outcomes. Increased cost per unit improvement in QOLID score for empagliflozin as a new antidiabetic agent compared to conventional antidiabetics is USD 1.89.

In conclusion, Empagliflozin may serve as a beneficial add-on in T2D patients, who respond poorly to the triple medication treatment (metformin, glimepiride, and teneligliptin) and suffer from resistant comorbid hypertension also. Addition of Empagliflozin to the triple medication is well tolerated and can improve BP, glycemic parameters as well as QoL. The findings from the study might help in the individualization of T2D medications in the Indian population as a patient-centered approach.

Chapter 9

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Annexures

CASE REPORT FORM

❖ **Registration detail**

S. No: Date:

Unique Study Patient Identification Number:

❖ **Identification and demographic information**

Age:

Gender: Smoking History:

Initial of Patient:

District:

Education:

Monthly Income:

❖ **Clinical and lab parameters (baseline/follow-up):**

- Weight: History of exercise:
- Height: BMI:
- Duration of diabetes: History of diabetes in family:
- Hip Circumference (cm): Waist Circumference(cm):
- Heart Rate:
- Basal Blood Pressure: SBP/DBP:
- FBG: PPG :
- Hba1c :

➢ **Lipid profile**

- Total cholesterol (mg/dl) :
- Triglycerides (mg/dl):

- LDL (mg/dl):
- VLDL (mg/dl):
- HDL (mg/dl):

➢ **Liver functions tests**

- Total serum bilirubin (mg/dl):
- AST (IU/L) :
- ALT (IU/L) :
- Alkaline phosphate (IU/L):
- Total serum proteins (mg/dl):

➢ **Renal functions tests**

- Serum urea (mg/dl) :
- Serum creatinine (mg/dl) :

➢ **Pancreatic beta cell function tests**

- Fasting Insulin (IU/mL) :
- Fasting c-peptide (ng/ml) :

➢ **Complete blood count**

- WBC (10^9/L):
- RBC (10^{12}/L):
- Platelets (10^9/L):
- Haemoglobin (g/dl):

MEDICATIONS FOR T2D WITH HYPERTENSION, FORMULATION, DOSE, PRICE

……

QOLID Questionnaire (English Version)

Role Limitation Due to Physical Health

1. How often do you miss your work because of your diabetes?

Always	Frequently	Often	Sometimes	Never
1	2	3	4	5

2. A person with diabetes has the requirement of adhering to a schedule for eating and taking regular medication. How often does this affect your work?

Always	Frequently	Often	Sometimes	Never
1	2	3	4	5

3. How often does diabetes affect your efficiency at work?

Always	Frequently	Often	Sometimes	Never
1	2	3	4	5

4. How often do you find diabetes limiting your social life?

Always	Frequently	Often	Sometimes	Never
1	2	3	4	5

5. To what extent do you avoid traveling (business tour, holiday, general outings) because of your diabetes?

A lot	Highly	Little	Very little	Not at all
1	2	3	4	5

6. Compared to others of your age are your social activities (visiting friends/partying) limited because of your diabetes?

Always	Frequently	Often	Sometimes	Never

1	2	3	4	5

Physical Endurance

An important part of understanding your general health and well being has to do with your ability to perform various activities. Thus for the following questions please indicate if your health has limited your activities in following areas in the past three months. Please tick any one option.

1. How often in last three months has your overall health problems limited the kind of vigorous activities you can do like lifting heavy bags/objects, running, skipping, jumping.

Always	Frequently	Often	Sometimes	Never
1	2	3	4	5

2. How often in last three months has your overall health problems limited the kind of moderate activities you can do like moving a table, carrying groceries or utensils.

Always	Frequently	Often	Sometimes	Never
1	2	3	4	5

3. How often in last three months has your overall health problems limited you from walking uphill or climbing 1-2 floors.

Always	Frequently	Often	Sometimes	Never
1	2	3	4	5

4. How often in last three months has your overall health problems limited you from walking 1-2 km at a stretch.

Always	Frequently	Often	Sometimes	Never

1	2	3	4	5

5. How often in last three months has your overall health problems limited you from bending, squatting, or turning.

Always	Frequently	Often	Sometimes	Never
1	2	3	4	5

6. How often in last three months has your overall health problems limited you from eating, dressing, bathing, or using the toilet.

Always	Frequently	Often	Sometimes	Never
1	2	3	4	5

General Health

1. In general would you say your health is.

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

2. How well are you able to concentrate in everything like working, driving, reading etc?

Not at all	A little	Moderate	Very much	An extreme amount
1	2	3	4	5

3. How many times in the past three months have you had fatigue/felt very tired?

Always	Frequently	Often	Sometimes	Never
1	2	3	4	5

Treatment Satisfaction

The following set of questions would enable us to know how satisfied you with your treatment for diabetes are. Please tick any one option.

1. How satisfied are you with your current diabetes treatment?

Very dissatisfied	Moderately dissatisfied	Neither satisfied nor dissatisfied	Moderately satisfied	Very Satisfied
1	2	3	4	5

2. How satisfied are you with amount of time it takes to manage your diabetes?

Very dissatisfied	Moderately dissatisfied	Neither satisfied nor dissatisfied	Moderately satisfied	Very satisfied
1	2	3	4	5

3. How satisfied are you with the amount of time you spend getting regular checkups (once in 3 months)?

Very dissatisfied	Moderately dissatisfied	Neither satisfied nor dissatisfied	Moderately satisfied	Very satisfied
1	2	3	4	5

4. A person with diabetes needs to exercise for 35-45 min, 4 times a week. Keeping this in mind how satisfied are you with the time you spend exercising?

Very dissatisfied	Moderately dissatisfied	Neither satisfied nor dissatisfied	Moderately satisfied	Very satisfied
1	2	3	4	5

Symptom Botherness

1. How many times in the past three months have you had thirst/dry mouth?

Always	Frequently	Often	Sometimes	Never
1	2	3	4	5

2. How many times in the past three months have you felt excessive hunger?

Always	Frequently	Often	Sometimes	Never
1	2	3	4	5

3. How many times in the past three months have you had frequent urination related to diabetes management?

Always	Frequently	Often	Sometimes	Never
1	2	3	4	5

Financial Worries

The following set of questions will help us know how your diabetes has affected you or your family's finances. Please tick any one option….

1. What do you think about the cost involved in your management of diabetes?

Very expensive	little expensive	Reasonable	not at all expensive
1	2	3	4

2. To what extent has your priority of expenditure shifted towards diabetes management?

A lot	Highly	Little	Very little	Not at all
1	2	3	4	5

3. To what extent has your family budget got affected by the expenses related to the management of diabetes?

A lot	Highly	Little	Very little	Not at all

1	2	3	4	5

4. To what extent has your diabetes limited your expenditure on other aspects of life (Movies, outings, parties etc)?

A lot	Highly	Little	Very little	Not at all
1	2	3	4	5

Emotional/Mental Health

1. How satisfied are you with yourself?

Very dissatisfied	Moderately dissatisfied	Neither satisfied nor dissatisfied	Moderately satisfied	Very Satisfied
1	2	3	4	5

2. How satisfied are you with your personal relationships (family, friends, relatives and known tos)?

Very dissatisfied	Moderately dissatisfied	Neither satisfied nor dissatisfied	Moderately satisfied	Very satisfied
1	2	3	4	5

3. How satisfied are you with the emotional support you get from your friends and family?

Very dissatisfied	Moderately dissatisfied	Neither satisfied nor dissatisfied	Moderately satisfied	Very Satisfied
1	2	3	4	5

4. How often are you discouraged by your health problems?

Always	Frequently	Often	Sometimes	Never

1	2	3	4	5

5. All people want to fulfill certain roles and lead their lives in a purposeful manner. To what extent do you feel that you have been able to lead your life in the same way?

Not at all	A little	Moderate	Very much	An extreme amount
1	2	3	4	5

Diet Satisfaction

Diabetes demands a little modification in diet, thus the following set of questions would help us know how much satisfied you are with modifications in your diet. (For participants who have been advised some dietary modification/counseling).

1. How often do you feel because of your diabetes a restriction in choosing your food when eating out?

Always	Frequently	Often	Sometimes	Never
1	2	3	4	5

2. As you have diabetes, how much choice do you feel you have in eating your meals or snacks away from home e.g. if you go in a party and there is a buffet where there are also a lot of fried snacks and desserts would you be able to make enough choice?

No choice	Very little	Little	Enough	A lot
1	2	3	4	5

3. How often do you eat the food items that you shouldn't, in order to hide the fact that you are having diabetes.

Always	Frequently	Often	Sometimes	Never

1	2	3	4	5

QOLID Questionnaire (Urdu Version)

جسمانی صحت کی وجہ سے کردار کی حد

- 1. ذیابیطس کی وجہ سے آپ کتنی بار اپنا کام چھوڑتے ہیں؟

کبھی نہیں۔	کبھی کبھی	اکثر	کثرت سے	ہمیشہ
5	4	3	2	1

- ذیابیطس والے شخص کو کھانے اور باقاعدگی سے دوائی لینے کے شیڈول پر عمل کرنے کی ضرورت ہوتی ہے۔ یہ آپ کے کام کو کتنی بار متاثر کرتا ہے؟

کبھی نہیں۔	کبھی کبھی	اکثر	کثرت سے	ہمیشہ
5	4	3	2	1

- ذیابیطس کتنی بار کام پر آپ کی کارکردگی کو متاثر کرتی ہے؟

کبھی نہیں۔	کبھی کبھی	اکثر	کثرت سے	ہمیشہ
5	4	3	2	1

- آپ کتنی بار ذیابیطس کو آپ کی سماجی زندگی کو محدود کرتے ہوئے دیکھتے ہیں؟

کبھی نہیں۔	کبھی کبھی	اکثر	کثرت سے	ہمیشہ
5	4	3	2	1

• آپ اپنی ذیابیطس کی وجہ سے کس حد تک سفر کرنے سے گریز کرتے ہیں (کاروباری دورے، چھٹیاں، عام سیر)؟

بالکل نہیں	بہت کم	چھوٹا	اعلیٰ	بہت زیادہ
5	4	3	2	1

• کیا آپ کی عمر کے دیگر افراد کے مقابلے میں آپ کی ذیابیطس کی وجہ سے آپ کی سماجی سرگرمیاں (دوستوں سے ملنا/جماعت کرنا) محدود ہیں؟

کبھی نہیں۔	کبھی کبھی	اکثر	کثرت سے	ہمیشہ
5	4	3	2	1

جسمانی برداشت

آپ کی عمومی صحت اور تندرستی کو سمجھنے کا ایک اہم حصہ مختلف سرگرمیاں انجام دینے کی آپ کی صلاحیت سے متعلق ہے۔ اس طرح درج ذیل سوالات کے لیے براہ کرم اس بات کی نشاندہی کریں کہ کیا آپ کی صحت نے پچھلے تین مہینوں میں درج ذیل علاقوں میں آپ کی سرگرمیاں محدود کر دی ہیں۔ براہ کرم کسی ایک آپشن پر نشان لگائیں۔

• پچھلے تین مہینوں میں کتنی بار آپ کے مجموعی صحت کے مسائل نے اس قسم کی بھرپور سرگرمیاں محدود کر دی ہیں جو آپ کر سکتے ہیں جیسے بھاری بیگ/اشیاء اٹھانا، دوڑنا، اچھالنا، چھلانگ لگانا۔

کبھی نہیں۔	کبھی کبھی	اکثر	کثرت سے	ہمیشہ
5	4	3	2	1

. پچھلے تین مہینوں میں کتنی بار آپ کی صحت کے مسائل نے اس قسم کی اعتدال پسند سرگرمیوں کو محدود کر دیا ہے جو آپ کر سکتے ہیں جیسے میز کو ہلانا، گروسری یا برتن اٹھانا۔

کبھی نہیں۔	کبھی کبھی	اکثر	کثرت سے	ہمیشہ
5	4	3	2	1

• پچھلے تین مہینوں میں کتنی بار آپ کے مجموعی صحت کے مسائل نے آپ کو اوپر چلنے یا 1-2 منزلوں پر چڑھنے سے محدود کر دیا ہے۔

کبھی نہیں۔	کبھی کبھی	اکثر	کثرت سے	ہمیشہ
5	4	3	2	1

• پچھلے تین مہینوں میں کتنی بار آپ کے مجموعی صحت کے مسائل نے آپ کو 1-2 کلومیٹر تک چلنے سے محدود کر دیا ہے۔

کبھی نہیں۔	کبھی کبھی	اکثر	کثرت سے	ہمیشہ
5	4	3	2	1

• پچھلے تین مہینوں میں کتنی بار آپ کے مجموعی صحت کے مسائل نے آپ کو جھکنے، بیٹھنے یا موڑنے سے محدود کیا ہے۔

کبھی نہیں۔	کبھی کبھی	اکثر	کثرت سے	ہمیشہ
5	4	3	2	1

• پچھلے تین مہینوں میں کتنی بار آپ کے مجموعی صحت کے مسائل نے آپ کو کھانے، کپڑے پہننے، نہانے، یا بیت الخلا کے استعمال سے محدود کیا ہے۔

کبھی نہیں۔	کبھی کبھی	اکثر	کثرت سے	ہمیشہ
5	4	3	2	1

• عام طور پر آپ کہیں گے کہ آپ کی صحت ہے۔

عمدہ	بہت خوب	اچھی	منصفانہ	غریب
5	4	3	2	1

• آپ کام کرنے، ڈرائیونگ، پڑھنے وغیرہ جیسے ہر چیز میں کتنی اچھی طرح سے توجہ مرکوز کر سکتے ہیں؟

ایک انتہائی مقدار	بہت زیادہ	اعتدال پسند	تھوڑا سا	بالکل نہیں
5	4	3	2	1

• پچھلے تین مہینوں میں کتنی بار آپ کو تھکاوٹ ہوئی/بہت تھکا ہوا محسوس ہوا؟

کبھی نہیں۔	کبھی کبھی	اکثر	کثرت سے	ہمیشہ
5	4	3	2	1

علاج کی اطمینان

مندرجہ ذیل سوالات کا مجموعہ ہمیں یہ جاننے کے قابل بنائے گا کہ آپ ذیابیطس کے علاج سے کتنے مطمئن ہیں۔ براہ کرم کسی ایک آپشن پر نشان لگائیں۔

• آپ ذیابیطس کے موجودہ علاج سے کتنے مطمئن ہیں؟

بہت مطمئن	اعتدال سے مطمئن	نہ ہی مطمئن اور نہ ہی غیر مطمئن	اعتدال سے غیر مطمئن	بہت غیر مطمئن
5	4	3	2	1

• آپ اپنی ذیابیطس کو سنبھالنے میں لگنے والے وقت سے کتنے مطمئن ہیں؟

بہت مطمئن	اعتدال سے مطمئن	نہ ہی مطمئن اور نہ ہی غیر مطمئن	اعتدال سے غیر مطمئن	بہت غیر مطمئن
5	4	3	2	1

• آپ باقاعدگی سے چیک اپ کروانے میں جتنا وقت گزارتے ہیں اس سے آپ کتنے مطمئن ہیں (3 ماہ میں ایک بار)؟

بہت مطمئن	اعتدال سے مطمئن	نہ ہی مطمئن اور نہ ہی غیر مطمئن	اعتدال سے غیر مطمئن	بہت غیر مطمئن
5	4	3	2	1

• ذیابیطس کے مریض کو ہفتے میں 4 بار 35-45 منٹ تک ورزش کرنے کی ضرورت ہے۔ اس بات کو ذہن میں رکھتے ہوئے کہ آپ ورزش کرنے کے وقت سے کتنے مطمئن ہیں؟

بہت مطمئن	اعتدال سے مطمئن	نہ ہی مطمئن اور نہ ہی غیر مطمئن	اعتدال سے غیر مطمئن	بہت غیر مطمئن
5	4	3	2	1

علامات کی پریشانی

• پچھلے تین مہینوں میں آپ کو کتنی بار پیاس/خشک منہ ہوا ہے؟

کبھی نہیں۔	کبھی کبھی	اکثر	کثرت سے	ہمیشہ

1	2	3	4	5

• پچھلے تین مہینوں میں کتنی بار آپ نے ضرورت سے زیادہ بھوک محسوس کی ہے؟

کبھی نہیں۔	کبھی کبھی	اکثر	کثرت سے	ہمیشہ
5	4	3	2	1

• پچھلے تین مہینوں میں آپ کو ذیابیطس کے انتظام سے متعلق کتنی بار بار پیشاب آیا ہے؟

کبھی نہیں۔	کبھی کبھی	اکثر	کثرت سے	ہمیشہ
5	4	3	2	1

مالی پریشانیاں

درج ذیل سوالات سے ہمیں یہ جاننے میں مدد ملے گی کہ آپ کی ذیابیطس نے آپ یا آپ کے خاندان کے مالی معاملات کو کیسے متاثر کیا ہے۔ براہ کرم کسی ایک آپشن پر نشان لگائیں....

• ذیابیطس کے انتظام میں آپ کی لاگت کے بارے میں کیا خیال ہے؟

بالکل مہنگا نہیں	معقول	تھوڑا مہنگا	بہت مہنگا
4	3	2	1

• آپ کے اخراجات کی ترجیح ذیابیطس کے انتظام کی طرف کس حد تک منتقل ہوئی ہے؟

بالکل نہیں	بہت کم	چھوٹا	اعلیٰ	بہت زیادہ
5	4	3	2	1

• ذیابیطس کے انتظام سے متعلق اخراجات سے آپ کا خاندانی بجٹ کس حد تک متاثر ہوا ہے؟

بالکل نہیں	بہت کم	چھوٹا	اعلیٰ	بہت زیادہ
5	4	3	2	1

• آپ کی ذیابیطس نے زندگی کے دوسرے پہلوؤں (فلموں، گھومنے پھرنے، پارٹیوں وغیرہ) پر آپ کے اخراجات کو کس حد تک محدود کر دیا ہے؟

بالکل نہیں	بہت کم	چھوٹا	اعلیٰ	بہت زیادہ
5	4	3	2	1

جذباتی/ذہنی صحت

• آپ اپنے آپ سے کتنے مطمئن ہیں؟

بہت مطمئن	اعتدال سے مطمئن	نہ ہی مطمئن اور نہ ہی غیر مطمئن	اعتدال سے غیر مطمئن	بہت غیر مطمئن
5	4	3	2	1

• آپ اپنے ذاتی تعلقات (خاندان، دوستوں، رشتہ داروں اور جاننے والے افراد) سے کتنے مطمئن ہیں؟

بہت مطمئن	اعتدال سے مطمئن	نہ ہی مطمئن اور نہ ہی غیر مطمئن	اعتدال سے غیر مطمئن	بہت غیر مطمئن
5	4	3	2	1

• آپ اپنے دوستوں اور خاندان کی طرف سے ملنے والی جذباتی مدد سے کتنے مطمئن ہیں؟

بہت مطمئن	اعتدال سے مطمئن	نہ ہی مطمئن اور نہ ہی غیر مطمئن	اعتدال سے غیر مطمئن	بہت غیر مطمئن

1	2	3	4	5

• آپ اپنی صحت کے مسائل سے کتنی بار حوصلہ شکنی کرتے ہیں؟

کبھی نہیں۔	کبھی کبھی	اکثر	کثرت سے	ہمیشہ
5	4	3	2	1

• تمام لوگ کچھ خاص کردار ادا کرنا چاہتے ہیں اور اپنی زندگی بامقصد طریقے سے گزارنا چاہتے ہیں۔ آپ کو کس حد تک لگتا ہے کہ آپ اپنی زندگی کو اسی طرح گزارنے کے قابل ہوئے ہیں؟

ایک انتہائی مقدار	بہت زیادہ	اعتدال پسند	تھوڑا سا	بالکل نہیں
5	4	3	2	1

غذائی اطمینان

ذیابیطس خوراک میں تھوڑی سی تبدیلی کا مطالبہ کرتا ہے، اس طرح درج ذیل سوالات سے ہمیں یہ جاننے میں مدد ملے گی کہ آپ اپنی خوراک میں تبدیلیوں سے کتنے مطمئن ہیں۔ (شرکاء کے لیے جنہیں کچھ غذائی تبدیلی/مشاورت کا مشورہ دیا گیا ہے)۔

• آپ کو کتنی بار لگتا ہے کہ آپ کی ذیابیطس کی وجہ سے باہر کھاتے وقت اپنے کھانے کے انتخاب میں پابندی لگتی ہے؟

کبھی نہیں۔	کبھی کبھی	اکثر	کثرت سے	ہمیشہ
5	4	3	2	1

• جیسا کہ آپ کو ذیابیطس ہے، آپ کو لگتا ہے کہ آپ کو گھر سے دور کھانا یا ناشتہ کھانے میں کتنا انتخاب ہے جیسے اگر آپ کسی پارٹی میں جاتے ہیں اور وہاں ایک بوفے ہوتا ہے جہاں بہت سے تلے ہوئے اسنیکس اور میٹھے بھی ہوتے ہیں تو کیا آپ کافی انتخاب کر پائیں گے؟

بہت زیادہ	کافی	چھوٹا	بہت کم	کوئی چارہ نہیں

1	2	3	4	5

- اس حقیقت کو چھپانے کے لیے کہ آپ کو ذیابیطس ہو رہی ہے، آپ کتنی بار کھانے کی اشیاء کھاتے ہیں جو آپ کو نہیں کرنی چاہیے۔

ہمیشہ	کثرت سے	اکثر	کبھی کبھی	کبھی نہیں۔
1	2	3	4	5

INFORMED CONSENT FORM

Study Title: Efficacy and Safety of Empagliflozin as an Add-on Drug Therapy with Metformin, Teneligliptin and Glimepiride in Type 2 Diabetes Patients with Hypertension

Study Number:

Subject Full Name:

Date of Birth/Age:

Address:

1. I confirm that I have read and understood the information sheet dated for the above study and have had the opportunity to ask questions. Or I have been explained the nature of the study by the investigator and had the opportunity to ask questions.
2. I understand that my participation in this study is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.
3. I understand that the sponsor of the clinical trial/project, others working on the sponsors behalf, the Ethics Committee and the Regulatory authorities will not need my permission to look at my health records both in respect of the current study and

any further research that may be conducted in relation to it, even if I withdraw from the trial. However, I understand that my identity will not be revealed in any information released to third parties or published.

4. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purposes.
5. I agree to take part in the above study.

Signature (or thumb impression) of the subject/legally acceptable representation**:**----------

Signatory's Name: ---------- Dated: ----------

Signature of the investigator: ---------- Dated: ----------

Study investigator's Name:----------

Signature of the Witness: ---------- Dated: ----------

Name of the witness:----------

ضابطہ/ تحقیق نمبر:		شرکت کرنے والے/ والی کا پہچان نمبر:	
موضوع:	ایمفگلیفلوزین کی افادیت اور حفاظت ، میٹفارمین ، ٹینیلیگلیپٹن اور گلیمیپائرائڈ کے ساتھ ایک ایڈ آن ڈرگ تھراپی کے طور پر اور ہائی بلڈ پریشر والے ڈیابیطس کے قسم 2 مریضوں میں		
نام اعلیٰ محقق:			

اس جانچ کے موضوات بتاریخ جو منجھے دئے گئے ہیں، کو میں بغور پڑھے / سمجھائے گئے اُس زبان میں جو میں سمجھتا/ سمجھتی ہوں اور میں نے تمام موضوعات مکمل طور سمجھے ہیں۔ مں تصدیق کرتا/ کرتی ہوں کہ مجھے سوالات پوچھنے کا موقع دیا گیا ہے۔ اس تحقیق کا طریقہ اور مقصد اور اس سے وابستہ خطرات اور فوائد اور اس تحقیق سے وابستہ دوسری تفصیلات مجھ پر واضح کی گئی ہیں۔ میں سمجھ چکا/ چکی ہوں کہ میری شرکت رضاکارانہ ہے اور مہیں وجہ کی وضاحت کے بغیر بھی تحقیق سے دستبردار ہونے میں آزاد ہوں۔ اس کے نتیجے میں میری طبعی نگہداشت اور میرے قانونی حق پر کوئی اثر نہیں پڑھے گا۔

میں سمجھ چکا / چکی ہوں کہ میری شرکت سے میرے بارے میں جانکاری حاصل کی گئی ہے اور سے وابستہ افراد میری طبعی جانچکے کسی بھی حصے کو دیکھ سکتے ہیں۔ میں ایسے افراد کو میری طبعی جانچ تک پہنچ کی اجازت دیتا/ دیتی ہوں۔ میں اس تحقیق میں شامل ہونے کے لئے رضامند ہوں۔

دستخط/ بایاں اننگوٹھہ۔

جگہ:

نام شرکت کرنے والا/ والی

گواہ اول **گواہ دوم**

دستخط دستخط

نام نام

پتہ پتہ

نوٹ: تین کاپیاں بنانی ضروری ہیں

1۔ سرکت کرنے والا/ والی 2۔ محقق 3۔ ادارہ