Current paradigms in the treatment of type 2 diabetes

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Type 2 diabetes is an expanding epidemic worldwide, with recent data indicating at least 415 million adults with diabetes worldwide with an expected increase to 642 million by 2040 mainly in developing countries [1].

Multiple worldwide efforts are being undertaken to prevent diabetes by mitigating its risk factors–mainly obesity, reduced physical activity, increased consumption of salt, sugar and processed foods and reduced consumption of fruits and vegetables–yet these efforts are met with limited success. New approaches and medications to better improve the care of patients with established diabetes and reduce its resultant complications are being continuously developed, and these will be the focus of our current article.

Multiple studies have established the fact that early tight glycemic control reduces the risk of diabetes complications – microvascular, as well as macro vascular if initiated early in disease onset [2,3]. Furthermore, addressing multiple cardiovascular risk factors, including lipids, blood pressure and anti-platelet therapy, has been shown to be crucial in the prevention of macro vascular complications [4,5]. Yet, the increased mortality observed in the ACCORD trial indicated a possible risk associated with the intensive glucose lowering approach, and have set back our enthusiasm to achieve tight glycemic control for all [6]. Of note, the ACCORD trial utilized higher doses of insulin and sulfonylureas in the intensive arm. Although a casual association between hypoglycemia and increased mortality had not been proven, this may be a plausible explanation for the trial results.

In the recent decade several new drug classes have emerged including the DPP-4 inhibitors, GLP-1 receptor agonists and SGLT-2 inhibitors. These drugs offer the benefit of glucose reduction with minimal risk of hypoglycemia and weight gain – or even weight loss – and have also demonstrated cardiovascular safety in some, and protection in others [7-10]. These novel medications have been widely accepted by the medical community, as well as by the patients, as hypoglycemia and weight gain are significant barriers to the tolerability of intensive glucose control regimens. A large scale trial assessing the benefits of tight glycemic control at disease onset, similar to the late 2000 trials (ACCORD, ADVANCE and VADT), but utilizing novel medications is not expected in the near future. However, one may speculate that such a trial will demonstrate a significant reduction in both in microvascular and macro vascular complications, since these drugs enable attainment of glycemic targets without excess hypoglycemia, weight gain and with concomitant cardio-protection or safety.

Additionally, it has long been recognized that beta-cell reserve is markedly depleted at the time of diabetes diagnosis, and the rate of further deterioration in beta-cell function dictates the progression of the disease [11,12]. Multiple approaches to preserve beta cell function have been studied. Early attainment of normoglycemia by intensive insulin therapy has demonstrated high rates of long-term diabetes remission [13]. The new drug classes such as DPP-4 inhibitors and GLP-1 receptor agonists have demonstrated beta-cell preservation as well [14-16]. SGLT-2 inhibitors have demonstrated preservation of beta-cell function as well, which has been attributed largely to the amelioration of hyperglycemia [17].

Therefore, the current paradigm in diabetes care aims to:

- Treat diabetes as early as possible-by lifestyle modification and glucose lowering

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medications–initiating therapy at the pre-diabetes stage for high-risk individuals.

- Aim for normoglycemia as long as is safely possible, using medications which do not carry a propensity for increased risk of hypoglycemia and weight gain and have established cardiovascular and overall safety.
- Use combination therapy early-on if needed, aiming to achieve and maintain patient tailored glycemic targets [18,19].
- Personalizing glycemic therapy for each individual based upon his prevailing comorbidities, concomitant cardiovascular risk factors, and the risk entailed by the hypoglycemic agents themselves [3,20].
- Address multiple cardiovascular risk factors in the patient with diabetes aiming for tighter control of lipids and blood pressure.

These concepts are reflected in the recent guidelines offered by the international societies, for example:

- The ADA/EASD position statement emphasizes personalized choice of medications after metformin and encourages aiming for normoglycemia in select individuals [21].
- The AACE guidelines have chosen to prioritize the drug choices after metformin based upon their glycemic efficacy, weight loss and safety profile [22].
- The guidelines of the Israeli National Council of Diabetes noted BMI as a determinant in the choice of second line therapy and propose multiple combination therapies to be used at the different disease stages [23].

Overall, the risk of diabetes complications is declining, and it appears that patients with diabetes are receiving better care nowadays, compared to a decade ago [24]. Yet, we are still very far from bridging the gap, and the morbidity and mortality rates of persons with diabetes are still far higher than their age-gender matched counterparts [24,25]. There is still work to be done in the prevention and treatment of diabetes, and efforts should be directed to minimizing inequities in care and enabling access of persons in developing countries to these new, better and safer medications.

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