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Multifaceted Lifestyle Interventions and Cardiometabolic Outcomes in Type 2 Diabetes Mellitus

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Arteriosclerotic and atherosclerotic Cardiovascular Disease (CVD) is the primary cause of mortality in Type 2 Diabetes Mellitus (T2DM), accounting for more than 65-75% of all deaths in these patients [1-3]. The linkage of T2DM with CVD risk has led to the suggestion that common subclinical pathophysiological mechanisms predispose individuals to these conditions and cardiovascular events [4]. Subclinical CVD pathogenesis associated with metabolic syndrome (MetS) has been attributed to a combination of the established risk factors in the context of obesity and insulin and glucose metabolic dysfunction [5]. Thus, the toxic effects of dysglycemia on the vasculature may begin well before glycemic levels reach the diagnostic threshold for T2DM [6]. The MetS is also recognized as a predictor of T2DM, independent of either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) [7]. Therefore, preventative methods directed at reducing the antecedent subclinical cardiovascular complications of T2DM have been a primary strategy to diminish their impact on societal health burden [8].

Because hyperglycemia is independently related to the development of macrovascular complications, the benefits of intensive versus conventional glucose control on cardiovascular outcomes have been examined. A meta-analysis of 5 RCTs (i.e., ADVANCE, ACCORD, VADT, VACSDM, UKPDS33/34) from 1990 to 2009, which had a total about 28,000 T2DM patients, indicated that intensive compared with conventional glucose control resulted in significantly more improved glycemic control (0.9% HbA1c difference). Although a 14% reduction in non-fatal myocardial infarction was observed, no significant effect on cardiovascular or all-cause mortality was found [9]. However, more recent subset analyses of the VADT, ACCORD and ADVANCE trials indicated a significant benefit of intensive glycemic control on CVD outcomes in persons with shorter diabetes duration, lower HbA1c at study entry, and/or absence of known CVD [10-12]. In sum, there may be some benefit on cardiovascular morbidity and mortality of more intensive glycemic control but only in subsets of patients.

RCTs using lipid- and blood pressure-reduction interventions have consistently shown efficacy in decreasing cardiovascular morbidity and mortality and all-cause mortality in T2DM patients [13]. Indeed, the STENO-2 trial employed a more multifactorial intervention approach combining glucose regulation, blood pressure control, aspirin use, and lipid-lowering agents [14]. Despite achieving a moderate to insufficient blood glucose control (HbA1c ~7.9%) in the intensive group relative to the control group in STENO-2, a significant decrement was observed in cardiovascular events (59%), cardiovascular-related mortality (57%), and all-cause mortality (46%). Thus, cardiometabolic risk factor treatment in T2DM appears to be critical to improve CVD morbidity and mortality [15]. Nevertheless, despite the success of the STENO-2 multifactorial approach, mortality upon 13 years of follow-up remained very high (30% for intensive-therapy; 50% for conventional therapy).

Other studies have evaluated the possibility that a multifaceted treatment approach including a focus on lifestyle factors (i.e., diet and physical activity) would be more beneficial than a primary treatment focus on glycemia. A number of large-scale RCTs (i.e., Da Qing DPS, MALMO Feasibility Study, Finnish DPS, United States DPP, Indian DPP, SLIM, and Japanese DPS trials) have been performed in persons who are at risk for T2DM (overweight/obese, IGT and/or IFG) in order to evaluate lifestyle modification of diet and physical activity [16-20]. Findings indicated that the combined lifestyle intervention of dietary and physical activity relative to the education control or usual/standard-care condition produced greater risk reduction for progressing to T2DM. Meta-analysis indicated that over all of these studies the risk of becoming T2DM was reduced by about 51% (range: 42%-67% reduction) by the combination intervention [21]. Similarly, the United States DPP and Look Ahead trials in T2DM at-risk individuals have reported substantial improvements in subclinical cardiometabolic markers for those treated with lifestyle interventions [22-27].

However, in contrast to the beneficial effects of lifestyle intervention on diabetes prevention or delay and on cardiometabolic outcomes, RCTs using lifestyle interventions have not resulted in significant reductions in cardiovascular mortality [28-31]. Of the RCTs assessing endpoint efficacy of lifestyle interventions, the Da Qing study is unusual in that data are now available following a long-term follow-up of 20 years. They reported a 27% reduction in CVD-related mortality, but this effect was not significant. Therefore, it appears that the beneficial impact of lifestyle intervention on cardiometabolic outcomes is less optimally sustained. The lesson of STENO-2 [14] may be that a more multifactorial approach is required with therapeutic management of pharmacological and lifestyle factors to promote a more long-term impact on cardiovascular mortality in persons at risk for T2DM. Because adherence to such interventions is influenced by many patient and provider factors, solutions will need to target several barriers to care simultaneously to be effective.

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