ABSTRACT

There lacks a clear consensus regarding the treatment of type 2 diabetes mellitus (T2DM) that is inadequately controlled using dual combination therapy. Acceptance of insulin is limited in various countries and communities which can be patient related or physician related. Old age, living alone, needle fear, fear of hypoglycemia, lack of refrigeration facilities, lack of facilities for blood sugar monitoring do raise the need of combination therapies of oral hypoglycemic agents (OHAs) for management of blood glucose levels. After the advent of dipeptidyl peptidase-4 inhibitors (DPP4i) and sodium-glucose cotransporter 2 inhibitors (SGLT2i) triple and quadruple therapies have shown promise, and newer studies have shown non inferiority of the various combination with comparison to insulin therapies for management of HbA1c and end organ damage. But, the regimens are still need to be time tested and have the drawback of not being preferred in patients who have already developed various organ damage or complications or have associated various comorbidities along with T2DM. Meta-analysis of the studies of the past does show similar efficacy result of the different combination therapy of the OHAs available but caution needs to be exercised. Only time will predict as how efficient and cost effective will be the triple and quadruple OHA combination therapy which will be evident from future.

Keywords: Type 2 diabetes mellitus, Triple therapy, Quadruple therapy, OHA, DPP4 inhibitor, SGLT2 inhibitor, Combination therapy for diabetes.

INTRODUCTION

Diabetes mellitus (DM) has become the leading health concern worldwide over the last few decades due to the rapid increase in prevalence of DM increased from 108 million (4.7%) in 1980 to 425 million (8.5%) in 2017, and it is estimated to be 629 million by 2045.1 Type 2 diabetes mellitus (T2DM) is the most common type of diabetes which encompasses 90-95% of the diagnosed DM.1 Although it is believed that the T2DM can be delayed in patients and even preventable with life style modifications,2 pharmacotherapy is an integral and indispensable modality for management of the glycemic status of the patient. The drug regimens include various oral hypoglycemic agents (OHAs) and insulin and their combinations as well as addition of insulin if target glycemic control is not yet achieved.3 Injection therapy using insulin is the preferred therapeutic agent for the management of hyperglycemia of T2DM patients and early initiation of insulin therapy has suggested to preserve the β-cell function and reduced microvascular complications.4,5 Although Insulin therapy has advantages but it has its own limitations especially in developing countries, such as lack of compliance, needle fear, likelihood of hypoglycemia. However, optimal management of T2DM is relatively difficult with international guidelines proposing individualized approach for management of the optimal HbA1c target and use of various hypoglycaemic agents.6 Hence, the required balance between the microvascular complications and the risk of hypoglycemia in the treatment of T2DM is usually achieved through a combination therapy and the patients’ acceptance to the therapy. Other factors considered include the effectiveness, effect on body weight, and other associated comorbidities.
The guidelines do recommend the use of metformin as the first line OHA unless contraindicated or patient is intolerant to the drug. International guidelines do also recommend, if the monotherapy is not successful in controlling the blood glucose level then dual therapy needs to be initiated. NICE (National Institute for Clinical Excellence), Canada, Australia, and New Zealand consider a combination of sulfonylurea and metformin as the accepted treatment. Furthermore, a consensus from American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) do recommend an add-on therapy such as dipeptidyl peptidase-4 inhibitors (DPP4i) and thiazolidinediones (TZDs) to assist the treatment after detailed counseling and information for the effectiveness and safety to make informed choices.

THE USE OF INSULIN AS THE PREFERENCE OVER TRIPLE/QUADRUPLE OHAs—A RECONSIDERATION

Evidence gathered from randomized controlled trials (RCTs) and longitudinal cohort studies about cardiovascular outcomes of insulin therapy in T2DM patients appears controversial. Favorable cardiovascular outcomes of intensive glycemic control using sulfonylureas or insulin versus conventional therapy using diet control were documented in the 10-year follow-up UK Prospective Diabetes Study. However, the benefit of insulin on cardiovascular outcomes as evident from other RCTs is questionable, or even increase in the non-fatal cardiovascular events. Two RCTs have even suggested the cardiovascular neutral effect of the use of insulin in the management of hyperglycemia. However, the above mentioned studies have the drawbacks including shorter follow-up periods, limited number of cardiovascular events, and even the sulfonylureas itself have an adverse effect on the cardiovascular outcomes in the long run. Even the study population included either patients at early stage of diabetes or those without existing CVDs. Longitudinal cohort studies with T2DM patients have also demonstrated an association between insulin therapy and increased risks of CVDs and all-cause mortality, but effects of insulin therapy only assessed at an earlier stage of the antidiabetic treatment course. Hypoglycemia, most commonly encountered with insulin therapy rather than the OHA therapy has been hypothesized as a risk for developing cardiovascular disease.

Because T2DM being a progressive disease, majority of the patients with T2DM need insulin therapy in the long run. Although it is quite common in real-world clinical practice that insulin therapy is initiated in a later stage of an antidiabetic treatment course, there is lack of data on effects of insulin used as the fourth-line antidiabetic treatment in T2DM patients with triple/quadruple OHA therapy failure.

GUIDELINES FOR TRIPLE/QUADRUPLE OHAs USE TO CONTROL HYPERGLYCEMIA

ADA-EASD Consensus statement includes specific pharmacologic recommendations based on a patient’s profile and health history, providing instructions in the context of Atherosclerotic Cardiovascular Disease (ASCVD), heart failure, kidney disease, weight, risk for hypoglycemia, or a need for low-cost options. The recommendation for considering the addition of a third non-insulin agent in patient with HbA1c above the individualized target after 3 months of treatment with a two-drug regimen has been recommended by various guidelines such as ADA and EASD consensus statement. The American Association of Clinical Endocrinologists (AACE) and International Diabetes Federation (IDF).

A number of triple and quadruple OHAs have been suggested, most commonly metformin with the addition of two or more other orally administered drugs. ADA, EASD, and IDF also do recommend the use of DPP4 as part of triple oral therapy along with metformin and/or sulfonylurea or a TZD and now the AACE along with ADA and EASD do recommend the use of sodium-glucose cotransporter 2 inhibitors (SGLT2i) as the add-on OHA. The SGLT2i have a unique mechanism of action to decrease the blood glucose level by increasing glucose excretion through the kidneys.

The uses of quadruple therapy using non-insulin four OHAs to manage the blood glucose are under evaluation after the emergence of SGLT2i drugs and has shown promise in management of T2DM patients who lack adequate management with triple therapy, but not accepting insulin due to fear of daily insulin injections and other injection related non-compliance. But, it does need to be studied in details as a long-term option in comparison to never available injectable therapies like the long acting glucagon-like peptide-1 receptor agonists (GLP-1-RA), which require weekly injections.
for management of blood glucose. Recently, the triple combination therapy of low dose dapagliflozin plus saxagliptin and metformin combination had higher efficacy than the two drug combination of metformin with dapagliflozin or saxagliptin individually with advantage in better HbA1c reduction, greater reduction of baseline fasting plasma glucose and weight.28 Combining meglitinide (SU) and voglibose (α-glucosidase) is approved in Japan.29

Triple Therapy combinations in ADA/EASD T2DM consensus statement (Fig. 1).24

**Figure 1**: Triple oral therapy combinations in the ADA/EASD T2DM consensus statement. DPP4i—Dipeptidyl peptidase-4 inhibitors; SGLT2i—Sodium-glucose cotransporter 2 inhibitors; SU—Sulfonylurea; TZD—thiazolidinedione.

THE RATIONALE OF USE OF TRIPLE/QUADRUPLE THERAPY BASED ON PATHOPHYSIOLOGY OF T2DM

As far as the use of combination of OHAs for T2DM management is considered, metformin, SU, and DPP4i target the two important mechanism which are impaired insulin secretion and hepatic glucose production.30 Sulfonylureas and DPP4i increase the insulin levels. Sulfonylureas does it with non-insulin dependent mediated by the SU receptors and the DPP4i does it in a glucose dependent fashion mediated by the increase in the level of body incretins. The drawback with sulfonylureas is that they act upon the gradually exhausting beta cells of pancreas and accelerate a process called the “burn-out.” Within 1–2 years, sulfonylureas begin to lose their effectiveness which limits the magnitude of the treatment success gained by sulfonylureas at initiation of treatment.31 Metformin has its major impact on decreasing hepatic glucose production but it has also been shown to increase the plasma levels of GLP-1 in healthy nondiabetic individuals.32 DPP4i also contribute in inhibiting hepatic glucose production and have been shown that the administration of sitagliptin with metformin does produce an additive increase in the postprandial active GLP-1 concentration in non-diabetic humans.33 The SGLT2i have an interesting effect of inhibiting the SGLT2 receptor in kidneys which is responsible for reuptake of glucose from renal tubules hence causing glycosuria and resulting in decreased blood glucose. TZD acts by improving the insulin sensitivity of the adipose tissue by PPAR-γ agonism. -glucosidase inhibitors like voglibose reduce the post prandial glucose by limiting the absorption of glucose in the gut. The addition of TZD and DPP4i in a combination regimen has also shown an synergistic effect on β-cell function.34

The combination of DPP4i, metformin, and TZDs addresses different pathophysiological defects which lead to manifestation of T2DM in a complimentary fashion:

- Increased hepatic glucose production—Metformin, TZDs and DPP4i via suppressing the glucagon secretion
- Insulin secretion—Sulfonylurea, DPP4i
- Peripheral insulin resistance—TZDs

All OHAs do improve the glycemic status in T2DM patients but the the HbA1c reduction and fasting plasma glucose levels with SGLT2i as an add on to metformin is the maximum in comparison to the add on of a DPP4, SU, or with α-glucosidase inhibitors. SU and the TZD have the limitation of being associated with weight gain whereas SGLT2i and DPP4i have the advantage of weight loss and less instances of hypoglycemia which is seen maximum with SU.35 After analysis of the data obtained from different RCTs for various OHAs, the risk of major adverse cardiovascular events (MACEs) or all cause mortality between the OHAs has no statistical difference.35 Although prior meta-analyses done did show the SGLT2i had a favorable cardiovascular effect.
in comparison to other OHAs. The favorable results were probably heavily affected by the EMPA-REG OUTCOME trial. The drawback of SGLT2i being used as the second OHA especially in poor demographic group is the cost, and it does pose a limitation over the use of SU or TZD as the preferred OHA.

SGLT2i which have been recently approved for treatment of T2DM have shown promise when used as triple and even quadruple combination regimens. Data from in vivo studies have shown beneficial effects on β-cell mass and function with SGLT2i. The interesting fact about the SGLT2i is the hypoglycemic effect being independent to the insulin levels or the insulin resistance and hence it very well complements the antihyperglycemic action of other OHAs and even insulin and also benefit patients who require weight loss for their insulin resistance.

### A BRIEF REVIEW OF STUDIES OF TRIPLE/QUADRUPLE THERAPIES FOR T2DM

Many studies have been done to evaluate the efficacy and the advantage of triple and quadruple OHA combinations and few important RCTs are enumerated in Table 1.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Trials</th>
<th>Duration (in months)</th>
<th>N (number of subjects)</th>
<th>↓HbA1c</th>
<th>Body weight (kg)</th>
<th>Hypoglycemia</th>
<th>FPG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Met + SU vs Met + SU + DPP4i</td>
<td>Hermansen et al. (2017)</td>
<td>24</td>
<td>441</td>
<td>0.74</td>
<td>↑0.8</td>
<td>12%</td>
<td>↓20.1</td>
</tr>
<tr>
<td></td>
<td>Owens et al. (2011)</td>
<td>24</td>
<td>1055</td>
<td>0.62</td>
<td>↔</td>
<td>↔</td>
<td>↓12.6</td>
</tr>
<tr>
<td></td>
<td>Lukashevich et al. (2014)</td>
<td>24</td>
<td>24</td>
<td>1.01</td>
<td>↔</td>
<td>↔</td>
<td>↓20.36</td>
</tr>
<tr>
<td>MET + SU + TZD</td>
<td>Moses et al. (2014)</td>
<td>24</td>
<td>257</td>
<td>0.66</td>
<td>↑0.2</td>
<td>10.1%</td>
<td>↓48</td>
</tr>
<tr>
<td></td>
<td>Dailey et al. (2004)</td>
<td>24</td>
<td>365</td>
<td>1</td>
<td>↑1.6</td>
<td>28%</td>
<td></td>
</tr>
<tr>
<td>MET + SU + GLP-1-RA</td>
<td>Kendall et al. (2005)</td>
<td>30</td>
<td>733</td>
<td>1</td>
<td>↓1.6</td>
<td>28%</td>
<td></td>
</tr>
<tr>
<td>MET + SU + SGLT2i</td>
<td>Russell-Jones et al. (2009)</td>
<td>26</td>
<td>581</td>
<td>1.33</td>
<td>↓1.39</td>
<td>1.2 (events/patient/year)</td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td>Wilding et al. (2013)</td>
<td>52</td>
<td>469</td>
<td>1.06</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>MET + SU + INS</td>
<td>Russell-Jones et al. (2009)</td>
<td>26</td>
<td>581</td>
<td>1.33</td>
<td>↓1.39</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>SU + DPP4i</td>
<td>Hermansen et al. (2007)</td>
<td>24</td>
<td>441</td>
<td>0.74</td>
<td>↑0.8</td>
<td>12%</td>
<td>↓20.1</td>
</tr>
<tr>
<td>MET + SU + INS vs MEWT + SU + GLP-1-RA</td>
<td>Russell-Jones et al. (2009)</td>
<td>26</td>
<td>581</td>
<td>1.33</td>
<td>↓1.39</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>Bergenstal et al. (2009)</td>
<td>24</td>
<td>372</td>
<td>1.23</td>
<td>↑2.85–4.08</td>
<td>61%</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>Heine et al. (2005)</td>
<td>26</td>
<td>549</td>
<td>1.11</td>
<td>↓2.3</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>Nauck et al. (2007)</td>
<td>52</td>
<td>501</td>
<td>1.04</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>MET + SU + TZD</td>
<td>Rosenstock et al. (2006)</td>
<td>24</td>
<td>216</td>
<td>1.5</td>
<td>↑3/+0.4</td>
<td>3.3%</td>
<td>↓</td>
</tr>
<tr>
<td>MET + TZD + DPP4i vs MET + TZD</td>
<td>Bosi et al. (2011)</td>
<td>52</td>
<td>803</td>
<td>0.70</td>
<td>↓1.8</td>
<td>1.5%</td>
<td>↓14.4</td>
</tr>
<tr>
<td></td>
<td>DeFronzo et al. (2012)</td>
<td>26</td>
<td>1554</td>
<td>0.9</td>
<td>↓1.8</td>
<td>1.5%</td>
<td>↓45.0</td>
</tr>
<tr>
<td></td>
<td>Derosa et al. (2013)</td>
<td>52</td>
<td>453</td>
<td>0.70</td>
<td>↓</td>
<td>1.5%</td>
<td>↓14.4</td>
</tr>
</tbody>
</table>
Triple and Quadruple Combination Therapy in Type 2 Diabetes…

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Trials</th>
<th>Duration (in months)</th>
<th>N (number of subjects)</th>
<th>Study outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>MET + SU + DPP4i vs MET + SU + SGLT2i</td>
<td>Schernthaner et al. (2013)54</td>
<td>52</td>
<td>755</td>
<td>↓HbA1c, Body weight (kg), → ↓ ↓ ↓</td>
</tr>
<tr>
<td>MET + SU + TZD</td>
<td>Liu et al. (2013)55</td>
<td>24</td>
<td>119</td>
<td>↑ ↑ ↓ 35.7</td>
</tr>
<tr>
<td>INS (Glargine) vs SGLT2i (Empagliflozin) + MET + SU/TZD/DPP4i (two OHAs among them)</td>
<td>Eu Jeong Ku et al. (2019)27</td>
<td>24</td>
<td>268</td>
<td>↓ ↓ ↓</td>
</tr>
</tbody>
</table>

DPP4i—Dipeptidyl peptidase-4 inhibitors; FPG—Fasting plasma glucose (mg/dL); GLP-1-RA—Glucagon-like peptide-1 receptor agonist; INS—Insulin; MET—Metformin; SGLT2i—Sodium-glucose cotransporter 2 inhibitors; SU—Sulfonylurea; TZD—Thiazolidinedione.

The systematic review and network meta-analysis by Downs et al. published in 2014 evaluated the evidence for triple therapy regimen using medicines available in Australia for T2DM. They reviewed twenty-seven trials which were at least of a duration more than 6 months. Evaluation of the various combination of triple therapy with reference to the HbA1c reduction in comparison to the reference combination of metformin with a sulfonylurea.6

The various inferences that were drawn from the systematic analysis was important in context of the different combinations that can be used as well as the different adverse events that can be possibly arise from the combination therapy. The important inferences that were evident were as follows:

All triple therapies were statistically superior to MET + SU dual therapy, except for MET + TZD + DPP4i.

None of the triple therapy combinations demonstrated differences in HbA1c compared with other triple therapies.

MET + SU + SGLT2i and MET + SU + GLP-1-RA resulted in significantly lower body weight than MET + SU + DPP4i, MET + SU + insulin and MET + SU + TZDs.

MET + SU + DPP4i resulted in significantly lower body weight than MET + SU + insulin, and MET + SU + TZD. MET + SU + insulin, MET + SU + TZD, and MET + SU + DPP4i increased the odds of hypoglycemia when compared to MET + SU.

MET + SU + GLP-1-RA reduced the odds of hypoglycemia compared to MET + SU + insulin. Hypoglycemia was the only drawback of most of the combination therapy trials. Addition of a third drug to dual OHA therapy was statically as well as clinically effective in reduction of HbA1c levels.

The drawback of the analysis was the short duration (24–30 weeks) of the trials taken into consideration. The study population of the trials also were not large enough to draw definitive conclusions. Furthermore, limited data for SGLT2i combination therapy was available at the time of publication of the analysis.

CONCLUSION

Triple and quadruple oral therapy are valid options for treatment of patients with T2DM especially the patients of developing countries where the acceptance of injectable therapy with insulin is not widely accepted due to various factors which range from needle fear to the non availability of adequate refrigeration facilities for insulin due to lack of electricity or financial constraints to buy refrigerators. Metformin is still the first choice of OHA and the second OHA can be chosen from the basket of OHAs with a distinct different mode of action to metformin. Caution needs to be exercised for combination therapy with sulfonylurea for their increased chance of development of hypoglycemia. The advent of DPP4i and SGLT2i has opened new...
frontiers for using quadruple combination but it is too early to include them as a viable therapy option as the advantages of insulin therapy have been time tested and have been proven advantageous in various trials and clinical practices for reduction of end organ damage and a productive life style.

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