Impact of Lifestyle Intervention and Metformin on Health-Related Quality of Life: the Diabetes Prevention Program Randomized Trial

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BACKGROUND: Adults at high risk for diabetes may have reduced health-related quality of life (HRQoL).

OBJECTIVE: To assess changes in HRQoL after interventions aimed at diabetes risk reduction.

DESIGN, SETTING, AND PARTICIPANTS: A randomized clinical trial, the Diabetes Prevention Program, was conducted in 27 centers in the United States, in 3,234 non-diabetic persons with elevated fasting and post-load plasma glucose, mean age 51 years, mean BMI 34 Kg/m²; 68 % women, and 45 % members of minority groups.

INTERVENTIONS: Intensive lifestyle (ILS) program with the goals of at least 7 % weight loss and 150 min of physical activity per week, metformin (MET) 850 mg twice daily, or placebo (PLB).

MEASUREMENTS: HRQoL using the 36-Item Short-Form (SF-36) health survey to evaluate health utility index (SF-6D), physical component summaries (PCS) and mental component summaries (MCS). A minimally important difference (MID) was met when the mean of HRQoL scores between groups differed by at least 3 %.

RESULTS: After a mean follow-up of 3.2 years, there were significant improvements in the SF-6D (+0.008, $p=0.04$) and PCS (+1.57, $p<0.0001$) scores in ILS but not in MET participants (+0.002 and +0.15, respectively, $p=0.6$) compared to the PLB group. ILS participants showed improvements in general health (+3.2, $p<0.001$), physical function (+3.6, $p<0.001$), bodily pain (+1.9, $p=0.01$), and vitality (+2.1, $p=0.01$) domain scores. Treatment effects remained significant after adjusting sequentially for baseline demographic factors, and for medical and psychological comorbidities. Increased physical activity and weight reduction mediated

these ILS treatment effects. Participants who experienced weight gain had significant worsening on the same HRQoL specific domains when compared to those that had treatment-related (ILS or MET) weight loss. No benefits with ILS or MET were observed in the MCS score.

CONCLUSION: Overweight/obese adults at high risk for diabetes show small improvement in most physical HRQoL and vitality scores through the weight loss and increased physical activity achieved with an ILS intervention.

KEY WORDS: quality of life; lifestyle; metformin; diabetes risk; weight loss.

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INTRODUCTION

Healthy People 2020 outlines numerous public health goals, as set forth by the US Department of Health and Human Services, including the reduction of diabetes and the economic burden of the disease, and improvement in the quality of life for all persons who are at risk for or who have diabetes.¹

Diabetes has not only been associated with increased morbidity and mortality, but also with a poor health-related quality of life (HRQoL).^{2,3} Studies have also shown that people with diabetes-related complications have a reduced HRQoL compared to those without complications.^{4–6}

There is limited information available on changes in HRQoL associated with prediabetes or the development of type 2 diabetes (T2D). A cross-sectional study examined the association of HRQoL with glucose tolerance status in an Australian population.⁷ While those with previously diagnosed diabetes were at a significantly greater risk of being in the lowest quartile of each domain of the 36-Item

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Trial registration DPP is registered in www.clinicaltrials.gov (NCT00004992).

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Short-Form (SF-36) scale, there was also evidence of reduced HRQoL on some SF-36 domains among those with newly diagnosed diabetes, and in those with impaired glucose tolerance (IGT). More recently, a study in Canadian individuals with prediabetes showed that those who were more physically active had better physical and mental HRQoL than those who were inactive.⁸

The Diabetes Prevention Program (DPP) is a large, multicenter, randomized trial that demonstrated the benefits of an intensive lifestyle intervention (ILS) and of pharmacotherapy with metformin (MET) on the reduction of T2D risk in overweight or obese adults with IGT.⁹ Previous analyses in DPP participants using the Self-Administered Quality of Well-Being scale showed that participants randomized to ILS or MET intervention groups accrued 0.07 and 0.02 more quality-adjusted life-years (QALYs), respectively, over 3 years, than participants randomized to the placebo (PLB) intervention group.¹⁰ There are limited prospective data on the impact that changes in known predictors of diabetes and glucose tolerance status have in each physical and mental HRQoL domain. Therefore, we tested the hypotheses that DPP interventions lead to better HRQoL in subjects at high risk for T2D, and that those randomized to intensive lifestyle will have a greater improvement in HRQoL than those in the metformin group.

METHODS

Participants

The eligibility criteria, design, and methods of the DPP have been reported elsewhere.^{9,11} In brief, selection criteria included: age ≥ 25 years, body mass index ≥ 24 kg/m² (≥ 22 kg/m² in Asian Americans), fasting plasma glucose levels between 95 and 125 mg/dl, and IGT (2-hour post-load glucose of 140–199 mg/dl). People were excluded if they were taking medications known to alter glucose tolerance, or if they had illnesses that could seriously reduce their life expectancy or their ability to participate in the trial.

The current report and analyses includes 3,234 participants seen at baseline, who were randomly assigned to one of the three treatment arms investigated. Written informed consent was obtained from all participants before screening, consistent with the Declaration of Helsinki and the guidelines of each center's institutional review board.

DPP Study Interventions

The ILS intervention was a goal-based diet and physical activity intervention designed to achieve and maintain modest weight reduction.¹² Goals were to achieve and maintain at least 150 min per week of moderate physical

activity and to reduce weight by 7 % from baseline. Participants in both MET and PLB arms received standard lifestyle recommendations in the form of written information, and an annual 20–30-min individual session that emphasized the importance of a low-fat diet and regular physical activity to achieve modest weight reduction. Treatment with MET was increased over 1 month to a full dose of 850 mg taken twice daily. The PLB group received a matching placebo tablet.

Procedures

Standardized interviewer-administered questionnaires were used to obtain demographic and clinical data. Physical activity was measured by the Modifiable Activity Questionnaire.^{13,14} Blood pressure and anthropometrics were measured using standard techniques. All analytical measurements for glucose, insulin, and lipids were performed at the Central Biochemistry Laboratory (University of Washington, Seattle). Insulin secretion was estimated with the corrected insulin response (CIR).¹⁵ Insulin resistance (IR) was estimated using the insulin sensitivity index (ISI), reciprocal of the IR-homeostasis model assessment.¹⁶ Development of diabetes was determined by an annual oral glucose tolerance test and semiannual fasting plasma glucose (FPG) tests, and required confirmation by a second test, using the criteria of the American Diabetes Association and the World Health Organization.^{17,18}

Generic quality of life assessments were collected annually using the SF-36.¹⁹ Extensive psychometric data support the reliability and validity of the SF-36.²⁰ The SF-36 was administered from the start of the DPP and is available for 3,206 participants. The SF-36 consists of two composite scores: the physical component summary (PCS) and mental health component summary (MCS) scores. Higher scores on the two SF-36 component summaries indicate more favorable quality of life. The SF-36 is divided into eight domains, measuring two main components: physical (general health, physical functioning, role limitation–physical, and bodily pain) and mental (mental health, social functioning, role limitation–emotional, and vitality). Scores in the SF-36 domains could be between 0 (worst) and 100 (best). The health utility index SF-6D (scale 0.0 to 1.0, with 1.0 indicating "full health") is a preference-based health state classification developed from the SF-36.²¹ The six dimensions captured by the SF-6D are physical functioning, role limitations, social functioning, pain, mental health, and vitality.

A minimally important difference (MID), defined as the smallest score difference that the patient perceives as beneficial or deleterious,²² was met when the mean of HRQoL scores between groups differed by at least 3 %. This is equivalent to the mean change in the SF-6D that has

been cited in the literature, including reported change in general health in nine patient groups.²³ This value is also approximately equivalent to an estimate of the MID for the EuroQoL (EQ-5D),²⁴ and it was used in a population-based study that compared healthier individuals with older patients with T2D.²⁵ Others have proposed alternative definitions of MID as being 5 %.²⁶ Therefore, we will consider small HRQoL changes as those <3 %, modest those changes between 3 % and <5 %, moderate between 5 % and <10 %, and large for those achieving changes 10 % and above.

Statistical Analysis

This analysis is based on data collected from the start of DPP (June 1996) through July 31, 2001, after which the participants were unmasked to the study results and treatment assignment. To test our hypothesis, we performed the analysis following the intention-to-treat principle in the three main DPP treatment groups. SAS was used for all analyses (version 8.2; SAS Institute, Cary, NC).

Mixed-effects models with the assumption of normally distributed errors were used to assess mean differences over time in the scores for the SF-6D, PCS, MCS, and eight SF-36 domains, and were adjusted for their baseline values, participant demographic characteristics, baseline weight and physical activity, and the presence of medical (hypertension, dyslipidemia, myocardial infarction, stroke) or psychological (depression, anxiety) co-morbidities at baseline. With controls for these baseline measures, additional models were obtained to assess the associations of HRQoL with factors that might account for the effect of treatment on HRQoL, including time-dependent changes in physical activity level, weight, fasting and 2-hour plasma glucose, IR, and beta cell function. Analyses were conducted to evaluate whether treatment group differences in HRQoL remain significant after accounting for the effect of converting to diabetes. In addition, comparisons in HRQoL scores within and across DPP treatment groups were performed among those who reverted to NGT, or progressed to diabetes.

RESULTS

Quality of Life at Baseline

Baseline demographic and clinical characteristics of DPP participants are shown in Table A in the appendix (available on line). The overall HRQoL scores, as well as the eight SF-36 domains, were similar across treatment groups at the time of randomization. Most scores are similar or slightly better than those reported in other populations with prediabetes.⁷

Quality of Life Change over Follow-up in Each Treatment Group

During DPP follow-up, HRQoL summary scores worsened in all three treatment arms, but the decline for SF-6D ($p < 0.05$) and PCS ($p < 0.01$) was slower in ILS participants compared to the changes in those in PLB or MET groups; however, none reached the MID of 3 % (Table 1). During the first year of intervention, physical function, general health (Fig. 1a, b), and vitality scores (Figure A-2 available on line) improved significantly in ILS participants, reaching MID when compared to those treated with PLB or MET. Subsequently, all scores decreased in the follow-up years but remained better in ILS than in PLB for the following specific domains: physical function, body pain, general health, and vitality (with the first two reaching MID). After adjusting for demographic factors, baseline weight and physical activity, and medical and psychiatric comorbidities, these small HRQoL benefits with ILS intervention remained significant when compared with the PLB group (Table 2, Model 1).

Mediating Factors for the Effects of Interventions on Quality of Life

We tested a series of factors that could mediate the HRQoL benefits of ILS intervention. A series of explanatory factors were added sequentially in regression models starting with those related to behavioral goals (i.e., changes in physical activity in model 2 and weight loss in model 3) and following with metabolic factors related to diabetes development (i.e., CIR and ISI at each time point in model 4). As shown in Table 2, the effect of ILS on summary and specific domain scores remained after adjusting for changes in physical activity; however, the adjustment for weight loss partially (physical function and general health) or fully (SF-6D, PCS, body pain, and vitality) accounted for these

Table 1. Changes in Health-Related Quality of Life over 3.2 years (Study Duration) in Lifestyle and Metformin Participants Compared to Placebo

Measurement	Lifestyle (n=1048)	Metformin (n=1043)
Short Form-6D	0.0084(0.0041)†	0.0019(0.0041)
Physical component summary	1.57 (0.30)‡	0.15(0.30)
Mental component summary	-0.29(0.32)	0.22(0.32)
Physical function	3.58(0.71)‡*	0.13(0.71)
Role physical	1.86(0.99)	1.32(0.99)
Body pain	1.93(0.78)‡	0.50(0.78)
General health	3.23(0.66)‡*	0.06(0.66)
Vitality	2.05(0.77)‡	0.09(0.76)
Social functioning	0.97(0.66)	0.81(0.66)
Role emotional	0.20(0.95)	0.78(0.95)
Mental health	-0.50(0.57)	0.32(0.57)

Data presented as mean (SD); * reached minimally important difference of 3 %; † $p < 0.05$; ‡ $p < 0.01$

Figure 1. Changes in physical function (1a) and general health (1b) scores across treatment groups. ILS, intensive lifestyle; PLA, Placebo; MET, Metformin. Data available in study participants decreased overtime from baseline (n=3206) to year 1 (n=3143), year 2 (n=2988), year 3 (n=2941), and year 4 (n=1859).

HRQoL benefits. No additional changes were observed after adjustments were made for CRI or ISI.

In an additional analysis, we evaluated changes in specific SF-36 domains across the following categories of weight change in ILS participants: weight gain (n=362), minimal weight loss (up to 3.6 %, n=196), moderate weight loss (between 3.7 and 7 %, n=201), and major weight loss (greater than 7 %, n=347). Those who experienced weight gain had significant worsening on specific HRQoL scores when compared to those that had weight loss, with the following differences reaching MID (Fig. 2a-d): more than 5 points in physical function (vs. those with moderate or major weight loss); more than 4 points in general health and body pain (vs. those with moderate or major weight loss); and more than 8 points in vitality (vs. those with major weight loss). A similar approach was used across categories of weight change in MET participants: weight gain (n=396), minimal weight loss (n=282), moderate weight loss (n=157), and major weight loss (n=183) (Fig. 3a-d). MET participants who had weight gain reported a similar pattern of worsening of HRQoL scores when compared to those who achieved major weight loss: approximately 5-point

difference on physical function, general health and body pain, but only 3-point difference in vitality.

Quality of Life and Progression to Diabetes

We further studied the patterns of HRQoL when participants experienced change in glucose-tolerance status. Progression to diabetes was associated with worsening in the PCS (−1.1, $p<0.05$), physical function (−2.6, $p<0.05$), and general health (−2.6, $p<0.01$) scores.

DISCUSSION

Subjects at high risk for T2D experienced a significant, but small, improvement in the overall and specific HRQoL scores through increased physical activity and weight loss achieved with an ILS intervention. In general, HRQoL scores of DPP participants decreased over the follow-up period, but were better in the ILS intervention. The findings of this study support the hypothesis that participation in an ILS behavior modification intervention for weight management is associated with relative improvement in HRQoL, as measured by the PCS, physical function, general health, body pain, and vitality scores of the SF-36. No clear overall benefits on HRQoL were observed in participants receiving MET intervention, except in those that experienced major (>7 %) weight loss. These results are aligned with one of the Healthy People 2020 goals: to reduce diabetes burden and improve HRQoL in those with or at high risk for diabetes.¹

The DPP demonstrated considerable differences in lifestyle behavior change and weight reduction in ILS participants, compared with those in the PLA-control group. Accordingly, we found a modest but significant improvement in the SF-6D and PCS scores with ILS, when compared with PLA after an average of 3.2 years of follow-up. In a previous analysis, we have shown small

Table 2. Effect of Lifestyle on Health Related Quality of Life after Adjustments for Covariates

Score	Model 1	Model 2	Model 3	Model 4
Short form-6D	0.009(0.14) [‡]	0.81(0.11) [†]	0.10(0.00)	0.07(0.00)
Physical component summary	1.39 (0.57) [‡]	1.31 (0.49) [‡]	0.41 (0.06)	0.43 (0.06)
Physical function	3.37(0.60) [‡]	3.22(0.53) [‡]	1.25(0.07) [†]	1.13(0.06) [¶]
Body pain	1.61(0.11) [‡]	1.48(0.09) [†]	0.06(0.00)	0.08(0.00)
General health	3.35(0.79) [‡]	3.21(0.69) [‡]	1.31(0.11) [‡]	1.45(0.16) [‡]
Vitality	2.44(0.31) [‡]	2.24(0.25) [‡]	−0.07(0.00)	0.15(0.01)

Data presented as the mean difference for the score ILS vs. placebo (adjusted R^2). [†] $p<0.05$; [‡] $p<0.01$; [¶] $p=0.05$; Model 1: age, sex, race/ethnicity, baseline weight and physical activities, medical and psychiatric comorbidities; Model 2: model 1+ changes in physical activity; Model 3: model 2+ weight loss; Model 4: model 3+ insulin secretion and insulin resistance

Figure 2. Changes in physical function (2a), general health (2b), body pain (2c), and vitality (2d) scores among lifestyle intervention participants over the DPP follow-up period and according to weight (Wt) change categories. * $P < 0.001$ for a comparison of the Wt. gain category with any of the Wt. loss categories.

improvements in HRQoL over the first year of the study, associated with weight loss.²⁷ DPP participants with a baseline BMI ≥ 35 kg/m² showed improvement in the PCS

and SF-6D scores over one year of ILS intervention.²⁷ Similarly, baseline BMI moderated the beneficial effect of the first year of lifestyle intervention on the PCS score in

Figure 3. Changes in physical function (3a), general health (3b), body pain (3c), and vitality (3d) scores among metformin intervention participants over the DPP follow-up period and according to weight (Wt) change categories. * $P < 0.01$ for a comparison between the Wt. gain category and the major Wt. loss category.

patients with T2D in the Look AHEAD trial.²⁸ Furthermore, we found that compared to those who experienced weight gain, HRQoL scores in three physical domains (physical function, general health, and body pain) and in one mental domain (vitality) reached MID in those who achieved moderate (3.7–7 %) or major (>7 %) weight loss. A previous report from the Women Health Initiative (WHI) has also shown that heavier weight negatively affects physical HRQoL (bodily pain, physical functioning, general health, and role limitations due to physical health), but not mental health.²⁹ In fact, weight-relevant physical health factors (such as diabetes and osteoarthritis) have a greater impact on this weight-HRQoL association than do emotional/ psychological factors. Similarly, a report from an urban population of Belgrade showed that increased BMI has much greater impact on physical than on mental health HRQoL.³⁰

To our knowledge, this study is one of the first to evaluate the potential mediation of treatment effects of lifestyle intervention or MET on HRQoL in those at high risk for T2D. We found that weight loss in the ILS group was the most important factor associated with these HRQoL benefits, in models that also accounted for the effects of changes in physical activity, insulin secretion, and insulin resistance. Similar analyses in the Look AHEAD trial showed that the improvement in the PCS score, associated with lifestyle intervention in subjects with T2D, was only partially mediated by the improvements in body weight and physical fitness and by the reduction in physical symptoms.²⁸ Other factors related to the ILS intervention (i.e., improved metabolic variables, improved functional abilities, counseling and group support, changes in the social and/or family environment) may account for the HRQoL benefits associated with weight management in overweight and obese adults at high risk for T2D. A similar pattern of the effect of weight changes and HRQoL was observed in MET participants. A previous study in women with polycystic ovary syndrome (PCOS) reported improvements in vitality, social function, emotional role and mental health, which were correlated with reduction in body weight and more pronounced in those who achieved normalization in menstrual disturbances.³¹ Future studies may provide additional insights on mediators of the ILS- and MET-specific benefits on improving physical function and reducing pain and fatigue (i.e., improving vitality).

We also found that changes in body weight among ILS participants were associated with clinically significant improvements (i.e., reaching MID) in two physical SF-36 domains (physical function and general health), and with statistically significant but smaller improvements in two other domains (bodily pain and vitality). These findings suggest that weight loss in overweight or obese adults with IGT is likely to result in small to modest direct

benefits on HRQoL. A recent systematic review found mixed effects of weight loss interventions on various generic and obesity-specific measures of HRQoL.³² However, this review was not designed to distinguish between changes in HRQoL mediated by weight loss and those resulting from other intervention effects unrelated to weight change.

Overweight and obesity in middle age are associated with lower HRQoL in older age, as shown in a prospective cohort study that followed up on men and women free of diabetes or myocardial infarction at baseline, for a mean of 26 years.³³ A recent analysis in the Longitudinal Australian Diabetes, Obesity and Lifestyle (AusDiab) study has shown that obesity is associated with deterioration in HRQoL over 5 years for seven of the eight SF-36 domains in women (excluding mental health), and six out of eight SF-36 domains in men (not on role-emotional and mental health).³⁴ In our study, we found that participants in both intervention groups (slightly more pronounced with ILS than with MET) who experienced weight gain had significant worsening on physical function, general health, body pain, and vitality, compared to those who achieved major weight loss. It is possible that ILS participants who gained weight, despite the specific goals for increased physical activity and weight loss set up for them, may have experienced a more negative reaction (i.e. worsening in HRQoL) than those in the MET group who were not asked to adopt new behaviors, except taking medication. However, patients taking oral antihyperglycemic agents who experience weight gain may also lower their HRQoL, as shown in a study using an internet-based survey and the EQ-5D.³⁵

Our study has some limitations worth mentioning. First, our population was a highly selected group of overweight and obese adults at high risk for diabetes. Therefore, these findings should not be generalized to other (less highly selected) populations. However, baseline SF-6D utility score was 0.801, which is consistent with a previously reported score in a general population of adults aged 45–54.³⁶ Second, HRQoL measurements used were not disease-specific (i.e., not for subjects at risk for diabetes or with newly diagnosed diabetes). It is also possible that our results would have differed if we had used an HRQoL instrument other than the SF-36. The relative emphasis of various specific domains differs across instruments. Third, the MID in SF-6D score and specific SF-36 physical and mental domains were based on comparison to other global health indicators, and not related to health outcomes or cost-effectiveness analysis. Fourth, although we used data from a large randomized clinical trial, it is possible that unmeasured confounders could have impacted our results. Finally, it is possible that the HRQoL benefits resulted from the so-called "regression to the mean," where individuals with worse HRQoL at baseline get the greatest benefits from the weight management intervention, as previously reported.^{28,37} In our study, we

adjusted for baseline values of each HRQoL measurement, in addition to the participant demographic characteristics, baseline weight and physical activity, and the presence of medical and psychological co-morbidities.

In summary, our study demonstrates that lifestyle modification characterized by intentional weight loss and increased physical activity has an independent but small to modest association with better HRQoL in overweight or obese participants at high risk for T2D. Future work is needed to determine whether these changes in HRQoL persist over much longer periods, as well as to replicate our findings in other study populations and to use different measures of HRQoL. Studies should explore whether lifestyle intervention may lead to greater and sustained HRQoL benefits in certain high-risk groups, such as those with greater obesity and the elderly.

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Conflict of Interest: The authors declare that they do not have a conflict of interest related to this manuscript.

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