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REVIEW ARTICLE

Prevention and Cure of Diabetes, 2017: A Review

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This review offers a discussion of various strategies for prevention of and possible cure for diabetes mellitus (DM); it includes results from various clinical trials targeting patients at high risk of developing DM.

WHO estimates that by 2025 as many as 200-300 million people worldwide may develop DM. It's a major public health problem of 21st century. The increasing of incidence of DM in children is perhaps the most alarming sign of something going wrong - roughly half of risk can be attributed to environmental exposure and the other half to genetics. Central themes for prevention are around the risk factors like overweight, sedentary lifestyle, certain dietary component and peri-natal factors. Being overweight is the most critical risk factor and should be targeted for prevention of type 2 DM, especially among children and youths. In US DPP for high risk individuals, there was a 58% relative risk reduction in the progression to diabetes in lifestyle group compared to controls. Within lifestyle group, 50% achieved the goal of >7% weight loss and 74% maintained at least 150 min of moderate intensity activity per week

Even more concerning is the fact that a large percentage of population has a condition called pre-diabetes (IFG/IGT/raised HbA1C), putting them at a significantly increased risk of 5-15 fold higher of progression to frank diabetes. This is a grave problem since the treatment only prevents some of dire complications of diabetes, usually failing to restore normal blood glucose level or to eliminate all adverse events associated with diabetes, resulting in enormous and increasing national and global economic and social costs. Most regrettably, the burden of diabetes continues to shift to low and middle income countries where almost 80% of diabetes deaths occur, precisely where there is limited access to affordable treatment.

The Imperative for prevention

The pandemic of type 2 DM is an enormous public health problem, with an expected doubling of prevalence globally from 171 million in 2000 to 366 million in 2030 (Hossain P, 2007)[19] with a maximum increase in India. In 2000, India topped the world with highest no of people with diabetes followed by China and USA in second and third place respectively; diabetes is fast gaining the status of potential epidemic in India with > 62 million diabetic individual currently diagnosed with disease (Joshi SR, 2007;)[21] and may afflict up to 79.4 million people by 2030; another big proportion being pre-diabetic with 5-15 fold higher risk of developing type 2 DM

over 3 – 5 yr period. Unfortunately, many patients are diagnosed relatively late, at a point when many patients have already developed complications; so screening of high risk group and managing them so as to prevent development of DM is essential.

Type 2 DM is a heterogeneous disorder characterized by 2 interrelated metabolic defects: insulin resistance coupled with impaired insulin secretion by beta cells in pancreas. Therefore, strategies that target these two mechanisms by improving insulin sensitivity and protecting beta cell function have become the focus of prevention efforts, weight loss, physical activity and some medications are thought to improve both insulin sensitivity and secretion.

Who should be targeted for diabetes prevention?

The first step in diabetes prevention is identifying patients who are at the highest risk. This group includes individuals of any age who are overweight and obese (BMI > 25 kg/m^2) with at least one risk factor (e.g. high risk ethnic group, 1st degree relative with DM, personal H/O GDM, woman with h/o PCOS, sedentary lifestyle, features of insulin resistance, h/o CVD, HTN, HDL < 35/TG > 250, impaired glucose tolerance in prior testing). ADA recommends that these patients should be screened every 3 years; all other patients should begin screening at the age of 45 yrs

Exercise/lifestyle

In a seminal RCT of obese older adults (Coker RH, 2009;27)[5], exercise with weight loss improved glucose metabolism (both hepatic and peripheral insulin resistance) and reduced visceral fat more than comparable weight loss without exercise. The Early ACTID RCT (Andrews RC, 2011)[1] compared physical activity (PA) of brisk walking for 30 minutes for five days a week (150 min/week), with physical activity and diet in newly diagnosed DM, found improved insulin resistance and A1C with reduced DM MEDICATION in both groups, demonstrating that PA itself added no additional benefit to an intense dietary interventions in which between 5-10% of body weight was lost.

The largest and arguably the most compelling evidence (Diabetes prevention program research group, 2002;25(12))[9] for prospective benefits of lifestyle modification in US is that of diabetes prevention programme (DPP), the first RCT to compare lifestyle and pharmacologic intervention to placebo, with weight loss established as the predominant predictor of reduced DM incidence, at a 16% reduction in risk per every kg of weight loss, although even those who achieved exercise goals only, not weight loss goals, also experienced significant reduction (44%) in diabetes risk.

But, other systemic review (DeFronzo RA, 2011)[7] of beta cell function which controls the storage and release of insulin found that although lifestyle modification reduces IGT progression to diabetes, both implementation and maintenance are difficult and complex, with 40 – 50% of IGT subjects progressing to diabetes despite weight loss. This contrasts with pharmacological intervention that reverses patho physiological abnormalities, especially beta cell function and insulin resistance, and uniformly prevent IGT progression to DM, with a reduction of DM development of approx. 50 – 70% from thiazolidinediones and 31% from metformin.

Evidence (Wing RR, 2001;24)[29] shows that maintenance of weight loss/physical activity is difficult to sustain over a longer period, something also demonstrated in DPP, where weight was largely regained when the DPP ended; and pharmacologically induced weight loss is also followed by weight regain when drug therapy is reverted to placebo despite continued dietary intervention. Indeed, weight regain is an undeletable characteristic of most weight loss programmes, regardless of the type of dietary intervention, so that efforts to translate the results of DPP to clinical practice have proven uncommonly stubborn.

Evidence from systematic review (Walker KZ, 2010;23(4))[28] strongly suggests that maintenance of weight loss is sustainable only via regular exercise that entails an additional expenditure of

approx. 2000 kcal/wk. Newest evaluative RCT (Ma J, 2013;173(2))[24] assessing the outcomes of DPP lifestyle interventions shows that the percentage of participants who achieved the 7% DPP based weight loss goal were 37% (coach led group) and 35.9% (self-directed group), leaving almost 2/3rd of the participants failing to achieve even that modest goal, and still higher percentage who are unlikely to maintain the loss into durable long term gains.

This indicates that lifestyle intervention alone is insufficient to prevent the development of diabetes in large proportion of subjects, in stark contrast to pharmacologic therapy which uniformly and significantly reduces IGT/IFG progression to DM.

Pharmacologic preventive intervention

Metformin is the most widely studied drug for diabetes prevention. In the DPP participants randomized to metformin (850 mg twice daily) achieved a 31% reduction in diabetes compared to placebo (group D. R., reduction in incidence of type 2 diabetes with lifestyle intervention or metformin, 2002)[14]; Metformin was most effective in more obese participants (BMI > 35), who achieved 53% reduction of diabetes incidence, and in participants < 45 years of age, who saw a 44% reduction. Metformin had little benefit for older individuals who were 60 – 85 years at baseline. The effectiveness of Metformin was attributed in part to weight loss, which averaged 1.7 kg and accounted for 64% of the beneficial effect of Metformin; importantly, after 10 years of follow up, the Metformin group had maintained an average weight loss of 2.5 kg, and DM risk was reduced by 18% compared to former placebo group (group D. R., 2009)[15]. In general Metformin is widely available, inexpensive and relatively well tolerated; so it is an appropriate treatment approach in appropriately selected patients, especially those who are younger and overweight.

Thiazolidinediones: In the first year of DPP, diabetes incidence was reduced by 75% in the troglitazone arm before it was discontinued because of evidence of hepatotoxicity (group D. R., Design and methods for a clinical trial in the prevention of type 2 diabetes, 1999)[13]; troglitazone was also studied in a cohort of woman with recent gestational diabetes and reduced DM by 50% compared to untreated controls. Rosiglitazone was studied in the DREAM trial, a large international study that randomized high risk patients to rosiglitazone, 8 mg daily, or placebo. After an average follow up of 3 years, the incidence of diabetes in the rosiglitazone group was reduced by 62% compared to placebo; however rosiglitazone has well known side effects such as weight gain, peripheral oedema; in DREAM trial, the TZD group gained 2.2 kg more weight than placebo group. Other concerns are cardio-toxicity and risk of fracture; documented efficacy of Metformin in preventing IGT conversion to DM is just about half (31%) of that observed with pioglitazone (62 – 72%). Proactive study (Dormandy JA, 2005)10 has demonstrated that pioglitazone may also decrease CV events, so pioglitazone may be a good alternative to Metformin.

GLP1 analogue: Evidence established that GLP1 analogs are effective in treating diabetes, while reducing IGT conversion to DM, improving beta cell function, promoting weight loss and improved CV risk factors while not inducing undesirable hypoglycemia; all with the convenience of administration, collectively making them near ideal agents for treating IGT, allowing a highly optimal combination regimen of a GLP1 agonist for preservation of beta cell function and promotion of weight loss, coupled with low dose pioglitazone for amelioration of insulin resistance and improvement of beta cell function ('anti-diabetic complex').

Acarbose: The alpha-glucosidaseinhibitoracarbose was studied in the STOP-NIDDM trial that randomized 1,429 participants with IGT to either acarbose, 100 mg or placebo three times daily for a mean of 3.3 years (Chiasson JL, 2002)[3]. In this study, subjects in the acarbose treatment arm had a 25% reduction in the incidence of diabetes. However, almost one third of the acarbose group was unable to complete the study because of GI side effects, which makes the results of the study difficult to interpret and the applicability to clinical care unclear.

Reduction in CV mortalty and CV events

Meta-analysis of ten prospective RCT (Hopper I, 2011;18(6))[18] shows that of both pharmacological and lifestyle interventions, no difference was observed between risk of all cause mortality in the intervention versus control group, nor any difference in cardiovascular death; but with borderline reduction in fatal and non-fatal stroke. So, presently there is a need for more effective preventive interventions that block both progression to DM and provide a net gain of significant reduction in adverse events.

Vitamin D deficiency

It is emerging strongly (Lim S, 2013;97(3))[23] that vitamin D plays a vital role in DM pathogenesis and several studies show that vitamin D deficiency increased the risk of diabetes independently of BMI/ homeostatic model assessment – insulin resistance and insulinogenicindex (which reflects acute phase insulin secretion) after adjustment of age, gender, BP, lifestyle, family history, season, PTH&hs CRP.

Personalised vs. blunderbuss approach

Genetics:

In two ingenuous single nucleotide polymorphism (SNP) RCTs from the innovative prevention programme research group at George Washington University, it has been shown that the AMPK subunit genes PRKAA1 and PRKAA2 appear to be genetic determinants of metformin resistance (Jablonski KA, 2010;59(10))[20] and that two SNPs (BDNF rs 6265, PPARG Pro 12A1a) were predictive of weight regain, while the minor A1a12 allele at PPARG was associated with short and long-term weight loss (Delahanty LM, 2012;35(2))[8]. When cross confirmed and commercially available, these genetic markers will prove invaluable in optimal selection of candidates for prevention interventions and also allow to focus more resources and therapeutic agents to those who are genetically predisposed towards weight regain and allow us to know to substitute TDZ and GLP1 agents instead of metformin for those at genetic predisposition against metformin response.

American diabetes association guideline

Life style intervention

- ***Nutrition therapy***
  - MNT delivered by a registered dietician is a/w A1C decrease of 0.3-1% in type1 DM and 0.5-2% in type 2 DM;
  - There is no ideal diet - diet should be individualized keeping in mind total calorie and metabolic goals in mind; the Mediterranean, DASH and plant based diets are all examples of healthy eating patterns.
  - Foods rich in omega 3 fatty acids, such as fatty fish (EPA, DHA), nuts and seeds (ALA) is recommended though not evidence based;No role of supplementary micronutrient intake with no suggestion of deficiency, rather there is safety concern of long-term antioxidant intake.
- Adults who drink alcohol should do so in moderation (no more than 1 drink for woman and 2 drinks for man).
  - sodium intake should be < 2300 mg/d, further restriction for those with HTN.
  - Use of non-nutritive sweeteners has the potential to reduce overall calorie and carbohydrate intake; they are safe to use within defined acceptable daily intake level.
  - Weight loss can be attained with life style programs that achieve a 500-750 kcal/day energy deficit or provide 1200-1500 kcal/day for women and 1500-1800 kcal/day for men. For obese type2 DM patients, a weight loss of > 5% is needed to produce beneficial outcomes in glycemic control, lipids, BP and sustained weight loss of > 7% is optimal
  - 20-35% of total energy consumed in fat but the most important is the type of fat consumed. Mediterranean style diet rich in MUFA can improve glycemic control and lipids

Physical activity

- *Children and adolescent* should engage in 60 min/day or more of moderate or vigorous intensity aerobic activity, with vigorous muscle

strengthening and bone strengthening exercise at least 3 days/week.

- For adults
  > 150 min/ wk spread over at least 3 days/wk with no more than 2 consecutive days without activity, shorter duration of 75 min/wk may be sufficient for younger and physically fit individual
  > 2-3 session/wk of resistance exercise on non-consecutive days.Prolonged sitting should be interrupted every 30 mins
  > 2-3 times/wk of flexibility training and balance training, yoga and tai chi may be included based on individual preferences.
- Structured exercise for 8 weeks has shown to reduce A1C by 0.66% even without a significant change of BMI.

Diabetes prevention programme (DPP): recommendations summary

- People with IGT, IFG, A1C 5.7 – 6.4% are ideal candidates for DPP. DPP demonstrated that intense life style intervention could reduce the incidence of type 2 DM by 58% over 3 years.
- ***Two major goals***: 7% weight loss and 150 min/ week of physical activity. 7% weight loss goal selected because it is feasible to achieve and maintain and likely to lessen the risk of DM, encourages to reduce 7% during first 6 months of intervention @1-2 lb/wk. 150 min/wk activity will cause 700 kcal/wk energy expenditure.
- DPP should be an individual model rather than a group-based approach-DPP was administered as a structured core curriculum f/b more flexible maintenance porogramme. Sixteen-session core curriculum completed within 24 wks
- pharmacologic intervention: ***metformin is recommended*** in DPP for prediabetes with BMI > 35 kg/m2, age < 60 yrs, women with h/o GDM (50% risk reduction) and/or those with rising A1C despite life style intervention.
- Other drugs, glucosidaseinhibitor, GLP 1 analogue, thiazolidinediones and orlistat, also shown to decrease incident DM to varying degree in those with prediabetes but metformin has the strongest evidence and long-term safety, other drugs require cost, side effects and durable efficacy consideration.
- Intervention remained effective in 10 year follow up - increased vigilance and RX of other RF for CVD should be identified and treated.

Prevention of type 1 diabetes

Type 1 DM is an autoimmune disease; although the process by which pancreatic beta cell is destroyed is not well understood, several risk factors and immune related markers are known that accurately identify many first degree relatives of patients with type 1 DM who may develop the disease. Because of the ability to predict the development of type1 DM in some people, investigators have begun to explore the use of intervention therapy to halt or even prevent beta cell destruction in such individual.

	❑ Stage 1	❑ Stage 2	❑ Stage 3
stage	.autoimmunity .normoglycemia .presymptomatic	.autoimmunity .dysglycemia .presymptomatic	.new onset hyperglycemia .symptomatic
Diagnostic criteria	.multiple auto Ab .no IGT or IFG	.multiple auto Ab .dysglycemia:IFG/IGT .A1C 5.7-6.4% or 10% increase in A1C	.clinical symptoms .DM by standard criteria

Presence of 2 or more Ab in an individual is a certain predictor of future hyperglycemia & type 1 DM.

An NIH sponsored multi-centered study, the Diabetes Prevention Trial (DPT1) that was designed to determine whether the development of type 1 DM can be prevented or delayed, has just been partially completed. The DPT 1 was designed to determine if low dose insulin administered either by injection or orally could delay or prevent type 1 DM in people with a significantly increased risk of developing the disease within 5 years; this large multicenter trial was based on animal studies and a small trial in humans indicating that insulin given could prevent type1 DM. The DPT1 randomly assigned 339 individuals deemed to be at high risk (>50%) for the disease development based on signs of autoimmune beta cell destruction and low insulin response to an intravenous glucose challenge to receive insulin or to serve as control subjects. The rate of development of DM was identical (60%) in both groups, indicating that the injection of low dose insulin does not delay

or prevent type1 DM. A second arm of DPT1 using oral insulin in those deemed to be at moderate risk (25-50%) of developing DM is ongoing.

Multiple clinical trials investigating the efficacy and safety of immunotherapeutic interventions in new onset of type 1 DM have failed to yield long-term clinical benefits.

Presently there are powerful tools to predict type 1 DM in susceptible individuals based on measurement of serum autoantibodies and HLA background; however, reliable biomarkers to predict therapeutic success following the intervention are still lacking.

Realizing immune based interventions for human type 1 DM will be necessary even if an unlimited source of new islets can be obtained from stem cells or other sources, because autoimmune memory cells will have to be controlled to avoid continued loss of beta cell over time. The key issue that must be tackled is achieving a tolerable balance between immunosuppression and the associated side effects and long-term tolerance. The likelihood that mono-therapies with systemically acting immunomodulators will achieve this is low because even in the best case scenario, side effects will emerge after 20-30 years, as has been seen with immunosuppressive regimens in transplantation (Dantal J, 2005)[6]. Therefore, adaptive Tregs that recognize beta cell Ags proliferate in the pancreatic lymph nodes (Homann D, 1999)[17], and can, at least in multiple animal models, mediate islet specific immunosuppression should be induced in conjunction with systemic immunomodulatory therapies, e.g immunization with GAD 65, (pro) insulin, (pro)insulin peptides or DNA vaccines.

Translation and cost-effectiveness of diabetes prevention

The protocols employed in most lifestyle intervention trials are labor intensive and require dedicated staff and resources, raising issues about the economics of implementing these programmes; the DPP investigators analyzed the cost per quality adjusted life year (QALY), comparing the lifestyle and metformin interventions to placebo (Herman WH, 2005)[16]. The cost per QALY for the ILS intervention was approximately $ 1,100 compared to $ 31,300 for the metformin intervention; this led investigators to conclude that compared to placebo the ILS intervention was not only the most effective treatment for diabetes prevention, but also the most cost-efficient. However, another analysis concluded that such programs are too expensive for widespread implementation and suggested that it may be preferable to delay intervention until diabetes diagnosed (Eddy DM, 2005)[11]; much of the discrepancy between these analysis derives from varying assumptions about rates of progression to diabetes and its complications and differences in analytic approach. However, cost-benefit analysis have been reported from other diabetes prevention trials with generally favourable results.

Curing diabetes?

There is increasing evidence that not only type 2 DM can be prevented but that can be cured; for decades it is known that gastric bypass surgery results in long term normalization of blood glucose but most of these studies have been on people with BMI > 35 (Buchwald H, 2009;122(3))[2]. This has now been shown even with people who have only class 1 obesity, BMI of 30-35, with 88% of 66 people with diabetes at baseline remaining diabetes free after 6 years of follow up (Cohen RV, 2012;35(7))[4]. The risk of diabetes in the surgical group was reduced by 86% at 2 years and 75% at 10 years of follow up (L, 2004)[22]. With refinement of minimally invasive/ laparoscopic surgery, the mortality rates with bariatric surgery has come down to 0.1-0.5% with major complication at the rate of 2-6% and minor complication at the rate of 10-15%, similar to that of cholecystectomy. So ADA strongly recommends bariatric surgery for patients with BMI > 35. Bariatric surgery has also been reported to induce remission of existing diabetes. Post-operative follow up for 1-5 years has shown sustained diabetic remission in 30-60% of the patients. Data suggest an erosion of cure of diabetes over time with 35-50% or more patients who initially achieved remission eventually experience recurrence; however, median disease-free

period in patients undergoing Roux en Y gastric bypass is 8.3 years. With or without diabetes relapse, patients who undergo bariatric surgery maintain substantial improvement of glycemic control from baseline over 5-15 years of follow up period (obesity management for treatment of type 2 diabetes, 2017)[25].

Now evidence appearing that similar results can be obtained with very low calorie diets; the counterpoint study has shown that in 10 of 11 people with DM a 600 kcal/day diet for 8 weeks resulted in normalization of glucose level. After 12 weeks of normal diet, glucose tolerance was normal in four, IGT in three, and diabetic but improved control in three. Both bariatric surgery and very low calorie diets produce rapid substantial weight loss with dramatic reduction of fat stores in the pancreas and liver. The counterpoint study not only demonstrated that very low calorie diets can produce weight losses similar to those of bariatric surgery, but offered an explanation of the anti-diabetic effect: reduction of triacylglycerol in liver improves hepatic insulin sensitivity and reduction of triacylglycerol in pancreas allows restoration of beta cell function. The upshot of these and similar studies is that if a patient is prepared to lose 15-20% of their body weight and keep it off, there is a very good chance of their diabetes being cured and this seems to be related to the degree of weight loss rather than the duration of their diabetes. Health motivated subset of population can reverse their diabetes completely and maintain a long-term normoglycemia. Taylor suggested that at the time of diagnosis health motivated people should be advised of this (R, 2012)[26].

Conclusion

Recent clinical trials have convincingly shown that lifestyle modification is the most effective tool in the prevention or delay of type 2 DM. For overweight or obese, a modest weight loss goal of 5-10% can substantially reduce risk of diabetes. Moderate intensity physical activity such as brisk walking for at least 150 minutes/week also plays an important role in reducing diabetes risk, even in the absence of weight loss. For patients who are unable to achieve these lifestyle goals or those who progress despite exercising and losing weight, metformin has also been proven effective, especially in younger obese patients. Acarbose, TZDs and GLP1 analogues are also promising; however, none of these medications are as robust in diabetes prevention as the lifestyle intervention strategies, and cost-effective analysis suggest that pharmacotherapy may have greater financial costs. Perhaps, the most pressing clinical question remaining is whether these prevention strategies will reduce the vascular complications of diabetes that are the cause of greatest financial burden and personal suffering in patients with DM. The preventive aspect in type 1 DM is currently under clinical trial and with better understanding of the disease pathology new immunomodulatory therapy to protect beta cell function has been tried. Whenever indicated, bariatric surgery should be performed so as to obtain long-term remission of diabetes; even if erosion of remission occurs there is always a substantial improvement of glycemic control post-operation compared to a baseline of 5-15 years of follow-up.

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"Educating the mind without educating the heart is no education at all."
— Aristotle