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Is Weight Loss the Most Effective Method for the Prevention of Type 2 Diabetes? A Discussion in View of Evidence from Landmark Studies

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Abstract **Review Article**

Type 2 Diabetes mellitus (T2DM) and obesity are a continuum and intertwined in a complex way. Both these chronic conditions pose a significant challenge to the global health system, if the current trend continues, it is estimated that by 2045 the number of people affected globally will increase by almost 700 million. Considering the above, effective strategies have to be implemented to tackle this global pandemic. The main strategies discussed in the literature are lifestyle intervention (ESI) with or without weight loss and medication. This article looked at the evidence from the various landmark studies which include the Diabetes Prevention Program (DPP) and Diabetes Prevention Study (DPS) Outcomes of these studies suggest that ELSI with loss is superior to ELSI without weight loss and metformin in risk reduction of T2DM. The evidence from the Swedish obese subject study also concludes that weight loss achieved through bariatric surgery reduces the risk. Lifestyle modification programmes even without weight loss have greater health benefits but as far as risk reduction for T2DM the evidence is not conclusive. This review article concludes that reducing weight is paramount for preventing T2DM, especially in high-risk individuals, compliance plays a vital role in overcoming these challenges and stresses the importance of tailored strategies for person-to-person characteristics to overcome those challenges.

Keywords: Type 2 Diabetes Mellitus (T2DM), Obesity, Lifestyle Intervention (LI), Weight Loss, Risk Reduction.

INTRODUCTION: WHY FOCUS ON DIABETES AND OBESITY

Type 2 Diabetes Mellitus (T2DM) is a progressive chronic disease, with significant clinical and social consequences. T2DM affects approximately 450 million people globally. There is a steady rise in the prevalence of T2DM and if the current trends continue 10.9% of the world population will be affected by the year 2045, which equals to 700 million people [1]. The reasons for this exponential growth sighted in literature as rapid urbanization, obesity, sedentary lifestyle and ageing population amongst others. The pathological process behind T2DM is insulin resistance and insulin deficiency in isolation or combination of the two.

In the majority of the cases, T2DM is insidious and initially asymptomatic. Due to this long preclinical phase, a significant number of individuals present late to medical professionals, the evidence from UKPDS suggests that 50 % of individual diagnosed with T2DM have some degree of damage to the vascular tree, at the time of diagnosis. The disease and its complications (microvascular and macrovascular complications) are the significant burdens on the health systems worldwide, for U.K NHS spends around 10 % of its annual budget on diabetes care and 80 % of the expenditure is on managing the complications of T2DM [2].

Healthcare organizations and public health departments worldwide are putting strategies together firstly to reduce the incidence of T2DM and secondly to reduce the complication rate in established disease. To achieve this goal, early detection of high-risk individuals is paramount.

The risk assessment can be done by using risk calculators [3, 4] or through population-based health check programs [5]. The individuals identified as high risk, are tested, and if the value of HbA1c is between 42

mmol/mol - 47 mmol/mol are diagnosed as having Prediabetes. Identifying people with Prediabetes is the first step in reducing the number progressing to T2DM.

Prediabetes is a blanket term that includes impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and glucose levels above normal but not high enough to be diagnosed as Diabetes, i.e. HbA1c between 42 and 47(mmol/mol). In this essay, the term Prediabetes will be used instead of IGF, as this is the newer and widely accepted terminology.

Prediabetes is not a benign condition, and approximately 5-10% of individuals with Prediabetes will go on to develop T2DM. The incidence of Prediabetes is estimated at 35.3% of the UK population and this figure is up from 11% in 2003 [6]. This data establishes that Prediabetes is a public health crisis in its own right.

Risk factors for Diabetes and Prediabetes are similar and divided into modifiable and non-modifiable. Non-modifiable risk factors include age, male sex, ethnicity, family history of T2DM, gestational Diabetes and modifiable risk factors are mostly behavioural and include weight, sedentary lifestyle, unhealthy diet, and social circumstance. Observational studies have shown that not all individuals who are overweight or obese will develop T2DM, but it is also true that 90% of individuals with T2DM will either be overweight or obese [7].

Obesity in general and truncal obesity, in particular, are major risk factors for developing T2DM. The prospective studies collaboration looked at obesity and its effects on the population. The finding was: In both sexes, mortality was lowest at BMI 22·5–25 kg/m², each 5 kg/m² rise in BMI was on average associated with about 30% higher mortality, 40% for vascular mortality, 60–120% for diabetic, renal, and hepatic mortality. An interesting fact from this study was that at BMI of 40–45 kg/m² reduced life expectancy by 8–10 years (this reduction is similar to the effects of smoking). As we can see, there is a definite correlation between obesity and poor health outcomes [8].

NCD Risk Factor Collaboration (NCD-RisC) has looked at Global trends of obesity and findings show that global BMI is showing a definite upward trend. For the first time in the past 40 years, there are more obese people globally than underweight people [9].

From the above one can conclude that T2DM, Prediabetes and obesity are a continuum, and it is not possible to address one without tackling the others.

Prevention of T2DM the Evidence

Studies have shown that there is an association between T2DM and obesity [10, 11]. The data presented above also demonstrates that there is an increase in the incidence of T2DM and obesity globally. There is evidence that T2DM can be put in remission by weight loss achieved by strict calorie restriction [12]. In current clinical practice, along with antidiabetic medication, Lifestyle management programmes (LSM) aimed at weight loss have a pivotal role in the management of established T2DM [13, 14].

A critical question remains: Is T2DM a preventable condition, and what is the best way to achieve this? The authors hypothesize that Diabetes is a preventable condition and weight loss is the most effective method for the prevention of T2DM.

Landmark studies have demonstrated that T2DM is a preventable condition. The strategies that are effective in reducing the risk for T2DM are restricting calorie intake, causing weight loss or by encouraging physical activity to burn the calories consumed, or using a medication, in isolation or combination. Not much evidence is available for the role of physical exercise as a sole intervention without weight loss in risk reduction for T2DM. The systemic review by Yates et al. concluded that the contribution of physical activity in isolation and independent of weight loss and calorie restriction to the prevention of type 2 diabetes in people with Prediabetes is equivocal [15]. Gill and Cooper looked at the published data and concluded that physical activity reduces the risk of T2DM in obese individuals. The risk reduction is greatly enhanced when accompanied by weight loss [16].

The evidence is conflicting and has to be looked at in more detail to draw definitive conclusions. Landmark studies on the prevention of T2DM have tried to address this area of uncertainty.

The Finnish Diabetes Prevention Study (DPS) [17] was Published in 2003; a landmark study looked at this specific question, i.e. efficacy of lifestyle management programme (LSM) in risk reduction of T2DM. The trial included 522 Finish individuals with Prediabetes with a BMI of 25 and above and randomized them to the usual care and Intensive lifestyle (ILS) management group. The LSM programme used in the study was explicitly designed for its transferability in primary care. The intervention aimed to reduce the risk of T2DM by weight loss and increased physical exercise. Data from DPS demonstrated that the LSM program is valid, and achieved a risk reduction of 58% as compared with the control group. DPS trial also demonstrated that LSM could achieve clinically significant weight loss, i.e. weight reduction of 4 kg at year one and 3.5 Kg at year three compared to 1 kg at year one and 0.9 Kg at year three in the control group. It is not definitive that weight loss or physical activity was the cause of this risk reduction.

DPS proved the efficacy of LSM in risk reduction, but the findings cannot be generalised firstly due to small cohort and secondly the cohort was not

ethnically diverse. This gap in evidence was filled by a trial conducted in the USA by the Diabetes Prevention Programme Research Group (DPP), which published its findings in 2002 [18]. A Large cohort of 3234, ethnically diverse participants with Prediabetes and a mean BMI of 34. The participants were randomized into three groups standard lifestyle advice plus placebo, intensive lifestyle management (ILM) programme, and standard lifestyle advice plus Metformin. They were followed up for an average of 2.8 years. ILM group had to achieve a 7% reduction from baseline weight and maintain weight loss throughout the trial by participating in the LSM programme. The programme included low calorie, low-fat diet, physical activity of moderate intensity for about 150 min per week, and participants supported by a face to face sessions with trained professionals. The participants also had to take part and complete 16 lesion curriculums. In contrast, the other two groups which received written advice on healthy lifestyles and an annual 20-30 min face-to-face session for enforcing and monitoring the progress (this is close to current real-life intervention in practice). The trial aimed to compare the effects of Metformin to the LSM programme in risk reduction of T2DM.

At the end of the trial, both the Metformin group and ILM group achieved weight loss and reduction in the incidence of progression to T2DM, but ILM proved to be superior to the Metformin group. LSM achieved a reduction of 58% in progression to T2DM as compared to 31% in the Metformin group compared to placebo. The numbers translated into 6.9 individuals would have to receive ILM support as compared to 13.9 individuals to receive Metformin to prevent one case of T2DM over three years. The average weight loss amongst the groups was placebo 0.1 Kg, Metformin group 2.1 Kg and ILM group 5.6 kg. ILM group achieved more significant weight loss and a higher reduction risk of developing T2DM.

The trial data demonstrate that ILM is superior to Metformin. However, in-depth analysis shows that lifestyle advice and support that individual groups received were significantly different, so not a like-for-like comparison. The ILM group had a specific target set for weight loss and set targets for physical activity. The study did not look at the individual contribution of calorie restriction, weight loss, or physical activity to overall risk reduction so not clear which of these was more effective but weight loss was the common denominator in the results.

The LSM programme used in DPP was time-consuming and would be very difficult to implement outside of the research setting and also produced similar results to one used in DPS. One can conclude that no added benefit is seen from elaborate programmes as long as weight loss is achieved.

The question remains to whether the reduction in the incidence of T2DM was due to calorie restriction alone or physical activity in its entirety is responsible for these results. Both of these are the components of LSM programme.

The Da qing study [19] Is another landmark trial investigated this area of interest. The trial set in the Chinese city of DaQing and published in 1997. The total number of individuals screened was 110,66 and out of which 577 individuals identified as having Prediabetes. These high-risk individuals were randomized into three active treatment groups, namely, diet only, exercise only, and a combination of diet plus exercise and a control group. These four groups of individuals were followed up for six years to look at the effects of diet and exercise separately and in combination as compared to the control group.

Results showed that the incidence of T2DM in the control group was 67.7% as compared to diet only group at 43.8%, exercise only at 41.1%, and the diet-plus-exercise group at 46%. The results skewed as dietary advice in the study differed according to baseline BMI, and the fact that lean individuals might have had visceral fat and could have benefited from dietary advice was not taken into account. The incidence of Diabetes in the control group varied depending on BMI, i.e. the incidence of T2DM was higher in overweight and obese participants than in the lean participants. On the other hand, the incidence of Diabetes in the intervention group was lower in both categories of BMI.

An interesting finding of the trial was that risk reduction and weight loss were similar for diet only and exercise group and no added benefit was demonstrated from combining both, so the conclusion can be drawn that weight loss no matter how achieved causes a risk reduction.

The Indian Diabetes Prevention Programme trial, a more recent study published in the year 2006 studied the effects of lifestyle modification and Metformin in lean Asian Indian subjects with Prediabetes [20].

IDPP-1 recruited 531 individuals and randomized them into control and three intervention groups (Metformin, LSM, LSM + Metformin). A significant reduction in progression to T2DM was demonstrated in all three groups, and all interventions were equally effective. No added benefit in combining the two interventions.

There was no significant change in BMI or waist circumference reported in the intervention groups. The risk reduction achieved was independent of weight loss.

The effects of LSM on risk reduction of T2DM are clear from these landmark studies. However, they do not offer definitive evidence on the influence of weight loss and physical exercise separately on this risk reduction. The results achieved are partially due to a reduction in insulin resistance due to weight loss by calorie restriction and partially due to increases in physical activity in its own right by increasing insulin sensitivity.

The landmark studies failed to provide convincing evidence in this debate; hence we have to look elsewhere for this missing piece of evidence.

Another way of analysing this question would be to look at the evidence from studies on risk reduction by weight loss in individuals with Prediabetes achieved by methods other than LSM, e.g. bariatric surgery and medications.

The Swedish obese subjects study (SOS) does precisely this and is an essential study on this subject completed in 2005 [21]. The study is a non-randomized clinical trial with a 15-year follow-up. The participants intended to lose weight either by bariatric surgery or by lifestyle intervention alone, 4047 obese patients enrolled with an average BMI of 34 and above. The trial demonstrated that weight loss (average maximum weight loss 31 Kg year one and about 20 Kg year 15 compared to control group 3 Kg) achieved with bariatric surgery reduces the incidence of T2DM in an obese patient by 78%. The risk reduction for individuals with Prediabetes was even higher at 87% .in other words in the intervention group; 10 out of 13 obese individuals did not develop T2DM, which is a significant number.

The results from the SOS study demonstrate that bariatric surgery is two times more effective than LSM in DPS and DPP in risk reduction of T2DM. The reason for this enhanced effect is the significant weight loss achieved. A further argument in favour of weight loss no matter how achieved LSM or bariatric intervention will reduce the risk of developing T2DM.

To take this discussion further, we look at the efficacy of pharmacological interventions in the context of weight loss and risk reduction of T2DM. The SCALE programme explored this area extensively [22]. A 56-week, multicentre, randomized, placebo-controlled trial to study the effects of Liraglutide (GLP-1 RA) as an add-on to LSM, 3731 patients were recruited and out of that 61.2% had Prediabetes and had a mean BMI of 38.3. Patients were randomized into two groups placebo and Liraglutide. Both groups received similar lifestyle interventions. At the end of 56 weeks, the Liraglutide group achieved a mean of 8.4 kg weight loss as compared to 2.8kg in the placebo group and achieved better metabolic control. This trial confirmed that Liraglutide is a viable intervention for weight loss as an add-on to lifestyle management. The individuals with Prediabetes then entered into a three-year extension of the trial. The aim of this study was to evaluate the long-term effects of Liraglutide on weight loss and delay in the progression of Prediabetes to T2DM [23].

The study demonstrated that 3% of individuals in the Liraglutide group and 11% in the placebo group progressed to T2DM. A risk reduction of approximately 80% for Liraglutide vs placebo. A significant number of individuals in the intervention group did not progress to T2DM. 66% even regressed to Normoglycemia as compared to 36 % in the placebo group.

The vital finding also from the data analysis was that more than 90% of individuals in each treatment group who progressed to developing T2DM lost less body weight during the trial as compared with individuals who did not progress to developing T2DM.

XENDOS study a four year trial with orlistat published in 2003 came to similar conclusions i.e. Incidence of T2DM was 9% with placebo and 6.2 % with orlistat a total risk reduction of 37.3% [24]. Orlistat achieved 5.8 kg vs 3 kg with placebo after four years of treatment this effect was similar in the individuals with Prediabetes and without. 37.3% risk reduction achieved with significant weight loss.

The evidence from the data above demonstrates that the prevention programmes are effective in achieving weight loss and reducing the risk of T2DM in trial settings but is this translated into real life or not was looked at by a systemic review published in 2014 [25]. The conclusion was that LSM programmes could achieve weight loss and prevention of T2DM. However, their effectiveness depends upon adherence to the recommendation, and significant drivers are weight loss and physical activity. Also, evidence from translational studies reflects that although these interventions are expensive and time-consuming, they do retain effectiveness in real life [26].

CONCLUSION AND RECOMMENDATION

Lifestyle modification reduces the risk of progression to T2DM by enhancing beta-cell function, increasing insulin sensitivity, and reducing insulin resistance. Both DPP and DPS achieved around 58% risk reduction by LSM. In turn, pharmacotherapy trials XENDOS trial with orlistat achieved 37% risk reduction and SCALE programme achieved 80% risk reduction and Metformin achieved a 31% risk reduction as compared with placebo in DPP study.

Collectively these results show that LSM programmes are effective in achieving risk reduction of developing T2DM by weight loss, and this effect is significantly enhanced by add on pharmacotherapy and surgery by achieving even more weight loss. Follow on studies have shown that the results are maintained over time [27]. IDPP-1 is an outlier as it showed lean Asian

Indians, achieved risk reduction without weight loss, but these findings cannot be generalized due to the non-diverse study group.

The evidence also suggests that an intervention that works in one population might not work in others due to social, economic, and cultural differences. However, one thing is evident from all the evidence presented, which is weight loss is the most effective way to reduce the risk for T2DM in obese and overweight individuals.

In real life, adherence to lifestyle modification is difficult despite proven benefits in clinical trials [28]. Due to the problems with adherence, LSM is not sufficient to achieve desired results, i.e. Reduction in the risk of T2DM hence alternatives should be considered as add on like bariatric surgery and pharmacotherapy.

Author's conclusion from the evidence is that weight loss is key to prevention of T2DM in overweight, obese patient but a healthy lifestyle in the way of regular exercise, calorie restriction is also beneficial without weight loss in lean individuals.

Reflection

Although the importance of lifestyle intervention focused on weight loss in the prevention of T2DM is well established, and the long-term benefits of weight loss on general health are well known still many individuals with Diabetes and Prediabetes remain overweight. We need to reconsider the current practice and raise awareness amongst health professionals about the benefits of treating Prediabetes more aggressively. In the UK. general practice is at the forefront of the fight against the Diabetes pandemic. In times of austerity and funding cuts, physicians lack the time and resources to implement the public health agenda of reducing the incidence of obesity and T2DM; instead, the focus is on the treatment of T2DM. Prediabetes is not considered a priority, and there is no incentive (funding) for clinicians to act swiftly. The authors' practice would definitely change in the sense that T2DM is a preventable condition with modest lifestyle intervention and weight loss. Also, obesity and T2DM have complex etiology, and it is not as simple as just eating less. Advice should be individualized and wary depending on the patient's baseline BMI, sex, age, and ethnicity. Pharmacological and non-pharmacological options are all valid and an option to reduce the risk of T2DM.

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