From Guidelines to Rational Care - A Perspective

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Landmark trials testify to the benefits of early aggressive intervention of T2DM (or at least the lack of benefit of later intervention)[1,2,3] There is evidence to suggest that there may be harm with aggressive intervention to reduce diabetes after an initial therapeutic window. There is also pathophysiologic evidence to support that there is a point of no return of the insult of hyperglycaemia beyond which there is continued progression of damage[4]. Conversely through the legacy effect / metabolic memory phenomenon its is plausible that gains obtained from early aggressive care may accrue over time even if there is a modest relaxation of therapeutic targets or intensity at a later time.

Targets in T2DM in patients are an HbA_1C generally < 7.0 with more intensive targets for patients with few comorbidities and longer life expectancy[5]. It must be remembered that the relationship between A_1C and microvascular complications is curvilinear. While at a population level the greatest number of complications will be reduced by moving patients from poor to fair or good control, additional benefit is apparent with reductions from 7 -6%. It must be remembered that the population normal is around 5.5% for Indians[6]. It must also be noted that the while the average western patient is their sixth decade at the time of diagnosis of T2DM, the average Indian patient is his or her fourth or fifth decade. Thus the average Indian patient will theoretically live longer with diabetes and therefore will benefit from early aggressive control. Given the benefit of early intervention and the apparent lack of it later, it is apparent that achieving A1Cs as near normal as possible in the first few years of care is desirable. With modern medications that work without significant hypoglycemia, "near euglycemia" may be achievable especially when mulitple drugs are used together.

As we continue to unravel the pathophysiology of diabetes and newer targets for therapy have emerged (the so called egregious eleven[7]). A mass of opinion has emerged with early evidence that targeting multiple pathophysiologic targets early in T2DM may be beneficial although long term studies are awaited. Such approaches may lead to meaningful remissions early in diabetes. Other approaches including early use of insulin have been demonstrated to provide remissions.

Clinical practice recommendations (CPR) by various societies are at variance with this evolving knowledge. It is prudent to demand evidence of benefit of early aggressive multi-pronged care; however it must be remembered that many guidances have a strong slant towards cost-effectiveness in a health care system with finite and rationed national resources for health care. These do not allow for systems in which patients pay out of pocket and may want a choice that will allow them into a more aggressive treatment care pathway in the early years even if it may be expensive. It is also important to start creating models of cost benefit in systems such as India where duration of diabetes is longer in a lifetime is longer, patients are at their most productive time of their lives and cost paradigms are different.

Until recently, most major CPRs would recommend a period of lifestyle changes prior to starting pharmacotherapy. This stance has been reluctantly given up of late by some but not all societies. Except one none the societies recommend initial combinations. The ADA recommends initial combination with $A_1C > 9$. Obviously there is a disconnect here between the targets and the ability of this graded tortoise paced intervention.

Let us assume that a 40 year old woman has presented to you with new onset T2DM and an initial A_1C of 7.5. She has no comorbidities. Given India's health trajectory - she has around 35 or more years of life and diabetes. Her target A_1C should be less than 6.5 and atleast an attempt should be made to achieve and maintain an A_1C of 6.0 or less. Lifestyle changes with help and other bells and whistle added achieves a modest A_1C benefit of 0.22. In the Look Ahead trial there was an initial drop of 0.6 but this could not be sustained. Clearly medications are required.

In this situation most guideline would recommend metformin (MF) - let us say the wait to MF is around 3 months. MF would bring the A_1C from 7.5 to 6.8 in most instances - may be 6.5 but not 6.0. (remember the influence of initial A_1C on the potency of any OHA). It two drugs were to be started - for e.g. a DPPIV + MF in this situation the expected A_1C lowering would be around 1.2, which you may decipher would lead us to an A_1C o < 6.5 but not < 6.0 which would be desirable. When drugs are combined, the A_1C reduction is seldom additive (in a predictable fashion) even if they are mechanistically synergistic[8]. It is thus obvious that in a patient with an A_1C of 7.5 to reach an A_1C of 6.0 we would need not two but three drugs.

One might argue that guidelines provide for sequential increase in drugs after three months. The counter to this is that guideline are blind to our track record of

intensification. It has been demonstrated the median time to intensification in most practices is 2-3 years. By the time additional drugs are contemplated the patient has already lost a couple of years in the path of no return. It must be also remembered that guideline based practice also does not allow for patients who reach A1C goals to remain in it. The average time a patient remained above goal after achieving it was more than 50% of the follow up time[9]. Clearly the time to act is the first visit and the number of drugs that must be used is more than one or two to reach the goal and stay there. As evidence evolves it may be worthwhile considering agents that work at different therapeutic targets.

In conclusion - current guideline driven care has done very little to provide aggressive optimal care for new and young diabetic despite evidence to show that this is the patient that will benefit with the book thrown at him or her. Our young population with a potential for long years with diabetes cannot afford the leisurely inertia ridden pace of the guideline based practice.

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