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Treatment options to prevent diabetes in subjects with prediabetes: Efficacy, cost effectiveness and future outlook

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Type 2 diabetes is a growing problem in industrialized countries, costing an estimated $245 billion for the United States (US) [1] and the annual global cost is estimated by the World Health Organization to be $825 billion [2]. These costs are estimated to continue growing over time. 9.3% of Americans (29.1 million) have diabetes and this number rises by approximately 1.4 million new cases each year [3]. Although there are many contributing factors to the development of diabetes, prediabetes is a condition of insulin resistance which converts to diabetes at a rate of 5–10% per year [3], making it a potential target for intervention in order to prevent the progression to diabetes.

Recently published evidence suggests that glucagon-like peptide 1 (GLP-1) analogues may be a promising medications to prevent the progression from prediabetes to diabetes and/ or to promote regression to normoglycemia. Most recently, in a study of 2254 individuals with prediabetes, treatment with 3.0 mg of liraglutide for three years resulted, in addition to weight loss, in a placebo-subtracted conversion from prediabetes to normoglycemia in 30% of subjects that reflects a 66% return of prediabetes to normoglycemia in the liraglutide group versus 36% conversion in the placebo group [4]. Additionally, 3% of patients in the liraglutide group developed diabetes as compared to 11% in the placebo group [4] i.e. a placebo-subtracted non-progression to diabetes in 8%. These results should be contrasted carefully with past findings for medications and other interventions, e.g. intensive lifestyle modification.

The broader question not only in the diabetes field, but in public health in general, given the increasing prevalence of obesity and diabetes, continues to be how could one either prevent progression to diabetes or even resolve prediabetes to normoglycemia in a cost-effective manner. The currently recommended first-line treatments for prediabetes are lifestyle modifications and metformin. Nearly 20 years ago, the Diabetes Prevention Program (DPP) in the US enrolled 3234 participants into three groups: placebo, metformin, and intensive lifestyle modification and observed rates of conversion to diabetes over the course of four years [5]. Intensive lifestyle modification showed about a 15% placebo-subtracted difference

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Author Contributions

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Conflict of Interest

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in the incidence of diabetes at 3 years and about 17% at 4 years [5], which was demonstrated to be approximately a 10% placebo-subtracted reduction in diabetes incidence in the 10-year continuation study [6]. Similar results were confirmed by the Finnish DPP study, which examined 522 individuals assigned to placebo or intensive lifestyle modification for four years, finding a placebo-subtracted 3% reduction in the development of diabetes (3% in intervention versus 6% in placebo) [7]. Metformin is a relatively inexpensive compound which acts as an insulin sensitizer and suppresses hepatic gluconeogenesis, and thus, is currently recommended for the treatment of diabetes [8–11]. A smaller study found that after a year of metformin, 84.9% of participants became normoglycemic as compared to 51.4% of participants who were given placebo i.e. a difference of 33.5% [12]. In the US DPP, participants treated for 3 years in the metformin group showed a placebo-subtracted 7% reduction in the incidence of diabetes and about 10% at 4 years [5]. At the ten year follow-up, the placebo-subtracted risk for the development of diabetes in the metformin group was approximately 7% [6]. In summary, these studies demonstrate efficacy of intensive lifestyle modification and, to a lesser extent, metformin on reducing the development of diabetes from prediabetes.

Older classes of diabetes medications have also shown variable efficacy in preventing the development of diabetes. Thiazolidinediones, which act on peroxisome proliferator-activated receptors, are approved for the treatment of diabetes [13–16]. In a study of 5269 participants over the course of three years, rosiglitazone demonstrated a conversion of 50.5% of prediabetes to normoglycemia and of 10.6% of prediabetes to diabetes as compared to the placebo, which demonstrated a 30.3% progression to normoglycemia and 25% conversion to diabetes respectively [17], effectively a placebo-subtracted 14.4% reduction in development of diabetes and a 20.2% increase in the conversion to normoglycemia. Similarly, a study of 602 patients for three years with pioglitazone showed a 48% conversion of prediabetes to normoglycemia and 2.1% from prediabetes to diabetes versus 28% and 7.6% on placebo [18], suggesting a placebo-subtracted 20% increase in the return to normoglycemia and a 5.5% reduction in the risk of developing diabetes. In the shorter-term, troglitazone was used in the DPP for 0.9 years average (0.5–1.5 years) but was discontinued from the study due to liver concerns [19]. At that time, of the patients taking troglitazone (n = 585), 2.5% versus 4.1% for lifestyle modification and 9.5% for placebo developed diabetes [19], or a placebo-subtracted 7% reduction in the risk of developing diabetes. Aside from the effects of troglitazone, thiazolidinediones display somewhat modest effects compared to lifestyle modification and metformin. Acarbose, an alpha-glucosidase enzyme inhibitor, has been shown repeatedly to reduce the conversion of prediabetes to diabetes and to increase the number of individuals with prediabetes to normoglycemia (for a recent review, see [20]). For instance, in the large STOP-NIDDM trial, 1529 patients with impaired glucose tolerance received placebo or acarbose for four years, demonstrating an additional decrease in the risk for cardiovascular disease [21]. Meglitinides, which bind to potassium channels on pancreatic beta cells, are also a promising class of medications for the treatment of prediabetes [22]. In a small study of thirteen patients, nateglinide showed a single-dose improvement in glycemic response [23]. In a large trial with 9306 patients, nateglinide did not reduce the incidence of diabetes (36% versus 34% for placebo), suggesting it would not be very effective at reducing the risk of diabetes [24]. Mitiglinide and repaglinide have not

yet been studied in humans with prediabetes. Dipeptidyl peptidase-4 inhibitors are another promising class of medications [25–29], but these have mostly been studied in rodents [30–33]. A five-year study is currently planned for sitagliptin to study the effects on prediabetes in humans [34]. These will need to be expanded and examined carefully for their efficacy in human trials.

Newer classes of medications are currently being researched and may provide additional efficacy. The newest class of medications, which treat both type 2 diabetes and obesity, is the GLP-1 analogues. Increasing evidence suggests that these medications are efficacious not only at reducing weight, but also at improving the comorbidities of obesity, including cardiovascular disease, non-alcoholic steatohepatitis [35,36] and overall mortality [37–39]. Similar results to the most recent study, above, with liraglutide were demonstrated by this study group in the shorter-term. In the first 0.38 year study, 3.0 mg liraglutide converted 84% of patients with prediabetes to normoglycemia as compared to 3% in the placebo group [40], or a placebo-subtracted 81% increased return to normoglycemia. In the two-year extension study of 564 patients, 2.4/3.0 mg liraglutide decreased the prevalence of prediabetes by 52% [41]. 69.2% of patients with prediabetes became normoglycemic after 1.08 years of 3.0 mg liraglutide became normoglycemic as compared to 32.7% on placebo [42], effectively a placebo-subtracted 36.5% increase in the return to normoglycemia. Treatment with exenatide, another GLP-1 analogue, for 0.46 years demonstrated a 77% conversion of prediabetes to normoglycemia versus 56% on placebo [43], suggesting a placebo-subtracted 21% increase in the conversion to normoglycemia. In a small study (n = 25/group), dapagliflozin/exenatide showed approximately a 54% return of prediabetes to normoglycemia while there was a 20% increase in the placebo group (due to drop out/no effective number change of 17 having prediabetes at both timepoints) over 0.46 years [44]. Other GLP-1 analogues, such as lixisenatide, albiglutide, and dulaglutide, have not yet been studied in terms of their impacts on prediabetes, but we could expect to see similar results. Additionally, aside from the study mentioned above, no other gliflozins have been studied in humans for their efficacy on prediabetes.

In terms of other anti-obesity medications, lorcaserin, a serotonin 2c receptor agonist, shows a modest decrease in progression from prediabetes to diabetes in the one-year BLOOM and BLOSSOM studies, with 3.2% of patients on lorcaserin versus 5.0% of patients on placebo developing diabetes [45], or a placebo-subtracted 1.8% reduction in risk. Furthermore, 40% of patients with prediabetes at baseline on lorcaserin became normoglycemic versus 29.5% on placebo [45], or a placebo-subtracted 10.5% increase in the return to normoglycemia. Phentermine/topiramate combined therapy for 2.08 years had an annual incidence for the development of diabetes from prediabetes of 1.3 for the 15/92 dose, 1.8 for the 7.5/46 dose, versus 6.1 for placebo [46]. The magnitude of these differences was related to amount of weight loss [46], suggesting that the benefits of these combined therapies on prediabetes are related to successful weight loss. In a study of 3304 patients, orlistat, a lipase inhibitor, when combined with lifestyle changes had a 6.2% incidence of progression to diabetes as compared to 9.0% in the group given placebo plus lifestyle changes or a placebo-subtracted 2.8% decrease in diabetes risk [47]. No studies have examined the effects of bupropion/naltrexone or phentermine alone on prediabetes. However, the impacts of these medications

on prediabetes may be more tied to weight loss than any direct effects on diabetes prevention.

Thus far, GLP-1 analogues appear to have the greatest efficacy in terms of medications currently tested to treat prediabetes. For approximately every three patients treated, one will return to normoglycemia from treatment alone [4]. However, this is slightly less than the effects of intensive lifestyle modification demonstrated by the DPP studies [5,7], which have the added benefits of improving the overall cardiometabolic profile and decreasing the use of other medications [5]. Importantly, in these but also in future studies we need to consider the differences in the risk of developing diabetes for the placebo groups (e.g. development of diabetes for 28% on the placebo in the DPP vs. 11% in the most recent study with liraglutide at 3 years). This may be due to differences used for the definitions of “prediabetes”, which can theoretically be defined according to impaired fasting glucose, impaired post-load glucose levels, and/or glycosylated hemoglobin levels. While post-load glucose levels may give an earlier marker for diabetes risk and impaired fasting glucose a later marker, glycosylated hemoglobin is the most integrated measure which takes into account general glucose control, and we would recommend the use of this definition standardized across studies. Furthermore, the placebo control should ideally be standardized in future studies. Although participants in most, if not all, studies received “standard” lifestyle intervention, the standard intervention changes over time, differs between the clinical and research setting (e.g. DPP or LookAhead studies), and is not always well defined/clear and may impose differences on the placebo group development of diabetes.

GLP-1 analogues are currently expensive and lifestyle modifications remain the most cost-efficient mechanism. This has been suggested by similar articles in the past as intensive lifestyle interventions remain the most significant way to prevent progression to diabetes in patients with prediabetes or metabolic syndrome [48]. As GLP-1 analogues become less expensive, and/or when potent oral GLP-1 analogues get developed and approved, these recommendations may change. Additionally, longer-term studies are needed to see whether the efficacy of GLP-1 analogues may be more potent at 10 years than lifestyle modification, whose effects become less potent. Differences in the time frame under consideration may also change the cost effectiveness balance. Newer delivery systems for GLP-1 analogues may also enhance adherence, and thus these effects, as they increase compliance with oral or implanted device deliveries [49]. These considerations should be weighed carefully when considering treatment options for prediabetes in the clinic. The future will offer exciting new developments in this scientific area.

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