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Original Research Paper

METFORMIN INDUCES SIGNIFIANT ROLE IN GLYCEMIC CONTROL IN TYPE 2 DIABETES MELLITUS AND ITS MECHANISM OF ACTION

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ABSTRACT:
In the current senerio of dibatic the administration of the metformin drug increses continuously. In this view discussion of the facts about the metformin and the Action of Metformin on Mitochondrial Chain Complex and a brief discussion on mechanism of action of metformine. Metformin is transported into hepatocytes mainly through OCT1 and accumulates in mitochondria. The major inflammation properties of the metformin are also highlite.

Keywords: Metformin, Type 2 DM, Glycemic control, Galegineofficinalis.

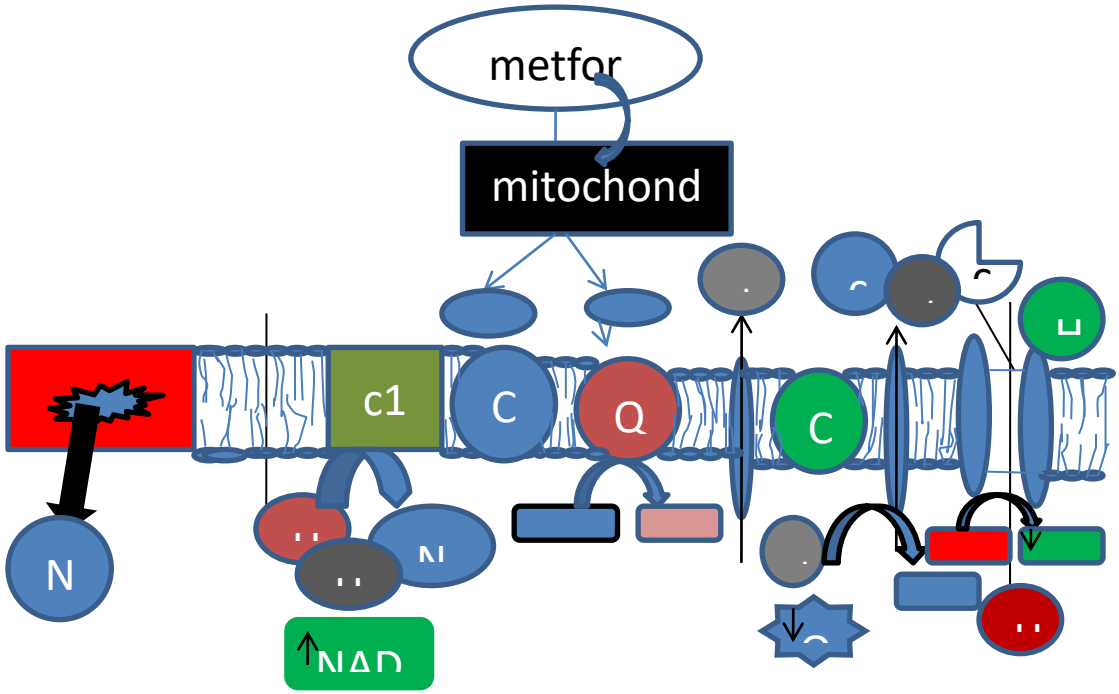
INTRODUCTION:

Metformin and therefore the related drug phenformin the latter withdrawn from diabetes treatment in most countries due to side effects of Lactic acidosis are derived from GALEGINE, a natural product from the plant galegine officinalis utilized in herbal medicine. GALEGINE was tested as a glucose lowering agent in humans within the 1920s, but was found to be toxic at about an equivalent time, two synthetic derivative of GALAGINE. At about an equivalent time, two synthetic derivative of galagine (1, 2, 31) Metformin and phenoformin were synthesized and tested although they weren't introduced to clinical use until 1950s (3, 32, 37.). Chemically GALEGINE is an isoprenyl derivative of guanidine while metformin and Phenformin are containing 2 couple molecules of guanide containing additional substitutes. Therefore, Metformine derived from a natural product utilized in herbal medicine and was designed to focus on a specific pathway or disease mechanism. it had been established as a secure and effective therapy before detailed mechanistic studies. Oral dose of immediate release metformin in humans ≈70 you look after the dose is absorbed from the SI and remaining passing into the colon before being excreted in feces(4,33,34). Metformin is excreted in urine unchanged, with no metabolites reported. Plasma concentration of Mertformin in humans are typically within the low molecular range (e. g 28 -24 μmol/L) A recent metformin positron emission tomography(PET) study demonstrated within the intestines, liver, kidneys and bladder with only slow accumulation in muscles.(5,35, 36) In rats dosed with I.V METFORMIN accumulation was observed within the Pancreas and fat at concentration of half that seen within the liver (6, 37).
Note: - The Human Pharmacokinetic datum to the liver, Kidney and Intestines as the key target organs of Metformin(1).

MECHANISM OF METFROMIN TREATMENT INCLUDE:

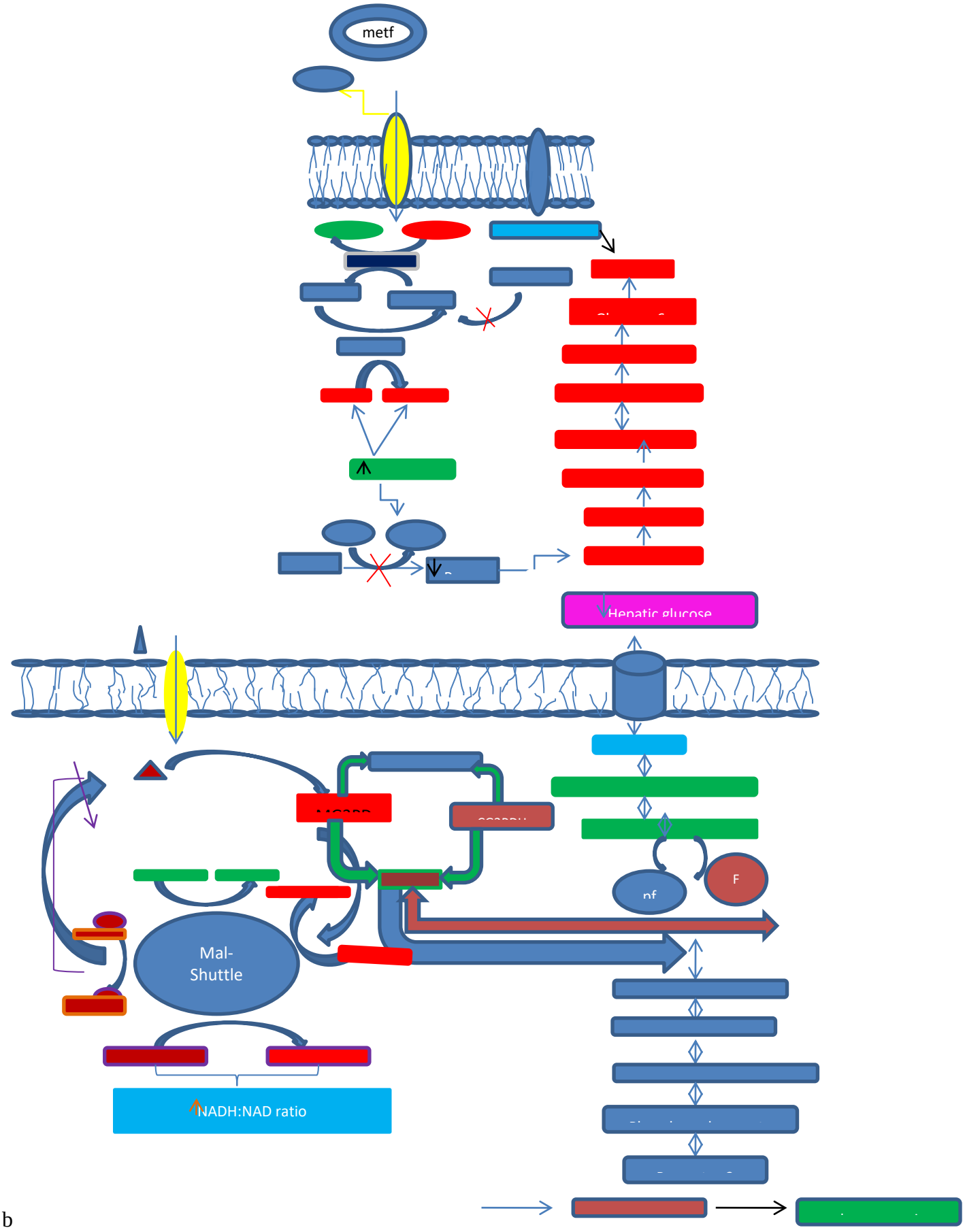
1. Reduced Gastrointestinal Absorption of Carbohydrates, as well as decreased insulin and leptin resistance, the reduction of Plasma ghrelin.
2. Induction of Lipolysis and Anorexis by activation of Glucagon like petide1(GPI)
3. Metfromin also reduces Ectopic Lipid deposited in Liver and skeletal Muscles through increased fat oxidation and decrease Lipid Synthesis.
4. The Pleiotropic properties of Metfromin suggest that the drug act as multiple tissues through various underlying Mechanism rather than on a single organ via a unifying mode of action.
5. Mitochondrial respiratory chain complex 1 is targeted by Metformin and its inhibition is involved in AMP activated protein kinase independent regulation of hepatic gluconeogenesis by triggering alteration in cellular energy change and redox state (7).

Figure 1:- Action of Metformin on Mitochondrial Chain Complex



After accumulation in the mitochondria by as – yet – unclear process might be associated with the positive charge of molecules. Metformin inhibits the Mitochondrial chacomplex1 (C1) in a reversible and non competitive manner.This inhibition presumably occur by direct intraction of the drug Cys39 containing matrix loop of the respiratory chain submit ND3 which stabilize the enzyme in anopen- loop deactive conformation state. The inhibition of c1 leads to a → ↓ in NADH oxidation a → ↓ in proton pumping across the inner mitochondrial membrane and a → ↓ in oxygen consumption rate, resulting in lower portiongradient (ΔΨ) and a → ↓ in protein driven ATP synthesis from ADP and in organic phosphate (P1) . Cytochrome c, c1 - c5 , Mitochondrial chain complex 1-5 IMS, inner membrane space ;Q, coenzyme Q(ubiquinone).

B. Figure :- Redox dependent mechanism of metformin induced inhibition of hepatic Gluconeogenesis.



b

2. Metformin is transported into hepatocytes mainly through OCT1 and accumulates in mitochondria.

a. In mitochondria, metformin partially inhibits mitochondrial respiratory chain complex1 (complex1) resulting in decreased ATP level and accumulation of AMP. Thus, metformin has a mild effect on the overall cellular energy charge. Metformin induces changes in the AMP-ATP radioactive AMPK through its phosphoylation by LKB1. Subsquently AMPK inhibits glycogenic gene transcription (PcK1 and G6 PC) via the Phosphorylation and cytoplasmic sequestration of the transcriptional cofactor CRTC2. This AMPK dependent mechanism has been challenged by the use of Liver AMPK – deficient mice.

b. Gluconeogenesis is highly energy consuming metabolic pathway. Therefore reduction in cellular ATP level is sufficient to reduce glucose production flux. In addition, elevation of AMP level contribute to inhibition of glucose reduction through allosteric inhibition of fructose-16-biphosphate1(FBP1), a key gluconeogenic enzyme.

c. Metformin induces AMP accumulation inhibits adenylate cyclase and decreases cAMP synthesis, resulting in decreased protein kinase A (PKA) activity and downstream signaling. Gluconeogenesis is suppressed through both the decrease in gluconeogenic enzyme activity and the inhibition of glucagon – induced gluconeogenic gene expression associated with lack of phosphoylation of regulators (for example CREB1 and 13PR).

d. Chronic metformin induced AMPK activatism might indirectly decrease gluconeogenesis by heptic insulin sensitivity. AMPK inhibits lipogenesis through phosphoylation and inhibition of acetyl- CoA carboxylase (ACC), thereby decreasing malnonyl-CoA synthesis, which activates carnitine palmitoyl tranferase1 ↑ (CPT1) and stimulates fatty acid oxidation by increasing the import of acyl –CoA into mitochondria. Overtime metformin induced AMPK activation decreases heptic steatosis and improve insulin sensitivity, which in turn inhibits gluconeogenesis GLUT2 glucose transporter type 2; PFK/dose, 6-phosphofructo-2- kinase or fructose 2, 6 diphosphatase1(10,11). Metformin might contribute to improvements in obesity associated
meta inflammation and tissue specific insulin sensitivity through direct and indirect effects on various immune cells in metabolic changes in organs.

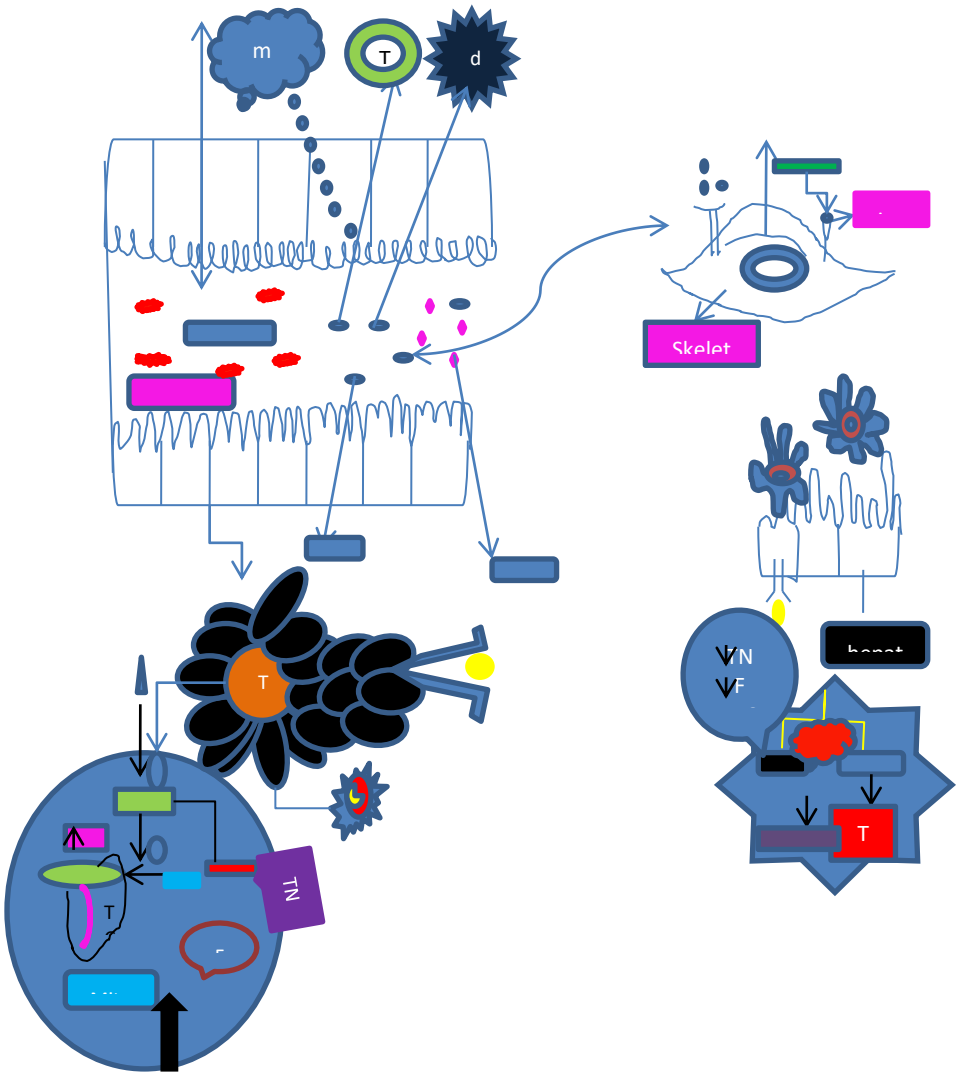
a. Metformin suppresses gluconeogenesis through ↑ m(G3PDH) a direct inhibition of mitochondrial glycerol-3- phosphate, dehydrogenease (PDH), an enzyme involved in the glycerol- phosphate shuttle. Metformin induces inhibition of mG- 3PDH disrupts glucose production from glycerol and increases cystolic redox potential (NADH: NAD+) which impede the utilization of lactate for glucose production.

b. The accumulation of metformin in mitochondria caused by positive charge leads to mitochondrial depolarization and inhibition of the electrogenic transporter for asparrte (ASP) of the Malate Asparate (Mal-ASP) shuttle, resulting in an ↑(increase) in the cystolic NADH: NAD+ ratio. Metformin induced inhibition of the Mal-asparate shuttle stimulates the glycerol – phosphate shuttle leading to a decrease in levels of glycerol 3 phosphate(glycerol-3P) a potent allosteric inhibitor of phospofructokinase 1 (PFK1). As a result gluconeogenesis is inhibited through the partitioning of gluconeogenic substrate towards glycolysis. DHAP, dihydroxyacetone Phosphate; FBP1, fructose-1, 6-biphosphate1; cG3PDH, cystolic G3PDH, GLUT2 , Glucose trasnporter type2; LDH, Lactate dehydrogenase;OCT1, organic transporter 1(8,9).

D. Metformin in Metainflammation

Obesity associated metainflammation results partly from Proinlfammatory activation of tissue – resident macrophages which secrete proinlfammatory cytokines in metabolic organ (i.e. Liver and adiose tissue) and contributes to insulin resistance at least partly by inhibiting insulin signaling. Moreover obesity is often associated with changes in microbiota composition (dysbiosis) that result bacterial secretion of various immunomodulatory components, for example :- short chain fatty acids (ScFAs) or Lipopolysaccharide (LPS), Metformin could improve tissue specific inflammation and insulin sensitivity by inducing regulatory Tcells and for maesophages to polarize towards alternatively activated anti inflammatory maesophages these effects are thought to occur through direct and indirect pathways that involve changes in the gut microbiota for example, increase in abundance of AKKermansia special and both AMP activated protein kinase (AMPK)-dependent and AMPK-independent mechanism ATF3 , activating transcription factor 3; mTOR, mechanism target of ropamycin ; NF –KB, nuclear factor- KB; OXPHOS oxidative – phosphorylation; TGF1B, transforming growth factor $-\beta$, TLR4 like receptor 4; TNF; Tumor necrosis Factor(12,13,14,15).

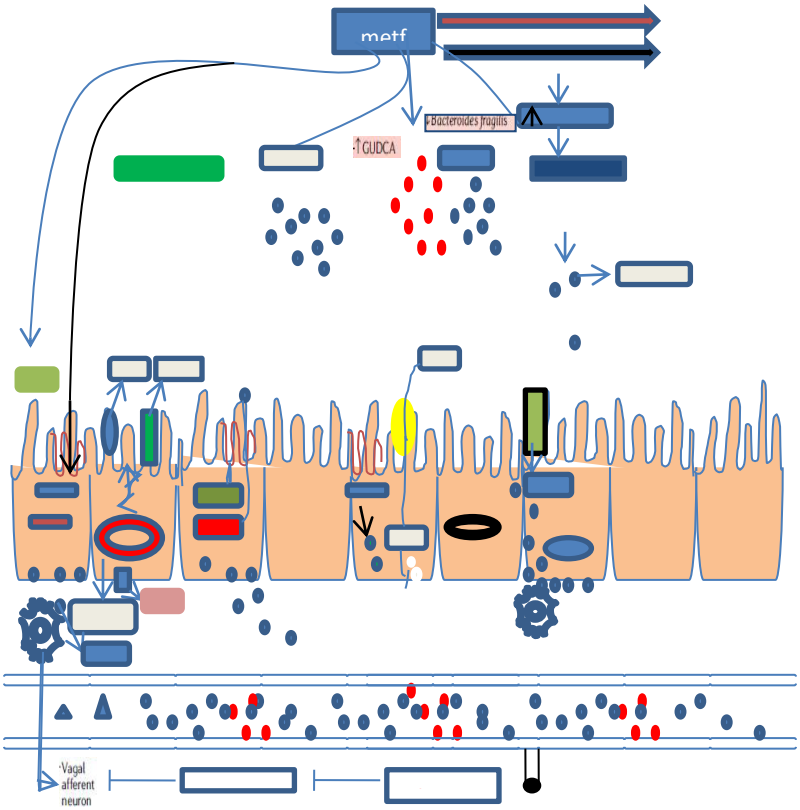
Figure: - Showing Metformin in Metainflammation



The gastrointestinal tract has an important role in the action of Metformin, which modulates bile acid recieculation and enhances the secretion of the glucose lowering gut incretion hormone Glucagon –like peptide 1.

B. The Gut Microbiota is a novel target in the mechanism of Metformin action and is involved in both the therapeutic an adverse effect of the drug.

E. Figure: - Metfromin action in the Gut



Metformin is taken up from the intestinal Lumen in enterocytes by plasma membrane monoamine transporter (PMAT) and OCT3 and transported into the bloodstream by OCT1. Metformin stimulats secretion of glucose – lowering hormone glucagon –like Peptide 1 (GLP-1) from enteroendocrine L cells by direct and indirect mechanism, of note, GLP 1 secretion is directly controlled by muscarinic M3 receptor (M3R). Signaling and AMPK activation in L cells. The GLP1 secretary effects directly induced by metformin are also mediated indirectly by modulation of the bile acid pool and gut microbiota composition. For example:- The inhibitory effect of metformin on apical sodium dependent bile acid transporter(ASBT) reduces the reasbsorption of bile acid, leading to an increase in Luminal concentrations of bile acids and subsequent stimulation of the bile acid receptor TGRs, as well as decrease in intracellular bile acid concentrations limiting activation of farnesoid X receptor (FXR) In addition metformin increase the abundance of short chain fatty acid (SCFA) –Producing bacteria and facilitates, SCFA- induced GLP1 secretion via signaling through GPR41 and GPR43 in L cells. Increase in the abundance of Lactobacillus species, increase release of GLP1 by a glucose SGLT-1 sensing mechanism. Decrease in the abundance of Bacteroides fragilis elevate the level of the bile acid glycoursodeoxycholic acid (GUDCA) a potent endogenous antagonist of FXR) to modulate GLP1 secretion. GLP1 acts locally in the gut by activating a gut brain – Liver neuronal axis that contributes to the regulation of blood level of glucose via a reduction in heptic glucose production. SGLT1 , sodium coupled glucose transporter1(16,17,18,19).

RESULT AND DISCUSSION:

A total of 122 citations were identified in the Literature search of these 18 studies were retrieved for detailed evaluation 10 of the 18 were excluded in the following Metformin therapy is the initial treatment for patients with Type 2 DM according to the current guidelines of the American Diabetes Association /European Association for the study of Diabetic and American Association of ClinicalL Endocrinologost /American College of Endocrinology (20).

1. Metformin is recommended as a combination therapy for patient with Type 2DM . These recommendations are based primarily on the GLUCOSE LOWERING EFFECTS< relatively LOW COST, generally low level a side effects of Metformin. Metformin often seems to be a safe agent in the population over 60(21).

2. In contrast to other antidiabetic treatments, METFORMIN seems to be a weight neutral or can even help to decrease weight by decreasing food intake(22.23).

3. Act as ANTIPSYCHOTIC drug also. Metformin treatment induces weight loss and prevents weight gain in non-diabetic patients taking a typical antipsychotic drugs(29).

4. Metformin have additional positive effects on antipsychotic induced hyperglycemic and metabolic dysfunction.

5. Metformin used in metformin disturbances during pregnancy PCos and GDM (Gestational Diabetes Mellitus)(24).

6. Metformin decreases the rate of conversion from prediabetes to diabetes.

7. Metformin used in prediabetic state and glucose intolerance.

8. Metformin is widely used drug that results in clear benefits in relation to Glucose metabolism and Diabetes related complication.

9. Metformin Induces small reduction in body weight with slight improvement of the blood lipid profile in Pt. above 60 yrs.

10. Metformin might contribute to improvement in obesity associated Metainflammation and tissue specific insulin sestivity through direct and direct effects on various resident immune cells in metabolic organs.

11. It also exerts tumor and anti ageing effects(14).

CONCLUSION :-

Metformin is the first line drug for treatment of the type 2DM, with an excellent safety profile , high efficiency in glycemic control. Moreover in contrast to other antidiabtic treatment. Metformin seems to be weight neutral or can even help to decrease body body weight and decreasing food intake(21,29).

LIMITATIONS :-

Age related complications:

1. Cachexia
2. Involuntarily weight loss in elderly
3. Sarcopenia
4. Diminished bonedensity

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