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REVIEW ARTICLE

Targeting the Ominous Octet Pathophysiology of Type 2 Diabetes using Combination Therapy—Treat Early, Treat Right!

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder. The core physiologic defects, often termed as *triumvirate* since its conception in 1988, are insulin resistance in muscle and the liver, along with progressive loss of β-cell function.[1] Decreased β-cell function results in reduced insulin secretion, while insulin resistance in muscle and the liver reduces glucose uptake from blood and its optimum utilization. Together, these defects elevate the blood glucose level (hyperglycaemia) in patients with T2DM. It has been postulated that patients who are in the upper range of impaired glucose tolerance (IGT) are near-maximally insulin resistant and have already lost over 80–85% of their β-cell function. It is the progressive β-cell dysfunction that determines the rate of disease progression.[1]

The evolution of pathophysiological pathways: with advancement of scientific discoveries, the *triumvirate* has been gradually replaced by several other terms with time. As additional mechanisms to address the pathophysiological abnormalities contributing to glucose intolerance get unfolded, as listed here:[2,3]

- Increased insulin resistance in adipose tissue cells (*disharmonious quartet*): The adipocytes become resistant to insulin's anti-lipolytic effect, leading to elevated plasma free fatty acid concentration and intracellular accumulation of toxic metabolites in liver, muscles and β-cells that aggravates insulin resistance and progressive β-cell failure/apoptosis.
- Decreased incretin effect in the GI tract (*quintessential quintet*): There is reduced glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) effect resulting from both impaired secretion and severe β-cell resistance to the stimulatory effect of GLP-1 and GIP.
- Increased glucagon effect (*setaceous sextet*): There is both increased secretion by pancreatic

α-cells and enhanced hepatic sensitivity to glucagon leading to increased basal hepatic glucose production and impaired suppression by insulin.

- Increased glucose reabsorption by the kidneys (*septicidal septet*): Contributes to the maintenance of already elevated plasma glucose levels mostly through up regulation of sodium-glucose co-transporters.
- Neurotransmitter dysfunction in the brain and central nervous system (*ominous octet*): There is resistance to the anorectic effect of insulin and altered neurosynaptic hormone secretion, which leads to increased appetite, weight gain, and insulin resistance.

The presence of multiple pathophysiologic abnormalities could dictate several important implications in management of T2DM patients:[2,4]

- Multiple drugs in combination may be required to manage the various pathophysiologic defects associated with hyperglycaemia.
- Drugs targeting the known pathophysiologic processes and helping to counteract or reverse them should be considered. Treatment should not be based on mere reduction of glycated haemoglobin (HbA1c) level, or controlling fasting/post-prandial blood glucose level.
- Intensive treatment should be started early to prevent or slow the progression of β-cell failure, which is already established in T2DM patients at diagnosis.

As multiple pathophysiologic abnormalities contribute to the development of hyperglycaemia in T2DM patients, multiple drug classes are available to help address them. One or more classes of anti-hyperglycaemic agents can target each of the eight abnormalities that comprise the *ominous octet*. Few of the abnormalities can be targeted with various agents, while few of the agents can target multiple pathways as well.[4]

Traditionally, the guidelines advocate sequential addition of anti-diabeticagents, which rather may becalled as the "treat to failure" approach. Whereas a "pathophysiologic" approach using initial combination therapy with agents known to correct the established defects in T2DM seems more rational. As of now, it has become common in clinical practice to treat patients with multiple therapies, as patient's HbA1c level goes beyond the target and good glycaemic control is not achieved. Recommendations from the American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE) through treatment algorithms also favour the use of combinations of multiple oral therapies or of oral and injectable therapies. It is a preferable to use combination therapies having complementary mechanisms of action that target different pathways addressing the multiple pathophysiologic abnormalities of T2DM. Thus a treatment paradigm shift is increasingly being recommended by experts suggesting early initiation of combination therapy with agents correcting the established pathophysiologic defects in T2DM and thus producing fast and sustained reduction in HbA1c rather than just focussing on the plasma glucose lowering potential of the individual agent.[4-6]

THERAPEUTIC APPROACH

As depicted in Figure 1, various classes of agents act differently to improve the components of *ominous octet*.

In liver, both metformin and thiazolidinediones (TZDs) act as potent insulin sensitisers whereas in muscles, only TZDs are potent insulin sensitizers but effect of metformin is weak. In adipocytes, TZDs are potent inhibitors of lipolysis and mobilise fat out of muscles, liver and β-cells, thereby ameliorating lipotoxicity. Thus a combination of TZD and metformin gives an additive effect to reduce HbA1c due to their different mechanism of action. Additionally, as none of the agents augment insulin secretion, so hypoglycaemia is not a concern.[4,7]

Though sulphonylureas augment insulin secretion from β-cells but neither sulphonylureas nor metformin exert any significant protective effect on the β-cells. Reversal of the pathophysiological effect damaging the β-cells is of utmost importance to halt disease progression. Only TZDs and GLP-1 analogues have

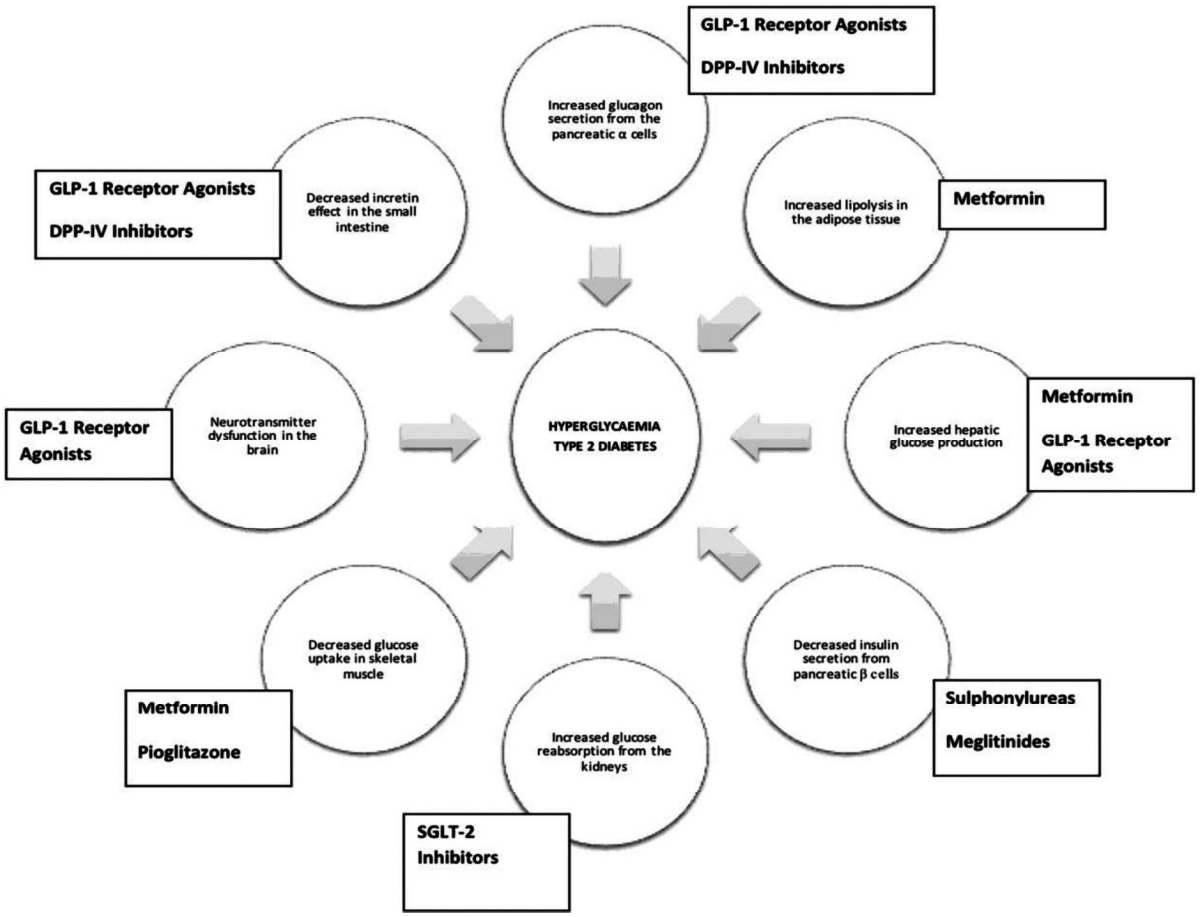

*Figure 1:*The ominous octet and the target sites for glucose-lowering therapies.
[Source: Adapted from Chatterjee S, Davies MJ. Current management of diabetes mellitus and future directions in care. Postgrad Med J. 2015;91:612-21.]

been shown to improve and preserve β-cell function and demonstrate durability of glycaemic control by producing sustained reduction in HbA1c. In contrast, the anti-hyperglycaemic effect of the sulphonylureas is not durable. After an initial decline in HbA1c, sulphonylurea use is associated with a progressive decline in β-cell function leading to loss of glycaemic control. In addition, GLP-1 analogues beneficially impact other members of the ominous octet through liver (reduced hepatic glucose production), α-cells (reduced glucagon secretion), gut (replace the deficient GLP-1 response, delays gastric emptying) and brain (reduced appetite along with weight loss).[4,7]

Dipeptidyl peptidase inhibitors (DPP4I), though augment insulin secretion, their β-cell effect is comparatively weak and their efficacy begin to decline within few years after initiation of therapy. Though hypoglycaemia does not occur with the DPP4Is, but they are weight neutral. The major anti-hyperglycaemic action of DPP4Is is mediated via inhibition of glucagon secretion with subsequent decline in hepatic glucose production whereas metformin has a beneficial effect on GLP-1 secretion from intestinal L-cells. Thus the combination of metformin and a DPP4I tend to exert more durable effect on β-cell function.[4,7]

Ninety percent of the daily filtered glucose in the kidneys (which amounts to nearly 162 gram) is reabsorbed by the high capacity SGLT2 transporters. It has been shown in animal studies that both in type 1 and T2DM, the maximal renal tubular absorptive capacity for glucose is increased. Also cultured human proximal renal tubular cells from T2DM patients demonstrate markedly elevated expressions of SGLT2 mRNA and protein. Thus, the adaptive response of the kidneys to conserve glucose, which is the essential fuel to meet the energy need of the

organs, becomes maladaptive in T2DM patients and instead of attempting to correct the hyperglycaemia, the kidneys choose to conserve more glucose. SGLT2 inhibitors, by reversing this maladaptive mechanism of glucose reabsorption in the renal proximal tubules, provide an excellent targeted approach to the treatment of T2DM. These agents also promote weight loss, reduce blood pressure, have very less incidence of hypoglycaemia and can be safely combined with any other anti-hyperglycaemic agents.[2,4]

Recently concluded robust cardiovascular outcome trials (CVOT), namely EMPA-REG OUTCOME (with empagliflozin, an SGLT2 inhibitor) and LEADER (with liraglutide, a GLP-1 analogue) have shown significant CV outcome benefits with these agents. Subsequently both of them got USFDA label approval for additional indication of reduction in CV mortality (with empagliflozin)[8] and major adverse cardiovascular events (with liraglutide)[9] in T2DM patients; empagliflozin being the only oral agent, while liraglutide is injectable. Based on the evidences, the recently published ADA 2018 guideline recommends considering initiating dual therapy in patients with newly diagnosed T2DM who have HbA1c ≥9%. They also suggest that in patients with stablished atherosclerotic CV disease, an additional agent (empagliflozin or liraglutide), over and above lifestyle modification and metformin, should be added at the earliest to reduce major adverse cardiovascular events and cardiovascular mortality, considering individual drug and patient specific factors.[5,10]

DPP4I and SGLT2I in combination fulfil the need for a treatment approach with complementary mechanisms of actions improving glucose control

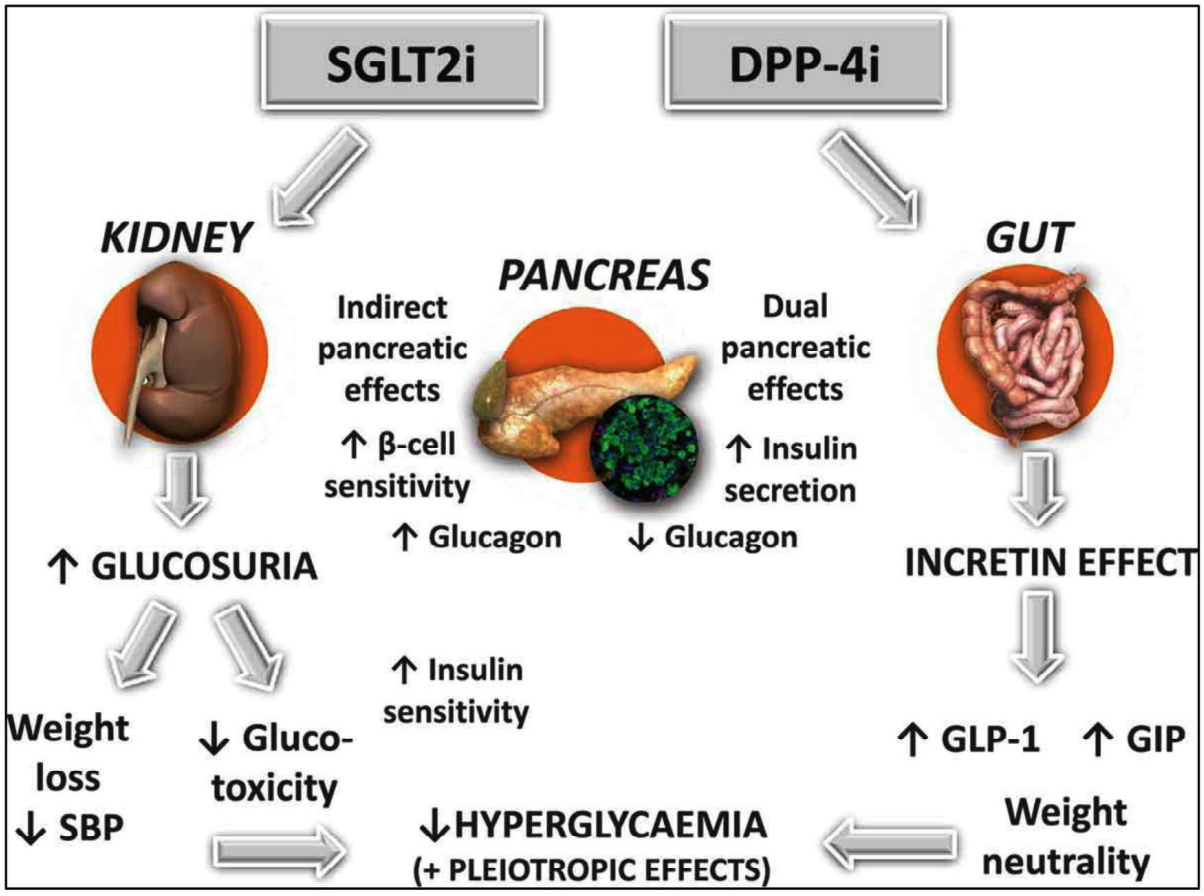

Figure 2: Illustration of the complementary glucose-lowering activities of DPP-4 inhibitors (DPP-4i) and SGLT2 inhibitors (SGLT2i) in type 2 diabetes.
[Source: Adapted from Scheen AJ. DPP-4 inhibitor plus SGLT-2 inhibitor as combination therapy for type 2 diabetes: from rationale to clinical aspects. Expert Opin Drug Metab Toxicol. 2016;12(12):1407-17.]

in broad range of T2DM patients, with a low risk of hypoglycaemia, benefit of weight loss and the potential of cardiovascular protection. Moreover because of the progressive deterioration of beta-cell function in T2DM, a mechanism of action, which is independent of pancreatic beta-cell function, makes SGLT2Is an appropriate option for patients with advanced T2DM or for patients who require additional medications over and above metformin to improve or maintain glycaemic control. Whereas SGLT2Is are known to increase the glucagon level in blood, DPP4Is are known to suppress the same by acting on the alpha cells. They are also known to halt the progression of chronic kidney disease by decreasing progression of albuminuria.[4,11] The complementary beneficial effect of this combination has been depicted in Figure 2.[12]

FURTHER DEVELOPMENT

The *ominous octet* is the pathophysiological core in the mechanism of diabetes, and it does not stop there. Newer research has led to postulation of other mechanisms. For example, the concept of *egregious eleven* includes systemic low-grade inflammation and immune dysregulation, changes in gut microbiota and decreased amylin production as potential contributors to the dysfunction of the β-cells which is the final common denominator in pathophysiology of diabetes.[13] Few authors have also proposed addition of four well-known hormones to the list of octet as the *dirty dozen* (catecholamines, vitamin-D, renin-angiotensin system and testosterone) and perhaps, the existence of *treacherous thirteen* (high iron intake in addition to the 12 mechanisms stated earlier).[14]

CONCLUSIONS

Every molecule has their different targets and these are individually targeted at different times in the entire course and duration of diabetes. Metformin is an absolute necessity for treating diabetes if there are no contra indications, and the patient can tolerate it. Newer class of drugs like SGLT2Is and DPP4Is have strengthened our treat-to-target goal for individual diabetic patients. As evident we know that reaching desired HbA1C goal is very difficult and we have to tailor our treatment protocols as per individual cases. We do not know which pathological pathway is affecting the individual and contributing to the diabetic status. SGLT2Is target kidneys and DPP4Is target the gut hormones by two entirely different (but complementary) mechanisms all together. It is debatable which one may be used first but clearly if one goes by the available evidence, therapy of T2DM with a background of CV disease must be initiated with an oral SGLT2I, preferably empagliflozin. Why we are interested in diabetes and CVD is a well-known and very important concept. Studies have shown that over two-thirds of patients of diabetes have subclinical CVD (which may remain undiagnosed due to being asymptomatic in nature), diabetes increases the risk of subclinical CVD by fourfold and subclinical CVD increases the risk of CV event by twofold.[15] Hence the burden of cardiovascular disease is so high in diabetics that the first choice should be a SGLT2i (preferably empagliflozin) over a DPP4i. Now DPP4i has its own advantages and can complement effects of SGLT2i in many ways. The combination of SGLT2i/DPP4i (either separately or as a fixed dose combination) not only complement each other well, this combination can targetat-least seven of the eight components in the ominous octet.[16] Hence after metformin or even before using metformin in suitable patients (metformin contraindicated or intolerant), this combination may give excellent "treat-to-target" benefit to the patients, thus facilitating the "treat early and treat right" approach. Clinicians should be recommending the least number of agents, which target the maximum number of pathophysiologic pathways, while minimizing hypoglycaemia, weight gain and other potential side effects.

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