ADIPOMIMETIN:

A Viable alternative for Metformin and Sulphonylureas for Type-II diabetes

Normal blood sugar levels are considered to be 80 mg/dl to 100 mg/dl in fasting state (https://www.all-about-beating-diabetes.com/normal-fasting-blood-sugar-levels.html) and in post-prandinal state the same is considered to be normal if the same is in the range 90 to 140 mg/dL (5.0 to 8.0 mmol/L), measured at two hours after eating (slighter higher **levels** are sometimes considered **normal** for people over 50 years of age)" https://www.type2diabetesguide.com/normal-postprandial-blood-sugar.shtml#.XZx7sm5uLIU . This balance is maintained by the body with one set of hormones for uptake of sugar from the blood and the other for returning the earlier absorbed sugar back into the blood. The two sets of hormone are in balance with each other, the set for uptake of glucose includes Insulin and associated hormones and the set that returns glucose to blood includes Glucagon and other associated hormones. When balance between these sets of hormones gets tilted and glucose releasing hormones work longer than they should, fasting and postprandinal sugar levels rise beyond above mentioned limits, that results in Type-II diabetes.

Charilaosn and Shamiml (2019)[1] pointed out the widely known fact that "Liver and secondarily the kidney are the organs that supply circulating blood and consequently, various tissues with glucose."

Kristine et al (2006)[2] have highlighted that Insulin Resistance Is Accompanied by Increased Fasting Glucagon and Delayed Glucagon Suppression in Individuals With Normal and Impaired Glucose Regulation. They have concluded that increased

fasting glucagon levels and delayed glucagon suppression, together with increased circulating insulin levels, develop in parallel with insulin resistance. Therefore, glucose maintenance during insulin resistance may depend not only on hyperinsulinemia but also on the ability to suppress glucagon early after glucose intake.

In a review article Lele (2010)[3] very appropriately summarized mechanism of hyperglycemia as follows: “If glucagon had been discovered earlier than insulin, T2DM would well be defined as a state of hyperglucagonemia resulting in hyperglycemia due to glucagon-induced hepatic gluconeogenesis. Hyperglucagonemia is a characteristic of both T1DM and T2DM. Unger R H (1971[27], 1974[28], 1977[29]) has discussed the role of pancreatic islet α and β cell inter-relationship in health and disease and the role of glucogon in diabetes. The normal reciprocal response of insulin and glucagon regulates post-prandial glucose levels. Impaired α cell regulation leads to excessive glucagon release in the fasting and post-prandial state, with increase hepatic glucose production (HGP) and hyperglycaemia.”

Thus, achieving decline in glucose releasing activity of liver and kidneys is an important strategy as a response to hyperglycemia.

Foretz et al. 2019[4], have pointed out that Metformin is thought to exert its primary antidiabetic action through the suppression of hepatic glucose production”, “although “the mechanisms underlying the plasma glucose level-lowering effects of metformin (1,1-dimethylbiguanide) still remain incompletely understood”. Consequently Metformin has become established since decades as the First Line Treatment for Type-II diabetes.

Most of the anti-diabetic drugs other than Metformin operate on mechanisms other than suppression of glucagon activity. Hence, appropriately, Metformin remained for

a very long time the only First Line therapy and all other therapies were practice as add-on to the basic Metformin therapy.

The only other therapies that operated on the principle of preventing Glucagon activity are described by Lele (2010)[3] as follows: “The incretin concept was put forward by Crutzfeldl W et al in 1979 indicating the role of two incretins – Glucagon- like peptide1(GLP-1) secreted by intestinal L cells, and Glucose-induced insulinogenic Polypeptide (GIP) secreted by intestinal – K cells in regulation of islet a and b cell function. Nauck ME et al in 1993 showed a new approach to achieve normalization of fasting hyperglycemia with exogenous GLP-1 in T2DM and the ability of GLP-1 to increase post-prandial insulin secretion and suppress post-prandial glucagon secretion.”.

However, GLP-1 medications are injectibles in combination with Insulin. These have remained less preferable to Metformin. In absence of any other orally consumed alternative that would act on the principle of suppression of Glucagon activity, Metformin continued to be first line therapy for Type-II diabetes and all other anti-diabetic drugs have been used as add-on to Metformin as basal treatment.

Dipeptidyl peptidase-4 inhibitors, the gliptins, increase blood concentration of the incretin GLP-1 by inhibiting its degradation by dipeptidyl peptidase-4. Information available on the link https://www.nps.org.au/radar/articles/dipeptidyl-peptidase-4-inhibitors-gliptins-for-type-2-diabetes-mellitus provides information that Gliptins are listed on the PBS as dual oral therapy with metformin or a sulfonylurea, when a combination of metformin and a sulfonylurea is contraindicated or not tolerated; Gliptins are not approved for use as monotherapy, triple oral therapy or in combination with other drugs for diabetes (acarbose, exenatide, insulin or repaglinide); ; the long-term benefit–harm profile of gliptins is yet to be established; Adverse effects with

gliptins include nasopharyngitis, headache, nausea, hypersensitivity and skin reactions; Postmarketing reports of acute pancreatitis have occurred with gliptins, a causal link has not been established; people with severe limitation have to be administered reduced dose.

In short, in addition to above limitations, Gliptins cannot be used as monotherapy as first line ant-diabetic therapy; and in most cases the same is administered in combination with Metformin, or Metformin plus sulphonylureas. Weight gain and/or hypoglycemia have been observed when DPP-4 inhibitors, were used with sulfonylureas;

Thus, Metformin continued to be the only first line treatment of Type-II diabetes.

However, Metformin is associated with a rare but severe adverse effect, the development of metformin-associated lactic acidosis (MALA) with high mortality rate Gonçalves and Coelho D (2019)[5]. Chen et al. 1999[6] acknowledge that “Although the prevalence of metformin-associated lactic acidosis (MALA) is much lower than that associated with phenformin, it is still being reported sporadically which raises concerns for the practicing clinicians.” They also acknowledge that “renal impairment appears to be the major precipitating factor for the development of MALA in metformin-treated patients. We also found cases of MALA where no precipitating factors were identified and the underlying mechanism in these cases remains unclear.” Devetzis et al. (2011)[7] also arrive at same conclusion for kidney injury patients.

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Thus, it is clear that Metformin should be specifically avoided for renal impairment patients and newly diagnosed Type-II diabetes patients for whom there is no guidance available for identifying precipitating factors for probability of lactic acidosis to decide safety of starting Metformin for them. An at least equally efficacious alternative to Metformin that has no unpredictable risk for such patients shall be a safer option for first line administration.

Huang et al (2014)[8] have observed that CKD is common in older adults prescribed metformin for type 2 diabetes, raising concern for potentially inappropriate medication use. No single equation to estimate kidney function may accurately identify CKD in this population. Medication safety deserves greater consideration among elderly patients due to the widespread prevalence of CKD.

Further, besides above, http://diabetes.emedtv.com/metformin/metformin-side-effects.html, based on published clinical studies, has enlisted the most common metformin side effects, which include: Diarrhea occurring in up to 53.2 percent of people, nausea or vomiting in up to 25.5 percent, gas in up to 12.1 percent, weakness in up to 9.2 percent, indigestion in up to 7.1 percent, abdominal discomfort (or stomach discomfort) in up to 6.4 percent and headache in up to 5.7 percent. This makes a substantial chunk of those who need ant-diabetic medicines, but do not tolerate Metformin, and have no alternative to it for first line treatment.

Add to it a latest report that Metformin induces death of beta cells in pancreas. Marqués et al. (2019)[9], reported that upon glucose decline, from 25 to 5 mM, caused by stimulation with either 2-deoxyglucose or metformin, only pancreatic β cells showed an increase in cell death. Thus, there is a need of an orally consumed product that would be a viable alternative to Metformin. Data of Marqués et al (2019)[9] indicate that metformin decreases cell viability, especially in β cells and additionally at lower doses compared to non-β cells.

This makes a case for an overdue need of a viable alternative for Metformin as first line product for responding to Type-II diabetes.

For Sulphonylureas, which are next-in line to Metformin for treatment of type-II diabetes, the case is no better than Metformin. Time is due for their viable alternative too. Research paper of Daniele Sola et al. (2015)[10] that has following information:

> "Sulfonylureas act directly on β-cells, leading to progressive dysfunction and worsening of insulin secretion. Thus, despite better glycemic control in the short term, diabetes could worsen in the long term. The clinical result of this phenomenon is known as "secondary failure", and it represents the inevitable fate of all oral hypoglycemic agents, especially older sulfonylureas. In fact, patients with previous higher dosages and longer treatment with sulfonylureas display a worse response to insulin after changing therapy: sulfonylurea dosage is independently associated with inadequate response to insulin analogues in patients with secondary failure [29].
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> Weight gain is an almost constant counterpart of treatment with sulfonylureas, even though to a lesser degree than that recorded with insulin [30]. This certainly constitutes a deleterious effect, especially in reference to a chronic illness such as diabetes mellitus, where the control of body weight represents, perhaps, the main target of treatment. Fortunately, the weight gain is usually mitigated by the concurrent administration of metformin.
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> Other infrequent side effects that may occur with all sulfonylureas include nausea, skin reactions such as erythema multiforme, exfoliative dermatitis and also, more rarely, photosensitivity. Occasionally, they can cause abnormalities in liver function tests, which may rarely lead to cholestatic jaundice, hepatitis and hepatic failure.
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> --------- Some studies suggest that sulfonylureas may affect cardiac function and also may be associated with poorer outcomes after myocardial infarction [33–35]. An increased mortality from cardiovascular disease in diabetic patients taking tolbutamide was reported in the past decades (University Group Diabetes Study) [36]
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> Subsequently, several studies were designed to shed light on this alarming association. In the Mayo Clinic, in 185 consecutive diabetic patients undergoing percutaneous coronary intervention after myocardial infarction, the odds ratio for death was 2.77 for patients treated with a sulfonylurea at the time of the myocardial infarction [37].
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> In the DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) trial, the patients treated with a sulfonylurea at the time of myocardial infarction were those with the poorest outcome [38].

> Finally, in a retrospective Canadian study using pharmaceutical data for 5795 subjects who received initial monotherapy with either a sulfonylurea or metformin, deaths per 1000 person-years during the follow-up period (mean 4.8 years) were 67.6 for first-generation sulfonylurea medications, 61.4 for glibenclamide, and 39.6 for metformin [39]. The risk of death or of an acute ischemic event was greater for subjects exposed to higher amounts of the sulfonylurea, but not to metformin [39]. The greatest risk was for subjects treated with tolbutamide or chlorpropamide (hazard ratio (HR) 2.1, 95% CI: 1.0–4.7).
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> ---------- Moreover, it has been demonstrated that the use of sulfonylureas can increase the risk of developing a neoplastic disease [47]."

A Viable alternative is provided by Adipomimetin, a product reported by Savangikar and Savangikar (2017)[11] (WO2017168453), an agonist of human hormone Adiponectin. Surprisingly this is NOT a medicine, it is a food supplement. It excels in merits over Metformin and Sulphonylureas in the fact that it does not treat the symptoms by modifying metabolic mechanisms; it goes to the root cause of these symptoms, supplements the deficient action of Adiponectin of activating AMP Kinase, the AMP Kinase does the job of bringing the metabolism very much near to normal balance; so that proper balance of blood sugar is promoted and hyperglycemia is reduced to a marked extent. Thus, Adipomimetin goes to the base of lifestyle diseases arising from deficiency to Adiponectin; and being a concentrate of a plant protein derived from usually eaten green leafy vegetable, has come up as a safest possible first line product as a viable alternative for Metformin and also for the next-in line product/s suphonylureas, to respond to Type-II diabetes. Its qualitative superiority is on account of the fact that it does not have any action other than the action done by Adiponectin: to activate AMP Kinase. The AMP Kinase does rest of the job in its normal metabolic way for regulating metabolic balance of blood glucose, lipids in the body, body weight and keeping health in respect of atherosclerosis. When Adiponectin becomes deficient, Adipomimetin fulfills the deficiency by supplementing

the activation step of AMP Kinase; and does not tinker with any metabolic process; hence, no side effect in short term as well as long term use. Adipomimetin is not a chemical, it is a protein, a part of which has same structure as that part of Adiponectin that activates AMK Kinase; hence, except for activation of AMP Kinase, Adipomimetin has no other action, hence, no side effect, whether in short term use or long term use. Metforim and Sulphonylureas act through modifying the metabolic processes or beta cells themselves and being chemicals in their nature their action is not only one, they are prone to have several unwanted reactions depending on the reactions of their functional groups, which generate side effects and destruction of beta cells of pancreas. Thus, Adipomimetin does the job of controlling hyperglycemia for which Metformin and Sulphonylureas are used; but without the side effects which are inherent in use of Metformin and Sulphonylureas.

Adipomimetin, being a plant derived concentrate of a protein, it is safe, it is not a medicine and can be administered to a pre-diabetic patients and early stage Type-II diabetes patients as sole product for managing hyperglycemia. Being a progressively degenerative disease, when Type-II diabetes becomes advanced in course of time even with administration of Adipomimetin, just as add-on treatments are considered for Metformin and Sulphonylureas, same can also be considered to be supplemented to the basic administration of Adipomimetin to the extent to which there are residual symptoms even after administering Adipomimetin. IN case of Metformin treatment, as type-II diabetes advances, it is not enough as solo treatment; it has to be supplemented with sulphonylureas, gliptins and insulin progressively in that order concurrent with progression of Type-II diabetes. Hence, in advanced stages of Type-II diabetes, if Adipomimetin is required to be supplemented with chemical anti-diabetic drugs, that can be left to the discretion of the medical practitioner from case-to-case. For such add-on treatment, alpha amylase inhibitors may be the first add-on choice

to be followed by other anti-diabetic drugs; but it is very much possible that the dosages of the add-on drugs required may be much smaller than when no Adipomimetin basic treatment is given.

Additionally, .Adipomimetin is a complete First Line single product response to multiple indications: hyperlipidemia, atherosclerosis, hypertension, heart disease and obesity in addition to Type II diabetes.

https://www.news-medical.net/health/treatments-for-atherosclerosis.aspx invites attention to the fact that "The treatment of Atherosclerosis aims to relieve symptoms and reduce the risk factors in an effort to slow, stop, or reverse the build-up of plaque.". Prevention of Atherosclerosis would include reduction in risk for plaque formation. Both these objectives are very much potentially served by Adipomimetin as shown in a rat trial by Vandit et al.[12].

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