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ALTERATIONS IN MANAGING THE DIABETIC MILLITUS BY USING NOVEL TECHNOLOGIES – A SYSTEMATIC REVIEW

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Abstract:
Diabetes mellitus is a metabolic disorder with an increasing global prevalence and incidence. High blood glucose levels are symptomatic of diabetes mellitus as a consequence of inadequate pancreatic insulin secretion or poor insulin-directed mobilization of glucose by target cells. Type 2 diabetes mellitus (T2DM) is a fast-growing disease and a leading global public health concern. Multiple complications are associated with T2DM. Patient education with lifestyle modifications and pharmacotherapy are the main methods for the treatment of patients afflicted with T2DM. Therapy of type 2 diabetes like DPP-4 inhibitors its action is mediated by increasing levels of the incretin hormones glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) Layer tablets are used for preventing any type of incompatibilities between drugs & also for sustained release in which one layer serves as immediate release "initial dose" layer & other layer serves as "maintenance dose" layer. Layer tablet also is forerunners in the field of drug delivery technology due to their advantageous properties like better patient compliance, decrease drug resistance due to less frequent dosing & different release profile with a different release mechanism in a single dose

KEY WORDS : *T2Diabetes Mellitus , DPP-4Inhibitors, Bi-layer tablets , Tri layer tablets.*

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INTRODUCTION:

Diabetes mellitus is a combination of heterogeneous disorders commonly presenting with episodes of hyperglycemia and glucose intolerance, as a result of lack of insulin, defective insulin action, or both[1]. Such complication arise due to derangements in the regulatory systems for storage and mobilization of metabolic fuels, including the catabolism and anabolism of carbohydrates, lipids, and proteins emanating from defective insulin secretion, insulin action, or both. Classification of diabetes mellitus is based on its etiology and clinical presentation. As such, there are four types or classes of diabetes mellitus, Type- 1 diabetes, Type - 2 diabetes, gestational diabetes, and other specific types[2]. Type - 1 diabetes is said to account for only a minority of the total burden of diabetes in a population although it is the major type of diabetes in younger age groups in the majority of well-to-do countries. The incidence of type 1 diabetes is increasing in both rich and poor countries. Furthermore, a shift towards type 1 diabetes occurring in children at earlier ages is imminent. 85 to 95% of all diabetes in high-income countries are of type 2 accounting for an even higher dominance in developing countries. [3] It is intimately associated with improper utilization of insulin by target cells and tissues. It is currently a common and serious health concern globally. According to, this problem has been aggravated by rapid cultural and social dynamics, aging populations, increasing urbanization, dietary changes, reduced physical activity, and other unhealthy lifestyle and behavioral patterns.

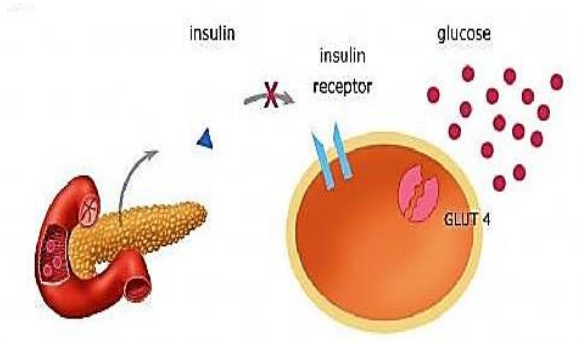

Fig 1: In Type 1 diabetes, the body's immune system destroys the cells that release insulin, eventually eliminating insulin production from the body. Without insulin, cells cannot absorb sugar (glucose), which they need to produce energy.

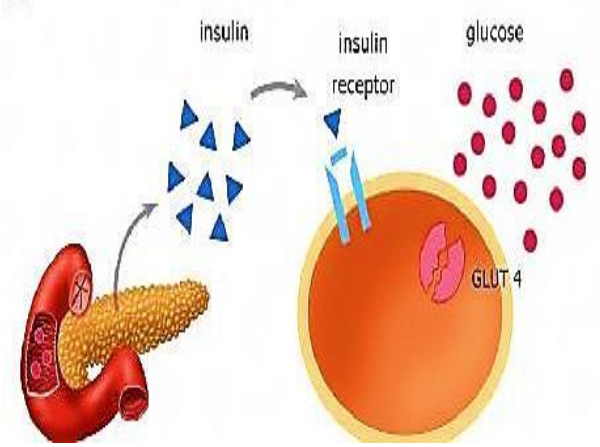

Fig 2: Type- 2 diabetes, insulin binds to the receptor normally, but the signal is not sent into the cell, the cells do not take up glucose and the resulting high blood glucose levels cause organ damage over time.

PHYSIOLOGICAL FUNCTION OF INSULIN IS PROMOTING THE SYNTHESIS:

Insulin is a polypeptide hormone synthesized in humans and other mammals within the beta cells of the islets of Langerhans in the pancreas, [4] the islets of Langerhans from the endocrine part of the pancreas, accounting for 2% of the total mass of the pancreas, with beta cells constituting 60-80% of all the cells of islets of Langerhans and the Insulin exhibits a multitude of effects in many tissues, with liver, muscle, and adipose tissue being the most important target organs for insulin action. [5] The basic physiological function of insulin in promoting the synthesis of carbohydrates, proteins, lipids, and nucleic acids. The effects of insulin on carbohydrate metabolism include stimulation of glucose transport across muscle and adipocyte cell membranes, regulation of hepatic glycogen synthesis, and inhibition of glycogenolysis and gluconeogenesis. The result of these actions is a reduction in blood glucose concentration in this regard to protein metabolism, insulin promotes the transfer of amino acids across membranes, stimulates protein synthesis, and inhibits proteolysis. Incorporation of fatty acids from circulating triglyceride into adipose triglyceride and lipid synthesis is stimulated by insulin; lipolysis is inhibited. Insulin contributes to nucleic acid synthesis by stimulating the formation of ATP, DNA, and RNA**.** [6]

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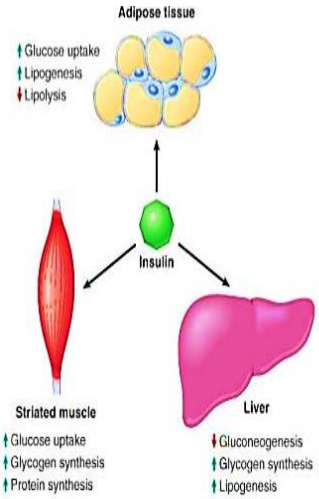

Fig 3: Insulin helps control blood glucose levels by signaling the liver and muscle and fat cells to take in glucose from the blood. Insulin, therefore, helps cells to take in glucose to be used for energy. If the body has sufficient energy, insulin signals the liver to take up glucose and store it as glycogen.

ENVIRONMENTAL AND LIFESTYLE RISK FACTORS:

It is estimated that 366 million people had Diabetes Mellitus in 2011 by 2030 this would have risen to 552 million. The number of people with type 2 Diabetes Mellitus is increasing in every country with 80% of people with Diabetes Mellitus living in low- and middle-income countries.[7] Diabetes Mellitus caused 4.6 million deaths in 2011. It is estimated that 439 million people would have type 2 Diabetes Mellitus by the year 2030. The incidence of type 2 Diabetes Mellitus varies substantially from one geographical region to the other as a result of environmental and lifestyle risk factors. The majority of the Diabetes Mellitus burden in Africa appears to be type 2 Diabetes Mellitus, with less than 10% of Diabetes Mellitus cases being type 1 Diabetes Mellitus [8] . 2011 Centre for Disease Control and Prevention (CDC) report estimates that Diabetes Mellitus affects about 25.8 million people in the US (7.8% of the population) in 2010 with 90% to 95% of them being type 2 Diabetes Mellitus [9]. It is predicted that the prevalence of Diabetes Mellitus in adults of which type 2 Diabetes Mellitus is becoming prominent will increase in the next two decades and much of the increase will occur in developing countries where the majority of patients are aged between 45 and 64 years [10]. It is projected that the latter will equal or even exceed the former in developing nations, thus culminating in a double burden as a result of the current trend of transition from communicable to non-communicable diseases [11].

LIFESTYLE MANAGEMENT OF TYPE 2 DIABETES MELLITUS :

Lifestyle management is the cornerstone of the management of diabetes mellitus. It is recognized as being an essential part of diabetes and cardiovascular disease prevention. Meta-analyses demonstrate that lifestyle interventions, including diet and physical activity, led to a 63% reduction in diabetes incidence in those at high risk. Lifestyle modification programs have demonstrated encouraging improvement in risk factors for diabetes; however, the effect on diabetes incidence has not been reported [12]. The dietary management of diabetes mellitus is a complement of lifestyle management. It has a positive effect on long-term health and quality of life. Dietary management aims at optimal metabolic control by establishing a balance between food intake, physical activity, and medication to avoid complications. In type 2 diabetes, the dietary objective is for improved glycaemic and lipid levels and weight loss as appropriate.

MATURITY ONSET DIABETES OF THE YOUNG (MODY).

Type 2 Diabetes Mellitus is due primarily to lifestyle factors and genetics[13]. Several lifestyle factors are known to be important to the development of type 2 Diabetes Mellitus. These are physical inactivity, sedentary lifestyle, cigarette smoking, and generous consumption of alcohol. [14] Obesity has been found to contribute to approximately 55% of cases of type 2 Diabetes Mellitus and it increases the rate of childhood obesity is believed to have led to the increase in type2 Diabetes Mellitus in children and adolescents. [15] Environmental toxins may contribute to the recent increases in the rate of type 2 Diabetes Mellitus is a weak positive correlation has been found between the concentrations in the urine. Maturity-onset diabetes of the young (MODY), constitutes up to 5% of cases. Many [16] medical conditions can potentially give rise to, or exacerbate type 2 Diabetes Mellitus. These include obesity, hypertension, elevated cholesterol (combined hyperlipidemia), and the condition often termed metabolic syndrome. [17] Other causes include acromegaly, Cushing's syndrome, thyrotoxicosis, pheochromocytoma, chronic pancreatitis, cancer, and drugs. Additional factors found to increase the risk of type 2 Diabetes Mellitus include aging, high-fat diets, and a less active lifestyle[18].

PHARMACOKINETIC PROFILES OF INSULIN ANALOGS

Insulin therapy was limited in its ability to mimic normal physiologic insulin secretion. Traditional intermediate- and long-acting insulin (NPH insulin, Lente insulin, and ultralente insulin) are limited by inconsistent absorption and peaks of action that may result in hypoglycemia. [19] The pharmacokinetic profiles of the new insulin analogs are distinct from those of the regular insulin's, and their onset and duration of action range from rapid to prolonged. Currently, two rapid-acting insulin analogs, insulin lispro, and insulin as part, and one long-acting insulin analogy, insulin glargine, are available.

Diabetes Mellitus is broadly classified into three types by etiology and clinical presentation, type 1 diabetes, type 2 diabetes. [20] Some other less common types of diabetes include monogenic diabetes and secondary diabetes.

JUVENILE DIABETES: Type 1 diabetes mellitus (T1DM) accounts for 5% to 10% of Diabetes Mellitus and is characterized by autoimmune destruction of insulin-producing beta cells in the islets of the pancreas. As a result, there is an absolute deficiency of insulin[21]. A combination of genetic susceptivity and environmental factors such as viral infection, toxins, or some dietary factors have been implicated as triggers for autoimmunity. Type 1 Diabetes Mellitus is most commonly seen in children and adolescents though it can develop at any age.

ADULT- ONSET DIABETES: Type 2 diabetes mellitus (T2DM) accounts for around 90% of all cases of diabetes. In Type 2 Diabetic Mellitus, the insulin response is diminished, and this is defined as insulin resistance. [22] During this state, insulin is ineffective and is initially countered by an increase in insulin production to maintain glucose homeostasis, but over time, insulin production decreases, resulting in Type 2 Diabetes Mellitus. Type 2 Diabetes Mellitus is most commonly seen in persons older than 45 years. Still, it is increasingly seen in children, adolescents, and younger adults due to rising levels of obesity, physical inactivity, and energy-dense diets.

INSULIN DEFICIENCY OR INSULIN RESISTANCE OF TYPE 2 DIABETES

Emanating from the prismatic demonstration of the presence of hyperinsulinism in type 2 diabetes, insulin resistance has been considered to play an integral role in the pathogenesis of the disease. [23] Recent critical reviews, however, have questioned the primacy, specificity, and contribution of insulin resistance to the disease state. As chronic hyperinsulinemia inhibits both insulin secretion and action, and hyperglycemia can impair both the insulin secretory response to glucose as well as cellular insulin sensitivity ·the precise relation between glucose and insulin level is a surrogate measure of insulin resistance has been questioned. Lean type 2 diabetic patients over 65yr of age are as insulin sensitive as their age-matched non-diabetic controls.

Moreover, in the majority of type 2 diabetic patients who are insulin resistant, obesity is almost invariably present. As obesity or an increase in intraabdominal adipose tissue is associated with insulin resistance in the absence of diabetes, it is believed by some that insulin resistance in type 2 diabetes is entirely due to the coexistence of increased adiposity. Additionally, insulin resistance is found in hypertension, hyperlipidemia, and ischemic heart disease, entities commonly found in association with diabetes, again raising the question as to whether insulin resistance results from different pathogenetic disease processes or is unique to the presence of type 2 diabetes [24] Prospective studies have demonstrated the presence of either insulin deficiency or insulin resistance before the onset of type 2 diabetes Two studies have reported the presence of insulin resistance in nondiabetic relatives of diabetic patients at a time when their glucose tolerance was still normal· Also, first-degree relatives of patients with type 2 diabetes have been found to have impaired insulin action upon skeletal muscle glycogen synthesis due to both decreased stimulation of tyrosine kinase activity of the insulin receptor and reduced glycogen synthase activity.

Other studies in this high-risk group have failed to demonstrate insulin resistance, and in the same group, impaired early-phase insulin release and loss of normal oscillatory pattern of insulin release have been described. [25] Based upon these divergent studies, it is still impossible to dissociate insulin resistance from insulin deficiency in the pathogenesis of type 2 diabetes. However, both entities unequivocally contribute to the fully established disease.

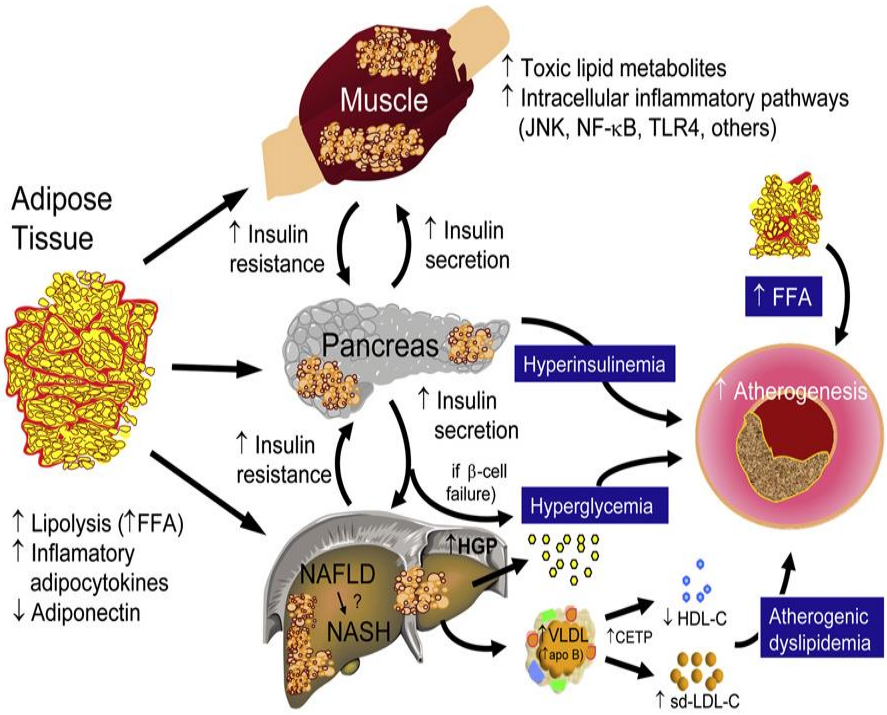

Fig 4: Insulin resistance is when cells in your muscles, fat, and liver don't respond well to insulin and can't easily take up glucose from your blood. As a result, your pancreas makes more insulin to help glucose enter your cells.

Diabetic Mellitus is associated with increased Atherosclerotic cardiovascular disease ASCVD, and treating Blood Pressure BP, statin use, regular exercise, and smoking cessation are of great importance in ameliorating risk. The overall excess mortality in those with Type 2 Diabetic Mellitus is around 15% higher but varies widely. The prevalence of vision-threatening diabetic retinopathy in the United States is about 4.4% among adults with diabetes, while it is 1% for end-stage renal disease. Today, with pharmacotherapy for hyperglycemia, as well as lowering Low-density level LDL cholesterol and managing Blood Pressure BP with Angiotensin-Converting enzyme inhibitors ACE therapy, with other antihypertensive medications and aspirin in secondary prevention, vascular complications can be managed adequately resulting in a reduction in morbidity and mortality.

ACUTE AND CHRONIC COMPLICATIONS :

Persistent hyperglycemia in uncontrolled diabetes mellitus can cause several complications, both acute and chronic. Diabetes mellitus is one of the leading causes of cardiovascular disease (CVD), blindness, kidney failure, and amputation of lower limbs. Acute complications include hypoglycemia, diabetic ketoacidosis, hyperglycaemic hyperosmolar state, and hyperglycaemic diabetic coma. [26] Chronic microvascular complications are nephropathy, neuropathy, and retinopathy, whereas chronic macrovascular complications are coronary artery disease (CAD), peripheral artery disease (PAD), and cerebrovascular disease. It is estimated that every year 1.4% to 4.7% of middle-aged people with diabetes have a CVD event.

PEARS AND OTHER ISSUES :

- Type 1 Diabetes Mellitus is characterized by autoimmune destruction of pancreatic beta cells in the majority.
- Type 2 Diabetic Mellitus is caused due to duel defects in insulin resistance and insulin secretion.
- Gestational diabetes is associated with maternal as well as fatal complications.
- Exercise and a healthy diet are beneficial in both type 1 and type 2 diabetes mellitus.
- Novel therapies, such as Good Laboratory Practise GLP -1 receptor agonists and Sodium-glucose transporter SGLT2 inhibitors are safer since they do not cause hypoglycemia, are weight neutral or result in weight loss and Blood Pressure BP, and impact vascular complications favorably [27].

HE MECHANISMS IN THE DEVELOPMENT OF INFLAMMATION – INDUCED INSULIN RESISTANCE

Insulin is a key endocrine hormone produced by β-cells of pancreatic islets. Insulin is regarded as a "hormone of abundance" owing to the array of functions it performs, the effects of which extend from metabolic to mutagenic activity (Figure: 05) It is likely that disruption of insulin-mediated pathways will have pleiotropic effects that are not confined to carbohydrate metabolism only [28]. Various mechanisms working separately or in synergy have been linked to the development of insulin resistance among which chronic inflammation represents as a triggering point·

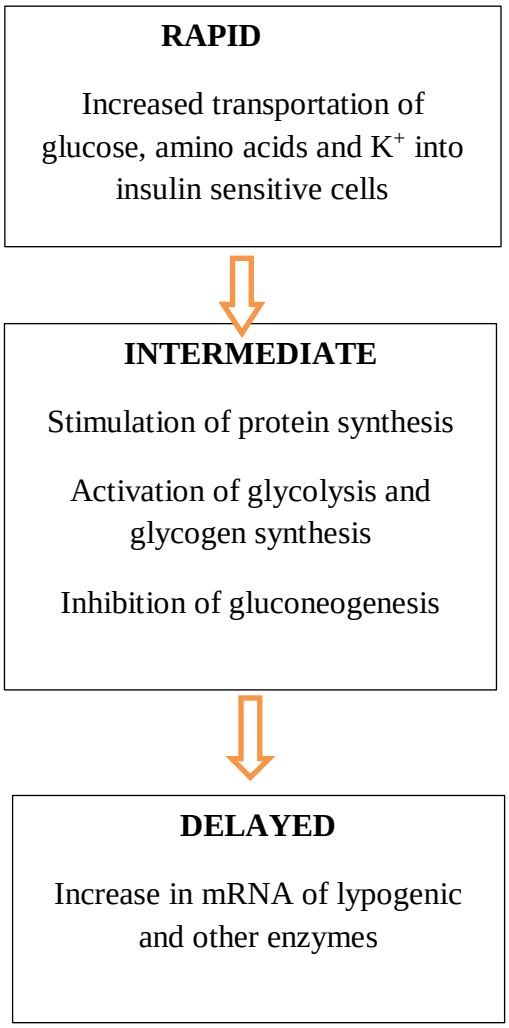

Fig 5: Various hormone functions of insulin.

BLOOD GLUCOSE MONITORING TO IMPROVE GLYCAEMIC CONTROL

How can the patient and primary care provider use blood glucose monitoring to improve glycaemic control (i) real-time decision support for the patient, and (ii) an aggregated summary of patient data for the clinician, are promising strategies. Several software approaches have been developed to achieve these goals. The trial was a small, randomized controlled trial of adults with poorly controlled Diabetes Mellitus using multiple-dose insulin therapy. The intervention was to provide a bolus dose calculator on the patient's glucometer that automatically recommends an insulin dose based on blood sugar reading and carbohydrate intake.[29] The trial documented improved glycaemic control and patient satisfaction. Glucometers that provide this bolus calculation are commercially available. Many patients are using one of numerous free or inexpensive apps for iPhone or Android that help to record medication administration, glucose logs, and diets. Notably, while health behavior applications are popular with patients and frequently recommended by physicians, more than 80% of diabetes

applications available for download have no privacy policies. Many actively transmit individual patient data to third parties without obtaining permission from the patient, suggesting against carte blanch recommendations of these tools.

Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency)
Immune-mediated diabetes.
In this form of diabetes, the rate of β-cell destruction is quite variable, being rapid in some individuals (mainly infants and children) and slow in others (mainly adults). Some patients, particularly children, and adolescents may present with ketoacidosis as the first manifestation of the disease. Others have modest fasting hyperglycemia that can rapidly change to severe hyperglycemia and/or ketoacidosis in the presence of infection or other stress[30]. Still others, particularly adults, may retain residual β-cell function sufficient to prevent ketoacidosis for many years such individuals eventually become dependent on insulin for survival and are at risk for ketoacidosis. At this latter stage of the disease, there is little or no insulin secretion, as manifested by low or undetectable levels of plasma C-peptide. Immune-mediated diabetes commonly occurs in childhood and adolescence, but it can occur at any age, even in the 8th and 9th decades of life.

Type 2 diabetes (ranging from predominantly insulin resistance with relative insulin deficiency to predominantly an insulin secretory defect with insulin resistance)
This form of diabetes, which accounts for ~90–95% of those with diabetes, previously referred to as non–insulin-dependent diabetes, type 2 diabetes, or adult-onset diabetes, encompasses individuals who have insulin resistance and usually have relative (rather than absolute) insulin deficiency At least initially, and often throughout their lifetime, these individuals do not need insulin treatment to survive. There are probably many different causes of this form of diabetes. Although the specific etiologist is not known, autoimmune destruction of β-cells does not occur, and patients do not have any of the other causes of diabetes listed above or below.

Most patients with this form of diabetes are obese, and obesity itself causes some degree of insulin resistance. [30] Patients who are not obese by traditional weight criteria may have an increased percentage of body fat distributed predominantly in the abdominal region. Ketoacidosis seldom occurs spontaneously in this type of diabetes; when seen, it usually arises in association with the stress of another illness such as infection. This form of diabetes frequently goes undiagnosed for many years because the hyperglycemia develops gradually and at earlier stages is often not severe enough for the patient to notice any of the classic symptoms of diabetes. Nevertheless, such patients are at increased risk of developing macrovascular and microvascular complications. Whereas patients with this form of diabetes may have insulin levels that appear normal or elevated, the higher blood glucose levels in these diabetic patients would be expected to result in even higher insulin values had their β-cell function been normal.

COMPLICATIONS OF TYPE 1 AND TYPE 2 DIABETES MELLITUS :
The global escalation of obesity and diabetes in developed and developing nations poses a great health challenge. Obesity is one of the major causes of type 2 diabetes. Type 1 diabetes is primarily due to the autoimmune-mediated destruction of the pancreatic beta-cell leading to insulin deficiency. This is usually accompanied by alterations in lipid metabolism, enhanced hyperglycemia-mediated oxidative stress, endothelial cell dysfunction, and apoptosis. Similarly, in type 2 diabetes, increased glucotoxicity, lipotoxicity, endoplasmic reticulum-induced stress, and apoptosis lead to the progressive loss of beta cells. While type 1 diabetes is characterized by the presence of beta-cell autoantibodies, a combination of peripheral insulin resistance and dysfunctional insulin secretion by pancreatic beta cells is implicated in the pathogenesis of type 2 diabetes. [31] However, both forms of diabetes are associated with a wide variety of complications such as cardiomyopathy, nephropathy, and neuropathy. Although insulin resistance has traditionally been associated with type 2 diabetes, mounting evidence indicates that the incidence of insulin resistance in type 1 diabetes is increasing therefore, novel mechanistic approaches deciphering insulin resistance are needed. Many pathophysiological factors are implicated in insulin resistance. Although the exact natures of these factors are not completely understood, it is widely accepted that oxidative stress, inflammation, and genetic, habitual, environmental, and other epigenetic factors play a significant role.

In the past two decades, significant strides have been made in elucidating important mechanisms associated with insulin resistance, overt diabetes, and related cardiometabolic diseases. However, more intense research is still needed for a more comprehensive understanding of the pathophysiological profile of

insulin resistance in diabetes, especially in situations where diabetes is comorbid with other chronic diseases. [32] Therefore, this special issue is a collection of research and review papers that address a broad range of mechanisms associated with insulin resistance, type 1 diabetes, type 2 diabetes, and related cardiometabolic complications. A common pathophysiological destructive force in type 1 and type 2 diabetes is the high levels of advanced glaciation end products generated by hyperglycemia. To unveil further insights on advanced glaciation end products. wrote an article on the putative pathophysiological role of advanced glaciation end products on deregulation of insulin signaling in type2 diabetes. To further expatiate on dysfunctional insulin signaling, investigated the impact of insulin resistance on lipid metabolism at a preclinical level and found that insulin resistance and diabetes are powerful predictors of quantitative and qualitative features of lipoprotein dysfunction and are directly associated with increased atherogenic risk.

Dyslipidaemia, obesity, and visceral adiposity are common risk factors for insulin resistance, type 2 diabetes, and cardiovascular complications. To shed more insight on this theme, investigated the relationships between the composition of free fatty acids and metabolic parameters and found that serum linoleic acid is negatively correlated with the accumulation of visceral fat and insulin resistance. On the other hand, investigated the effects of overexpressing gamma-glutamyltransferase on insulin sensitivity and found the short-term overexpression of liver-specific gamma-glutamyltransferase ameliorates insulin sensitivity. Although liver disease commonly occurs in diabetes, other organ complications including cardiomyopathy, neuropathy, and nephropathy are highly documented. To underscore the role of the kidney in diabetes and hypertension, U. gave their insights on the effects of renal denervation on insulin sensitivity in nondiabetic patients with treatment for resistant hypertension in an article featuring in this special issue.[33] On the other hand, to give further insight into diabetic neuropathy. wrote an article underscoring gene profiles of neurotropic-mitogen-activated protein kinase (MAPK) signaling in patients with diabetic peripheral neuropathy.

LIPAUTOPHAGY

Finally, despite a clear pathway of understanding in the development of hepatic IR, the discovery by Czaja and colleagues that the elimination of fat stores by lysosome degradation pathway, or autophagy, may have profound [34] implications for not just NAFLD but hepatic IR because the storage of FFA may be dangerous and also perpetuate hepatocyte IR. Furthermore, the process of rapid clean-up of fats either by macroautophagy or chaperone-mediated autophagy promotes hepatocyte resistance to oxidative stress Although limited here, for further review readers are encouraged to see the most recent review on autophagy and the liver because data implicate the failure of hepatocyte autophagic function can lead to the development of a fatty liver.

RECENT DEVELOPMENTS IN GENETICS

The issue of susceptibility of race or ethnicity to NAFLD progression was recently highlighted by the discovery of a point mutation in the gene encoding for adiponectin, or PNPLA3, in which Hispanics were far more likely to have more hepatic fat and inflammation if they had an allelic variant.

Conversely, non-Hispanics and African-Americans were more likely to have a protective allelic variant and were less likely to have either excess hepatocyte fat or inflammation. It should be noted that the association between PNPLA3 polymorphisms and NAFLD is independent of IR.

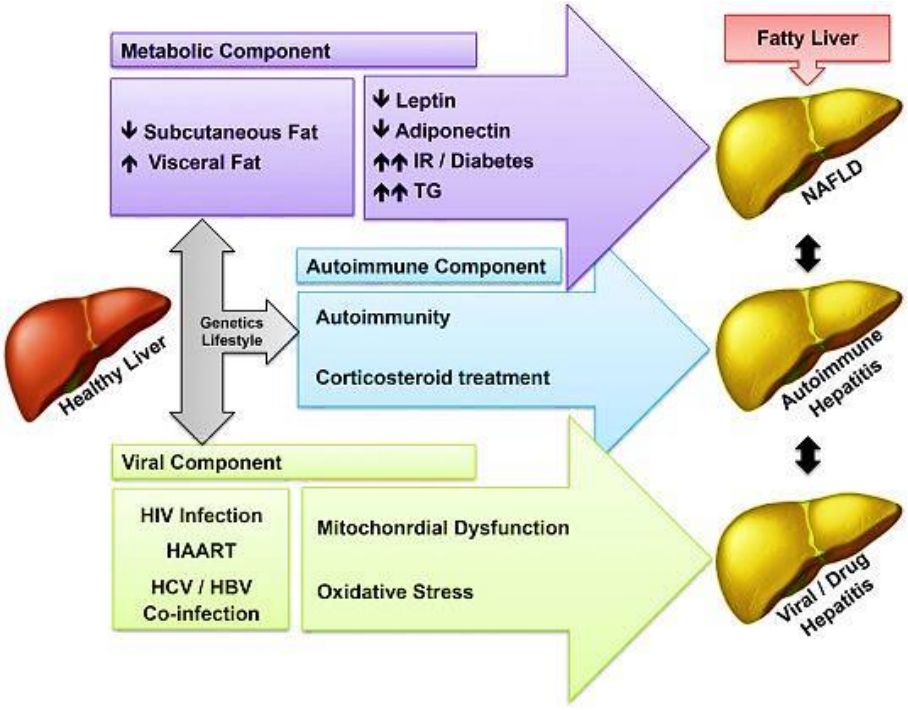

Fig 7: Molecular mechanisms involved in the vicious circle linking fatty liver to diabetes and diabetes to progressive liver injury. Left, the first part of the journey, leading from initial insulin resistance to fatty liver and eventually to the development of T2D in those predisposed individuals in whom pancreatic lipotoxicity occurs.

DATA – SYNTHESIS AND ANALYSES

Meta-analysis was not carried out because of the variability of the outcome measures and the heterogeneous nature of the interventions. [35] Therefore, a narrative synthesis is carried out based on the interventions, and textual description is clustered based on the outcome.

The outcomes were effect on the following items:

1. Glycaemic control (changes in HbA1c as the main indicator of treatment effectiveness in diabetic patients, and effect on patient self-monitoring of blood glucose (SMBG) or frequency of blood glucose testing)
2. Pharmacological and overall approaches to treatment
3. Diet and healthy eating
4. DSMS (Diabetes self-management education and support)
5. Physical activity
6. Blood pressure control (changes in systolic and diastolic blood pressure)
7. Lipid management (effect on blood levels of LDL)
8. Foot care

QUALITY ASSESSMENT

As described above, studies that had no control group, a population with less than 10 patients or with less than 3 months of follow-up, were excluded. [35] Out of the remained studies, 52 items were randomized controlled trials and three of the studies were non-randomized controlled trials. Another 11 studies were observational studies with control.

DATA EXTRACTION

Titles and abstracts of all selected studies were reviewed independently by two reviewers. Papers identified as relevant or of uncertain relevance based on the abstracts were further independently evaluated by both reviewers. Any discrepancies between the two reviewers were resolved by discussion. [35] Reasons for exclusion were documented according to the exclusion criteria.

The data extraction and quality assessment of the studies were performed by the first author and individually checked by the second one for accuracy and to identify missing information.

A data extraction form was developed, piloted, and used to extract data which was a modified version of the template form suggested by the Center for Review and Dissemination guidance for systematic review.[36] This form contains the following items:

1. Article properties e.g. title and UID;
2. The study attributes e.g. population, duration of following, mean age, and gender;
3. Research type include RCT, NRCT, Other Observational studies with control, and Observational study without control;
4. Intervention type according to the description of inclusion criteria;
5. Diabetes type (I, II, GDM, unknown or mixed); and
6. Outcomes according to the American diabetes association recommendations for diabetes management.

INSULIN PUMP DELIVERY AND CLOSED-LOOP DELIVERY SYSTEM:

Technology also provides novel options for the delivery of insulin to the patient. Syringes and pre-loaded pens work well for many patients using once daily or multiple daily injections (MDI), but some patients benefit from continuous subcutaneous insulin injection (CSII). Several things are commercially available in insulin pumps. [37] The most commonly used insulin pumps on the market use push-button control panels to program and direct basal and bolus delivery from an insulin reservoir (e.g. pumps from Medtronic, Animus). Increasingly, pumps are being designed with a touch screen control interface (e.g. Tandem t: slim), tubeless delivery systems (e.g. Insulet Omnipod), or wireless communication between the pump and the patient's glucometer as well as the CGM device. At the opposite end of the complexity spectrum, a simple pump is being marketed for patients with T2D that delivers basal insulin at one of three pre-set constant basal rates and allows the user to provide boluses on-demand in two-unit increments. Patients receiving MDI insulin therapy who might be candidates for an insulin pump should be referred to an Endocrinologist for a full discussion of treatment options.

In patients with T1D, meta-analyses have shown better glycaemic control (as measured by HbA1c) and lower rates of hypoglycemia with CSII in adults and children when compared with MDI. Whether or not the use of a pump will lead to improvements in long-term clinical outcomes compared to optimized MDI is still uncertain. One recent study from Sweden showed that among adults with T1D followed for 6.8 years, patients using insulin pump therapy had a 27% decreased risk of all-cause mortality, a 45% reduction in fatal coronary heart disease, and a 42% decrease in fatal cardiovascular disease.

GENETIC DEFECTS OF THE β- CELL

Several forms of diabetes are associated with monogenetic defects in β-cell function. These forms of diabetes are frequently characterized by the onset of hyperglycemia at an early age (generally before age 25 years). They are referred to as maturity-onset diabetes of the young (MODY) and are characterized by impaired insulin secretion with minimal or no defects in insulin action. They are inherited in an autosomal dominant pattern. Abnormalities at six genetic loci on different chromosomes have been identified to date. The most common form is associated with mutations on chromosome 12 in a hepatic transcription factor referred to as hepatocyte nuclear factor (HNF)-1α. A second form is associated with mutations in the glucokinase gene on chromosome 7p and results in a defective glucokinase molecule. Glucokinase converts glucose to glucose-6-phosphate, the metabolism of which, in turn, stimulates insulin secretion by the β-cell. Thus, glucokinase serves as the "glucose sensor" for the β-cell. [38] Because of defects in the glucokinase gene, increased plasma levels of glucose are necessary to elicit normal levels of insulin secretion. The less common forms result from mutations in other transcription factors, including HNF-4α, HNF-1β, insulin promoter factor (IPF)-1, and NeuroD1.

Genetic abnormalities that result in the inability to convert proinsulin to insulin have been identified in a few families, and such traits are inherited in an autosomal dominant pattern. The resultant glucose intolerance is mild. Similarly, the production of mutant insulin molecules with resultant impaired receptor binding has also been identified in a few families and is associated with an autosomal inheritance and only mildly impaired or even normal glucose metabolism.

GENETIC DEFECTS IN INSULIN ACTION.

There are unusual causes of diabetes that result from genetically determined abnormalities of insulin action. The metabolic abnormalities associated with mutations of the insulin receptor may range from hyperinsulinemia and modest hyperglycemia to severe diabetes. Some individuals with these mutations may have acanthosis nigricans. Women

may be virilized and have enlarged, cystic ovaries. In the past, this syndrome was termed type A insulin resistance. Leprechaunism and the Rabson-Mendenhall syndrome are two pediatric syndromes that have mutations in the insulin receptor gene with subsequent alterations in insulin receptor function and extreme insulin resistance. The former has characteristic facial features and is usually fatal in infancy, while the latter is associated with abnormalities of teeth and nails and pineal gland hyperplasia.

Alterations in the structure and function of the insulin receptor cannot be demonstrated in patients with insulin-resistant lipoatrophic diabetes. Therefore, it is assumed that the lesion must reside in the post-receptor signal transduction pathways.

METABOLOMICS IN TYPE 2 DIABETES :

Metabolomics is the comprehensive characterization of metabolites in biological systems. The term metabolomics is similar to that of older technologies such as *genomics* (dealing with genes), transcriptomics (dealing with gene transcripts), and *proteomics* (dealing with proteins). [39] The metabolome is comprised of small intermediary molecules and products of metabolism, including those associated with energy storage and utilization, precursors to proteins and carbohydrates, regulators of gene expression, and signaling molecules. Thus, the metabolome as the entirety of metabolites represents a real-time functional portrait of the cell or the organism.

The metabolome is influenced by a plethora of factors, such as diet, lifestyle, medications, gender, and age. In this regard, metabolomics becomes a very powerful tool as it views the effects of pathological factors from vastly different origins in a single measurement. Specific methods employed in the study of metabolomics include nuclear magnetic resonance (NMR), gas chromatography-mass spectrometry (GC-MS), liquid chromatography-mass spectrometry (LC-MS), capillary electrophoresis mass spectrometry (CE-MS), [40] and high-performance liquid chromatography (HPLC). NMR measures differences in the magnetic properties of atomic nuclei, mass spectrometry measures differences in the mass and electrical charge of the metabolites, and chromatography distinguishes metabolites by differences in adhesion properties.

Storage conditions are a crucial factor for metabolomics studies, especially for prospective studies, where samples may be analyzed many years after being collected. Studies found no differences between plasma that was frozen immediately versus plasma that was stored at 4∘C for 8 and 24 hours before freezing, respectively. Likewise, no significant differences in metabolite profiles were found when comparing storage at −20∘C and −80∘C . Plasma samples stored at −80∘C for 13 to 17 years showed no influence of storage time on the metabolic profile.

COLLECTING AND USING SELF MONITORED BLOOD GLUCOSE DATA

How can the health care provider make use of the self-monitored blood glucose (SMBG) data that the patient brings to a clinic? How often should patients be asked to check their blood sugars, and how should the clinician access that data and modify treatment plans? Self-monitored blood glucose is important to improve outcomes and decrease complications in patients with type 1 diabetes (T1D) and intensively treated type 2 diabetes (T2D). However, in adults with Type 2Diabetes who are not treated with intensive medication regimens, meta-analyses of trials using SMBG have not shown improvement in clinically meaningful endpoints, and the SMBG is associated with higher financial costs and patient dissatisfaction. This is probably due to the somewhat random collection of SMBG data by patients, and the failure to develop a treatment plan that uses the collected information. Several studies have shown that the most effective use of SMBG is to link that data into a structured clinical action plan involving the patient and health care provider. The STeP trial was a cluster randomized control trial of 483 insulin naive adults with poorly controlled T2D. The intervention was the collection of blood glucose monitoring in a standardized pattern for three days before clinic visits, and review of the data with the clinician. Over 12 months of follow-up, there was a small but significant improvement in HbA1c in the intervention arm compared to the control group, and a much higher likelihood of medication change (new diabetes medication or adjustment in dose of existing medication). Patients also reported higher levels of self-confidence and autonomy in diabetes management in the structured self-monitoring arm of the trial. This is just one of many examples of structured glucose collection plans that could be integrated into an office workflow to maximize the utility of information and utilize scarce resources including time and money for both patients and providers. Examples of structured self-monitoring of blood glucose plans for patients not treated with multiple daily injections of insulin.

In the simplest implementation, patients would be asked to bring paper diaries of glucose readings to the

office visit. Alternatively, most glucometer manufacturers have readily available software that can be downloaded from the web or installed via CD on an office PC to enable providers to print summarized data from the patient's glucometer. The provider would also need an inexpensive transfer cable, obtained from glucometer manufacturers or an electronics store. This is an easy technological upgrade that can be provided at minimal cost and training and should assist in improving the quality of the actionable data available at an office visit. Similarly, point of care HbA1c testing is an easy upgrade to provide immediate results during a clinic visit.

CONTINUOUS GLUCOSE MONITORING

The recent development of continuous glucose monitoring (CGM) devices has expanded the capacity for self-monitoring. CGM measures interstitial glucose levels in the subcutaneous tissue via a small implanted catheter that is connected to an electrochemical recorder. The hardware can be discretely worn under clothing. Several challenges persist with the technology[41]:

1) CGM must be calibrated using a glucometer several times daily,
2) Glucose reading is not as accurate as capillary glucose measurements, and
3) Interstitial fluid lags behind the plasma compartment.

ANTIHYPERGLYCAEMIC AGENTS USED IN TYPE 2 DIABETIC MELLITUS

The elimination and excretion are mainly renal (75% of an oral dose is found in the urine as an unchanged drug), and the rest is metabolized via the cytochromes CYP 3A4 and CYP 2C8. Drug-drug interactions were not observed under Sitagliptin therapy in clinical studies, and especially no such interactions were found with other anti-hyperglycaemic agents in type 2 diabetic patients. [42] The elimination half-time is 12–14 hours. Doses of 50–200 mg/d Sitagliptin administered once daily lead to an ≥80% inhibition of DPP-4 over 24 hours and Sitagliptin plasma levels of >100 nm. As a result, the concentrations of biologically active, intact GLP-1 are increased 2–3-fold in the postprandial state. In all the studies performed the safety data are very good and hypoglycaemic episodes or other adverse events did not differ significantly from those observed in the control groups. In immunotherapy or studies investigating a combination with metformin or thiazolidinedione's (TZDs), Sitagliptin did not cause hypoglycemia.

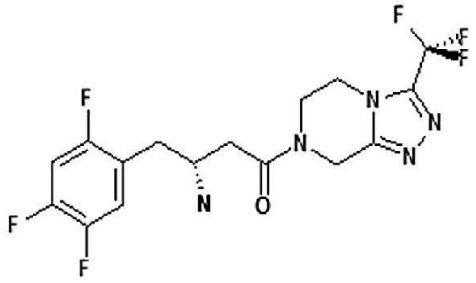

Fig 9: Sitagliptin.

Metformin has proven to be safe and effective and is usually well tolerated. However, many patients cannot tolerate the medication due to its side effects. Therefore, optimal metformin use requires a clear understanding of its side effects and safety. Metformin oral tablets can cause side effects that can be mild or serious. The usual side effects include nausea, abdominal bloating, flatulence, vomiting, diarrhea/constipation, heartburn, headache, agitation, chills, dizziness, tiredness, abdominal cramps or pain, loss of appetite, asthenia, myalgia, upper respiratory tract infection, and an altered or metallic taste. However, evidence shows that the gastrointestinal symptoms (GI) and symptoms of the digestive tract are mostly observed with metformin treatment. GI symptoms were confirmed to be more in participants who had metformin compared to the ones who had placebo (average 28% versus 16%, p=0.01). The reason for this could be because the microbiome within the intestine changes due to metformin. One of the main sites of metformin action in the liver, however current research shows that metformin also affects the gut due to an association with the gut-brain-liver axis. The bile acids in the intestine increase with metformin, which can affect the microbiome and as a result, the secretion of GLP-1, cholesterol levels, and stool consistency are affected.

CAUTIONS & CONTRAINDICATIONS

Metformin has been associated with a rare, metabolic condition called Lactic Acidosis (LA), which is very dangerous, often fatal, and life-threatening. Symptoms of Lactic Acidosis are not very specific and patients can have tiredness, lethargy, weakness, diarrhea, vomiting, nausea, abdominal pain, anorexia, blue or cold skin, chills, muscle pain, hypotension, fast or difficult breathing, dizziness, hyperventilation, severe drowsiness, a metallic taste in the mouth or slow or irregular heartbeat. Studies have reported that Lactic Acidosis occurs because of substantial tissue hypoperfusion and hypoxia. In Lactic Acidosis, blood lactate concentrations increase, the pH of blood decreases (below 7.35), and disturbances of the

electrolytes occur with increased gaps in the anions [43].

However, this study had some limitations because firstly, causation could not be concluded from the results. After all, the researchers did not include randomization, as it was not a clinical trial. Secondly, all the confounding factors, for example, duration of Type 2 Diabetes Mellitus or liver disease, were not included in this single-centered study. A previous study found that metformin usage in patients who had Type 2Diabetes Mellitus and advanced CKD had significant associations with enhanced risks of all-cause mortality in comparison with participants who had Type 2Diabetes Mellitus but did not use metformin. This was concerning because reduced renal functions in patients who had moderate CKD and were also taking metformin could have increased risks of getting toxic reactions with metformin.

DRUG INTERACTIONS AND PRECAUTIONS FOR METFORMIN

Drug interactions involving metformin that are clinically significant are not very common. However, a few medications can interfere with metformin's actions. The concentrations of metformin can increase if cimetidine is also administered simultaneously. Dosages should be adjusted if a patient. Testosterone, contraceptive pills, or other diabetes medicines and blood glucose levels may need to be checked more often. Some medications excreted by renal tubular secretion, such as morphine, quinine, ranitidine, digoxin, quinidine, procainamide, triamterene, vancomycin, and trimethoprim, may be competing against metformin for being eliminated. Therefore, patients who take metformin simultaneously with these agents need close monitoring for any toxic reactions. Metformin can be used in pregnancy for both pre-existing and gestational diabetes. During pregnancy, it is usually safe to take metformin either on its own or when combined with insulin. Studies have shown no or minor risks for the usage of metformin during pregnancy. However, treatment with metformin should not be continued in women who have gestational diabetes, after giving birth. In women who have pre-existing diabetes, metformin can be used during breastfeeding. Although metformin passes into breast milk, the amount is very small. There is a lack of sufficient evidence on metformin with herbal supplements and remedies. However, this review does not cover an extensive list of side effects and others that can occur. Additionally, people taking metformin may/may not experience any or all of the above side effects.

BI LAYER TABLETS FOR VARIOUS DRUGS APPLICATIONS:

Bi-layer tablet is suitable for the sequential release of two drugs in combination.

- Separate Two Incompatible Substances
- Sustained release tablet in which one Layer is immediate release as initial dose and the second layer is maintenance dose.
- Promoting Patient Convenience and Compliance.
- Bilayer tablet is improved beneficial technology to overcome the shortcoming of the

Single layered tablet

- Bilayer tablets are used to deliver the loading dose and sustained dose of the same or different drugs.
- Bilayer tablets are used for bilayer floating tablets in which one layer is the floating layers another one is the immediate release layer of the drug.
- Bilayer tablets are used to deliver the two different drugs having different release profiles.

ADVANTAGES [44]

- They are used as an extension of conventional technology.
- Potential use of single entity feed granules.
- Separation of incompatible components.
- Patient compliance is enhanced leading to improved drug regimen efficacy.

DIS ADVANTAGES [45]

- Adds complexity and bilayer rotary presses are expensive.
- Insufficient hardness, layer separation, reduced yield.
- Inaccurate individual layer weight control.
- Cross-contamination between the layers.

IDEAL PROPERTIES OF MULTILAYER TABLETS[46] :

- Drugs should not be affected by compaction of each layer and physically stable and

  Withstand the mechanical shock.
- Separation of layers should not occur during various stages such as compression, crating, packing, shipping and storage.
- The layer should not fuse into the non-disintegrating matrix, should have clear,

parallel, visual separation in final compressed tablets.

- If it consists of a disintegrating matrix, it should be disintegrated within GIT, modified release part should not be affected dissolution profile of IR part and slow and gradual erosion.
- Layer tablets should have chemical & physical stability to maintain their physical attributes over time either if drugs are physical & chemical incompatible.

COMBINATIONAL DOSAGE REGIMEN IN FIXED DOSE FREQUENCY FOR BETTER SAFETY AND EFFICACY

Metformin and Sitagliptin have independent glucose-lowering properties and may increase GLP-1 levels by working through complementary mechanisms. [47] They also have few pharmacological interactions and a low risk of hypoglycemia, making co-administration an attractive therapeutic prospect. Fixed-dose combination tablets are available in doses of 50 mg Sitagliptin + 500 mg Metformin (**or)** 50 mg Sitagliptin + 1000 mg Metformin. In a randomized, open-label, 2-part, 2-period crossover study, bioequivalence between Fixed-dose combination and co-administration of corresponding doses of Sitagliptin and Metformin was established in 48 nondiabetic subjects supporting the efficacy and safety of fixed-dose combination treatment. In a placebo-controlled, multiple-dose, crossover trial in 13 patients with type 2 diabetes, steady-state pharmacokinetics of Sitagliptin and metformin were not altered by their co-administration, and no drug-related adverse effects were reported. Currently, no trials are comparing the effect of a fixed-dose combination of Sitagliptin and Metformin on patient compliance although it might be expected that treatment with a Fixed-dose combination could improve patient compliance compared with treatment with separate agents. Studies comparing patient compliance for Fixed-dose combination with separate co-administration of metformin and glyburide generally report improved treatment adherence when patients were changed from a combination of free doses to a Fixed-dose combination. The product information for the Fixed-dose combination advises precaution against lactic acidosis for the metformin component and pancreatitis for the Sitagliptin.

COMBINATIONAL DOSES IN BILAYER TABLETS

For the administration of fixed-dose combinations of different APIs, prolong the drug product life cycle, buccal/mucoadhesive delivery systems; fabricate novel drug delivery systems such as chewing device and floating tablets for gastro-retentive drug delivery.

- The controlled delivery rate of either single or different active pharmaceutical ingredients.
- To modify the total surface area available for the API layer either by sandwiching with one or two inactive layers to achieve swellable/erodible barriers for modified release.

GENERAL PROPERTIES OF BI-LAYER TABLET DOSAGE FORMS

- A bi-layer tablet should have an elegant product identity while free of defects like chips, cracks, discoloration, and contamination.
- Should have sufficient strength to withstand mechanical shock during its product packaging, shipping, and dispensing.
- Should have the chemical and physical stability to maintain its physical attributes over time.
- The bilayer tablet must be able to release the medicinal agents in a predictable and reproducible manner.
- Must have a chemical stability shelf-life, so as not to follow alteration of the medicinal agents.

TRIPLE LAYER TABLET

Triple-layer tablets consist of three layers of which the first layer is for the immediate release of drug and the second layer is for sustained release. These two layers are separated by the middle barrier layer. This is more suitable for the delivery of two drugs that have interactions in them. It consists of several different granulations that are compressed to form a single tablet composed of two or more layers and usually each layer is of a different color to produce a distinctive-looking tablet.[48] Dust extraction is essential during compression to avoid contamination. Therefore, each layer undergoes light compression as each component is laid down.

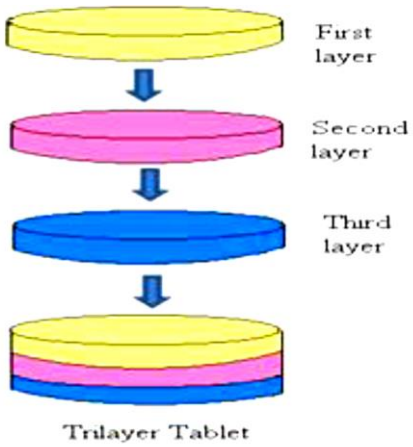

Fig10: Trilayer tablet

COMPRESSION COATED TABLETS

This type of tablet has two parts, the internal core, and surrounding coat. The core is a small porous tablet and prepared on one turret. For preparing the final tablet, a bigger die cavity in another turret is used in which first the coating material is filled to half and then core tablet is mechanically transferred, again the remaining space is filled with coat material and finally compression force. This tablet readily lends itself to a repeat action tablet as the outer layer provides the initial dose while the inner core releases the drug later on. But, when the core quickly releases the drug, an entirely different blood level is achieved with the risk of overdose toxicity.

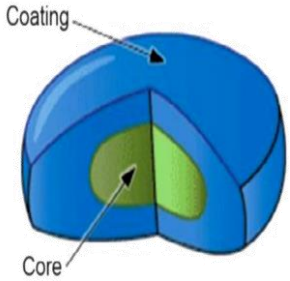

Fig 11: Compression coated tablet

To avoid immediate release of both the layers, the core tablet is coated with an enteric polymer So that it will not release the drug in the stomach while the first dose is added to the outer sugar coating. Even so, coating operation requires interpretation while manufacturing and dawdling the manufacturing process. Sometimes, the inner core may be of liquid formulation to provide immediate release of core after the coat gets dissolved.

INLAY/CORE COATED TABLETS

In this type of layered tablet in which instead of the core tablet being surrounded by coating, the top surface is completely exposed shown in figure 4. While preparing, only the bottom of the die cavity is filled with a coating material, and the core is placed upon it. When compression force is applied, some coating material is displaced to form the sides and compress the whole tablet.

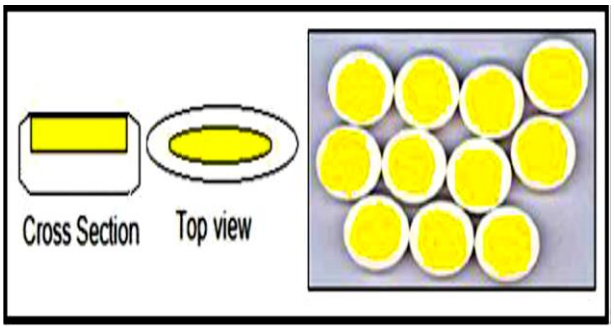

Fig 4: Core Coated Tablet

ECONOMIC BURDEN OF DIABETES MELLITUS

Economic aspects of diabetes and diabetes care currently attract considerable attention as the world diabetes epidemic takes hold and the healthcare activities of countries come under pressure to accomplish more within constrained resources. [49] Diabetes mellitus is a very expensive disease and has profound implications in terms of long-term microvascular and macrovascular complications and their associated cost. These complications reduce both life expectancy and quality of life. Diabetes mellitus poses a big economic burden with regards to health system costs, indirect costs arising from losses occasioned by patient disability and premature mortality, time spent by family members accompanying patients when seeking care, and intangible costs in terms of psychological pain to the family and loved ones. The prevalence of diabetes in the WHO African Region was estimated in 2000 to be at 7.02 million people.

SIGNIFICANT REDUCTION IN THE RISK OF DEVELOPING TYPE-2 DIABETES

The beneficial effect of the dietary pattern on diabetes mellitus and glucose metabolism in general and traditional food patterns was associated with a significant reduction in the risk of developing type-2 diabetes. [50] The dietary pattern emphasizes consumption of fat primarily from foods high in unsaturated fatty acids and encourages daily consumption of fruits, vegetables, low-fat dairy products, and whole grains, low consumption of fish, poultry, tree nuts, legumes, very less consumption of red meat. The composition of the diet is one of the

best known dietary patterns for its beneficial effects on human health that may act beneficially against the development of type-2 diabetes, including reduced oxidative stress and insulin resistance. High consumption of vegetables, fruits, legumes, nuts, fish, cereals and oil leads to a high ratio of monounsaturated fatty acids to saturated fatty acids, a low intake of trans fatty acids, and high ingestion of dietary fiber, antioxidants, polyphenols.

The diets are characterized by a low degree of energy density overall; such diet prevents weight gain and exerts a protective effect on the development of type-2 diabetes, a condition that is partially mediated through weight maintenance. Greater adherence to the diet in combination with light physical activity was associated with lower odds of having diabetes after adjustment for various factors.

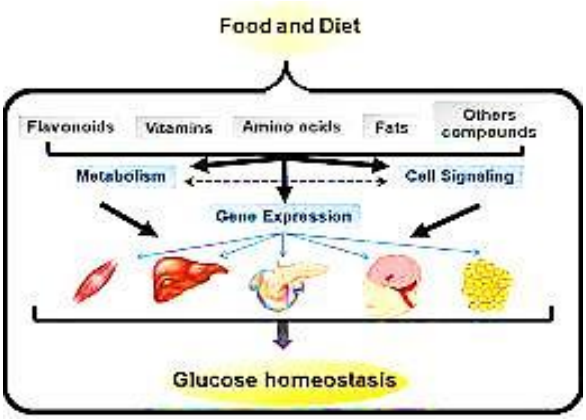

Fig 10: A diet high in fat, calories, and cholesterol increases your risk of diabetes. A poor diet can lead to obesity (another risk factor for diabetes) and other health problems. A healthy diet is high in fiber and low in fat, cholesterol, salt, and sugar.

FUTURE PROSPECTS IN DEVELOPMENT OF BILAYER OR MULTILAYER DESIGNS

The design of multi-layer through modulating layers which allows different tablet designs for the production with specific release to achieve different dissolution patterns like bimodal, delayed, and multi-modal delivery has been given below

- Zero order sustained release
- Time programmed delivery system

ZERO – ORDER SUSTAIN RELEASE

It comprises either a hydrophilic or hydrophobic intermediate layer containing the active drug or one or two barrier layers which are press coated to the faces of the tablet core, leaving the sides of the core exposed. Many authors have evaluated this design. The widely used barrier polymers for sustaining the drug delivery are either hydrophilic and/or hydrophobic materials. In general, linear release profiles can be obtained by applying hydrophilic barrier layers on both the faces of a hydrophobic matrix tablet or by applying a hydrophilic barrier layer on one face and a hydrophobic barrier layer on the other face of the matrix tablet. However, net formulation and variables within the matrix and barrier layers are important to be controlled rather carefully to achieve zero-order drug release from hydrophobic matrix tablet coated with hydrophobic barrier layers on both faces.

TIME PROGRAMMED DELIVERY SYSTEM

Time is programmed followed by time-controlled release when the delivery of the drug is required in a time-controlled fashion in the gut, rather than the release of the drug in a continuous manner according to circadian rhythm. This system consists of a core that is coated with different polymeric barriers. The release of the drug, from the core tablet after swelling or after eroding of a hydrophobic or hydrophilic barrier of coating that's how pulsatile release of the drug followed by the extended or prolonged release of the drug delivery system provides an immediate release of the drug.

BIMODAL RELEASE PROFILE

Bimodal release profile shows an initial rapid release followed by slow release and again the second phase of rapid drug release i.e. sigmoidal release profile. This system compensates for the slow absorption in the stomach and small intestine and for programmed pulse releases that perform more effectively at the site of action to undertake periodic changes.

ADVANTAGES OF MULTI-LAYERED TABLET :

Greatest chemical and microbial stability overall oral dosage form.

- Unpleasant odor and bitter taste can be masked by coating technique.
- Flexible Concept.
- Improved patient compliance.

DIS ADVANTAGES OF MULTI-LAYERED TABLET :

- Some drugs resist compression into dense compacts, owing to their amorphous nature, low-density character.
- The physician has less flexibility in adjusting the dose regimens.

THE OBJECTIVES OF PREPARING MULTILAYER TABLET :

- To use different APIs in combination having proven advantages over single compounds Administered separately for therapeutic effect.
- To overcome the limitations in case of a single drug which is unable to treat or avoid adverse drug effect, if any.
- To get dual release profile to reduce dosing frequency and thereby increasing patient Compliance.
- To combine compatible or incompatible drugs with different release characteristics in the same dosage form and enhancing the stability of dosage form as compared to its dosage form.
- To treat critical disease condition when single active unable to produce complete therapeutic action and to maintain over a period 12 h or more.

- **CONCLUSION:**

Diabetes is a chronic disease, in which the body does not produce insulin, it a hormone that is needed to convert the glucose from food into energy. Non-insulin-dependent diabetic Mellitus or Type 2 Diabetes, secretes insulin from the pancreas, Type 2, is partially or completely unable to use this insulin due to resistance. Type 2 DM is a metabolic disease that can be prevented through lifestyle modification, diet control, and control of overweight and obesity Management should be tailored to improve the quality of life of individuals with type 2 DM. Metformin and Sitagliptin are oral diabetes medicines, that help to control blood sugar levels. Metformin works by decreasing glucose production in the liver, by decreasing drug absorption, and Sitagliptin works by regulating the levels of insulin in the body. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and the second layer is maintenance dose. The preparation of tablets in the form of multilayers is used to provide systems for the administration of incompatible drugs, and to provide controlled release tablet preparations by providing surrounding or multiple swelling layers.

CONFLICT OF INTEREST

There is no conflict of interest in this work

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