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Opinion

Should the Diabetes Therapy Recommendations Be Totally Revised?

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Abstract

With the development of new classes of anti-diabetes medications and expanded approval regarding benefits beyond glucose reduction, perhaps it is time to review what we call guidelines or algorithms.

In the past, there were no algorithms/guidelines. Now that we have them, are we imprisoned by the current ones? Shall we continue with the dogma of metformin first, after dietary and exercise "failure"? Then, in almost all cases, add Sulfonylureas (SU)? Or as some are now advocating, using another agent instead of the SU due to potential hypoglycemia risks and at best, no Cardiovascular Disease (CVD) benefits? Are we neglecting the pathophysiology of the progression of diabetes, by just adding one more medication to the pile, instead of considering that restarting from the beginning with a different class might be more beneficial? Should we be now favoring classes that have proven CVD event reduction and perhaps even renal protection? Another point is that when an organization makes recommendations, these recommendations tend to become codified, legally codified. Practitioners may find themselves in court, having to justify why they did not strictly follow the "guidelines".

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Discussion

Prior to these practice recommendations, everyone had an opinion on how to treat diabetes, but some practitioners, perhaps not as expert as others, needed some guidance. To fill this need, the American Diabetes Association (ADA) began publishing the opinion of a group Endocrinologists in diabetes care and online [1]. In the fine print, at the end, it was noted that these were the opinions of the group, not the official recommendations of the ADA itself. It was a practical group of suggestions that helped those in need of that guidance. As the American Association of Clinical Endocrinologists (AACE) came into being and developed its voice, it started publishing, and updating, what it called the "AACE Algorithm". This Algorithm has been based strictly on randomized, double blinded, placebo controlled, multi-centered trials (RCT's). It has been frequently updated, based upon the latest scientific-not economic considerations. The caveat was to individualize therapy, as no one size fits all.

Most practitioners agreed with the suggestion that one should begin with "diet and exercise" (lifestyle or Therapeutic Lifestyle Care) ("TLC") first, for three months or more. Give the person a chance at "self-improvement" before we "condemn" them to a lifelong "sentence" of medications. If unsuccessful, then add metformin, to obtain and maintain glucose control. However, AACE partially broke that mold by stating that a Hb A1c equal to or less than 7.5% should be treated with metformin at the same time we start lifestyle changes. Their HbA1c goal is equal to, or less than 6.5%. If the initial HbA1c is above 7.5%, we should start with dual therapy, often a SU was recommended. Some practitioners maintained that the goal should be normality. That goal has been softened to include the consideration of limiting comorbidities in the 2018 AACE Algorithm [2]. This occurred when the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [3] was halted due to cardiovascular deaths in the tightly controlled arm, felt to be nocturnal hypoglycemia. Therefore, the guidelines were relaxed a bit.

Current treatment options

When metformin was introduced on to the US market in the 1980's, it was met with a little concern, although it was chemically related to phenformin, a medication removed from the US market after deaths attributed to lactic acidosis. Metformin was approved by the Food and Drug Administration (FDA), but with "blackbox warnings". These warnings still exist today. Moreover, many practitioners were more worried about Sulfonylureas (SU's) which carry their risk of hypoglycemia, as seen in the University Group Diabetes Program (UGDP) trial. The tolbutamide arm results of the UGDP were leaked at the Annual ADA Scientific Sessions in 1970, revealing that as many as 8000 deaths were attributed to this agent. No conclusion was ever arrived at, but hypoglycemia was posited. The SU-K-ATP channel problems with their own potential for cardiovascular mortality are still currently being seen in the cardiovascular literature today.

Therefore, the guidelines recommended the use of metformin as first line medication replaced SU's, due to its wide usage, in spite of

the various associated problems. Many practitioners have forgotten the metformin black box warnings, gastro-intestinal problems, and risk of vitamin B12 deficiency [4]. Younger ones may not even be aware of them. To wit, many hospitals and practices, such as ambulatory surgical centers, radiologists, anesthesiologists, and nephrologists routinely mitigate these potential problems with their own risk stratifications. Therefore, not withstanding its potential problems, metformin is universally available as an inexpensive generic, and thus became the anti-diabetic agent of first choice. Metformin acceptance has relegated SU use to a lower tier in all guidelines.

Since then, new classes have made it to market. These new classes often have shown in recent RCT's, advantages over the previously discussed non-insulin medications not seen before, such as cardiovascular risk and even event reduction- as well as renal benefits. However, as they are more expensive then metformin and SU's, their acceptance has been hindered.

We know that in drug naive subjects with an HbA1c of about 8%, we can realistically achieve the ADA goal of 7% with metformin [4]. The "weight loss" attributed to its use is mostly due to the initial GI side effects, it is not a weight loss medication as some people believe. Nor is it a great insulin sensitizer, acting mostly at the liver, as Inzucchi and others showed, in comparison to troglitazone, a thiozolidinedione [5]. In addition, the Diabetes Prevention Program (DPP) [6] showed that diet and exercise was a superior glucose control option to metformin, in the more elderly population.

Towards a new treatment paradigm

Let us consider what we currently do when metformin monotherapy is no longer sufficient to keep the diabetes controlled. We are told by the algorithms and guidelines to add another agent. We are not advised to change to another class. This is interesting, as there are three potential reasons why after a period of time, metformin monotherapy may no longer control the blood sugar. One reason could be that the person's insulin resistance has increased beyond metformin's abilities. Perhaps increasing obesity, or the adoption of a less active lifestyle could be a cause. Progression of the disease, attributed to the waning of appropriate beta cell secretory capacity and secretory patterns, be it basal or post prandial, or both. The third could be due to tachyphylaxis, or what we used to attribute to sulfonylureas as "secondary failure".

We may remember that SU's carry a significant risk of secondary failure (tachyphylaxis), but we may not be aware-or have forgotten-that metformin does as well. This was shown in the head-to-head-to-head ADOPT trial [7], which directly compared time to failure of glyburide, metformin, and rosiglitazone failures in drug naive patients). Drug naive patients were given one or the other medication, and studied until the HbA1c rose to a pre-defined HbA1c point, defined as of loss of control. The order of secondary failure noted was SU, metformin, while rosiglitazone began to fail much later.

Not many practitioners have questioned the "add on to metformin approach", as we only had agents that were either weaker or had no other significant benefits beyond moderate blood sugar reduction. They often carried comorbidity risks that needed to be considered, or were insulin products that patients were reluctant to use. Recently, however, we have seen newer classes achieve FDA approval. The class of Dipeptidylpeptidase Inhibitor IV (DPP IV's), Gucagon Like Peptide-1 Receptor Agonists (GLP-1 RA's), Sodium Glucose Co-Transporter-2 Inhibitors (SGLT-2 Inhibitors), and now the combination SGLT-1 and -2 inhibitor, pending FDA approval-for not only Type 2 DM but Type 1 as well. In addition, we have seen a re-introduction of bromocriptine, in its short acting form, bromocriptine-CR [8].

Several of these classes have shown benefits "beyond glucose control". While several have shown not to increase CVD risk, but no CVD risk reduction and nor CVD event reduction either. Some classes produce benefits in weight, blood pressure, and renal function (SGLT-2 inhibitors). Empagliflozin, an SGLT-2 inhibitor (EMPAREG-OUTCOME Trial) [9] has shown significant secondary CV event reduction, as has liraglutide, a GLP-1 RA (LEADER trial) [10]. It is also marketed in the US as a weight reduction agent (under a different trade name). The former has earned the FDA CV event reduction addition to their product label. Recently the results from the CANVAS and CANVAS-R trials (canagliflozin) [11], have shown significant primary and secondary CV event reduction as well as renal protection-perhaps even renal function improvement. Canaglifozin product label changes are currently under consideration by the FDA. The decision is due by late July-early August. CREDENCE [12], a renal protection-preservation/improvement trial with canagliflozin is ongoing. There is a suggestion that bromocriptine-QR may also provide some CV risk reduction [8].

In addition to glucose control, we have weight loss to consider with all its potential benefits beyond even reduction of insulin resistance. The GLP-1 RA class has shown this benefit, as has the SGLT2 inhibitor class. Liraglutide, is marketed (under a different name) for weight loss. Blood pressure control has always been a concern. The SGLT2 class has shown significant blood reduction, perhaps due to a diuretic effect, perhaps a direct renal effect. We need the data from CREDENCE to answer this question.

If we consider that metformin due to its availability, price point, and tolerability, should be maintained as the first line therapy, what do we do when glucose control is lost? We can discontinue metformin and see if there is any change in HbA1c (tachyphilaxis versus progression), or we can add another agent-just as we have been doing-with little true long term success. Perhaps, we should discontinue metformin and change to another class of agents, or combination of agents.

Perhaps, we should even re-think our first line choice of agents and chose another class or combination of classes, not for price, but for the overall therapeutic benefits. We should reconsider our options if we see loss of diabetic control, or if newer benefits are seen in new or even established therapeutic agents.

Conclusion

Using the current state of the art studies and pathophysiology, we need to reconsider our first-line medication choices. We should also consider which medication(s) to use as second line. With this in mind, we also need to re-evaluate the validity of the "add-on step theory".

If we chose an SGLT2-inhibitor or a GLP-1RA alone, or in combination, we will have reduction of not only CVD risk, but CVD event reduction, excellent glucose reduction, weight reduction (with insulin

resistance improvement), blood pressure reduction, as well as renal protection/improvement (postulated at this point in time as we await CREDENCE).

The GLP-RA is theorized to prevent the observed SGLT induction of hyperglucaconemia leading to potential ketoacidosis, and prevent secondary increase in appetite. In addition, both classes produce weight loss, improve hypertension control, produce A1C reduction, with putative beta cell preservation, and renal function preservation. It has been clinically seen that the use of SGLT2 inhibition can leads to reduction in needs for blood pressure medications, especially diuretic use. CREDENCE will evaluate the theory of renal preservation in a complementary fashion to RAAS inhibition glomerular vascular dysfunction. Another agent has been submitted to the FDA for approval-an SGLT1 and SGLT2 dual inhibitor, sotogliflozin for both Type 1 and Type 2 diabetes [13]. This will be a unique compound, although canaglflozin has some SGLT-1 activity and aids in postprandial glucose control. Semaglutide, an approved GLP-1RA is currently being investigated in an oral form [14]. Currently all GLP-1RA medications are injectable.

Final Point

We need to change our treatment paradigm. We must make our prime consideration that most people suffer and die from, and what is the most costly, is diabetes associated complications and co-morbidities. Not less than ideal glucose control. We need to stop prioritizing the short term costs related to the medications. We need to change our treatment paradigm to prioritize the prevention of the long term complications and co-morbidities of diabetes, as well as the suffering caused by them. The financial costs to society and the health care system, resulting from this paradigm shift will be savings in the long run and a healthier and happier society.

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