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Assessing Diabetes Integrated Patient Education And Glucose Control And Differential Diabetes Treatment Response By Gender In Jordan

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ABSTRACT

Background*:** Between 1994 and 2004 the prevalence of diabetes in Jordan increased from 13.0% to 17.1%. Among individuals with diabetes in Jordan, 54% had unsatisfactory blood glucose control. In response to the diabetes epidemic in Jordan, the National Center for Diabetes Endocrinology and Genetics (NCDEG) was founded. NCDEG's primary objective is to improve diabetes treatment in Jordan, and does so by offering treatment facilities specific for diabetic patient needs. In 2008 NCDEG began implementation of an integrated patient education strategy (IPE). Certified diabetes educators joined NCDEG and were provided space within each diabetes clinic within the center for individual patient counseling. The program was fully implemented by 2009. However, NCDEG did not have a feedback mechanism to assess the effectiveness of the program. ***Methods: To assess the effectiveness of the integrated education program and assess whether response differed between gender, we sampled patients attending NCDEG prior IPE implementation (01Jan2006 – 31Dec2007) (P1) and patients enrolled at NCDEG after implementation (01Jan2010 – 31Dec2011) (P2). Patients eligible for study were diabetic, were new patients within each time period, had at least three visits to the center within each time period, and could not be pregnant during the periods of study. To collect data, an iPad application was developed to extract data from charts on the first 3 visits to the center. A team of physicians at NCDEG was assembled to collect the data. Chi-square tests and F-Tests were used to compare categorical variables and t-tests were used to compare continuous variables. A linear model was created with period being the primary predictor variable. ***Results*:** Univariate analyses showed that change in HbA1c did not differ between P1 (-1.54 SD=1.81) and P2 (-1.52 SD=1.85) (p=0.894). Univariate analysis showed that change in HbA1c differed between females (-1.30 SD=1.80) and males (-1.77 SD=1.84) (p<0.001). Univariate analysis showed the change in HbA1c was different between females and males within each period: female P1 (-1.26 SD=1.77) versus male P1 (-1.80 SD=1.81) (p=0.007) and female P2 (-1.32 SD=1.82) versus male P2 (-1.74 SD=1.87) (p=0.019). When controlling for Gender, Age, Duration of Diabetes, HbA1c at V1, Time between V2 and V3, BMI between V1 and V3 Chronic Kidney Disease status, Hyperthyroidism status, Sulfonylurea prescription, MIX Insulin prescription and NPH prescription the average change in HbA1c in P2 was -0.177 (SD=0.012) higher than in P1 and the average change of male HbA1c decrease was -0.222 (SD=0.088) higher than for females. ***Conclusions*:** Glucose control improved after implementation of diabetes education intervention and this improvement was more pronounced among male than female patients.

INTRODUCTION

The Disease

Type 2 Diabetes mellitus (T2DM) is a metabolic disorder characterized by chronic hyperglycemia (high blood glucose level) attributed to insulin resistance and eventual decreases in insulin production levels (*1*). High blood glucose levels are associated with dysfunction and damage of endothelial cells which form the thin layer of cells that line the interior surface of blood vessels (*2*). As a result of endothelial damage, through microvascular and macrovascular complications T2DM is associated with significant increases in morbidity and mortality (*3*). Major macrovascular complications include coronary artery disease (*4*), peripheral artery disease (*5*), and stroke(*6*). Major microvascular complications include retinopathy (*7*), which can lead to blindness (*8*), nephropathy (*9*), which can lead to renal failure (*10*), and/or neuropathy (*11*), which can lead to limb amputation (*12*), all of which contribute to significant morbidity and mortality (*13*). The lack of blood glucose control is the underlying reason for many of the complications associated with diabetes (*14*). If patients with diabetes achieve blood glucose control, endothelial cell damage will not be as severe, and the risk for developing diabetes complications is significantly reduced (*15*).

Glycemic Control

T2DM can be diagnosed through several tests including (glycosylated hemoglobin) HbA1c test, fasting plasma glucose (FPG) tests, as well as an oral glucose tolerance test (OGTT) (*16*, *17*). An HbA1c of ≥6.5%, a FPG ≥125 mg/dL, or an OGTT ≥200 mg/dL are indicative of diabetes (*17*). Of the three tests, HbA1c provides a measure of long-term blood glucose levels,

as it is representative of average blood glucose over 3 months (*18*). It also does not require that patients take preparative steps before the test, reducing patient burden (*19*). HbA1c tests are provided to all patients being treated at the National Center for Diabetes Endocrinology and Genetics (NCDEG) as they are cost-effective, easily administered, and do not require special preparation of the patient.

On A Global Scale

In 2000, it was estimated that by 2030, nearly 366 million people would have T2DM (*20*), however we approached that prevalence by 2011 beating projections by 19 years, and now it is predicted that by 2030 530 million people will be afflicted with diabetes (*21*). As of 2010, T2DM accounted for 4.6 million deaths in 2011 for those between the ages of 20-70, which represents 8.2% of the mortality in that age group (*22*). Diabetes has now become the most common non-communicable disease around the world (*23*).

In addition to contributing to morbidity and mortality, T2DM is associated with significant economic burdens that have increased pressure on already overextended healthcare systems, especially in developing countries with limited healthcare recourses (*13*). As of 2010, the global healthcare costs attributed to T2DM were 376 billion USD, and are projected to reach 490 billion USD by 2030 (*24*). That represents nearly 11% of total global healthcare costs.

A major contributor to the increasing prevalence of T2DM has been rapid urbanization of many developing countries that have experienced the greatest increases in incidence and prevalence of T2DM (*25-27*). Urbanization and economic development have contributed to more sedentary lifestyles as well as high calorie diets, that have contributed to increasing

prevalence of obesity, a major risk factor for diabetes (*28*). Furthermore, as T2DM has a late age of onset (*29*), as populations have aged, so has the prevalence of T2DM.

The diabetes epidemic in Jordan

Between 1994 and 2004 the age standardized prevalence of diabetes in Jordan rose from 13.0% to 17.1% (*30*). The most dramatic increases in prevalence occurred in the 50-59 years and older than 60 years age categories (*30*). As of 2004, nearly 54% of individuals with diabetes in Jordan had unsatisfactory glycemic control as indicated by an HbA1c greater than 7.5% as defined by the study (*30*). With these dramatic increases in diabetes, a National Strategy Committee on Diabetes, Obesity, and Dyslipidemia (NSCDOD) was initiated by the Jordanian government, and is headed by Former Minister of Health Kamel Ajlouni. With the goal of identifying the cause for the rapid increase in prevalence, the NSCDOD identified several factors associated with the increasing prevalence of T2DM including rapid urbanization contributing to sedentary lifestyle, coupled with Jordanian specific cultural practices. Once such practice included the excess consumption of the calorie rich native Jordanian dish, *Mansaf* that is composed of rice, lamb cooked with fermented dried yogurt, and garnished with fried pine nuts. Another cultural factor identified as contributing to the increasing prevalence of diabetes included the cultural emphasis of displaying generosity to guests as indicated by serving calorie rich foods. OZ was able to attend two NSCDOD meetings in which the rollout of a nationwide education program was discussed.

As a result of initiatives like the formation of the NSCDOD, the Jordanian government also moved to develop facilities and increase capacity and expertise for the treatment of diabetes. This resulted in the founding of The National Center for Diabetes, Endocrinology, and

Genetics (NCDEG), a center in Amman, Jordan that treats T2DM and T2DM related complications. NCDEG physicians treating T2DM follow the American Diabetes Association guidelines for diabetes treatment (*31*).

NCDEG Integrated Diabetes Patient Education Program

In 2008, after recognizing that patients were using their medications incorrectly, an integrated patient education program (IPEP) was implemented that provided patients with educational material on diabetes, individualized instruction from diabetes educators on use of treatment, and dietary and lifestyle advice. The program was fully implemented by 2010. The program's aim was to provide diabetes patients with a comprehensive understanding of how to properly manage their diabetes.

After interviewing the founding head of the IPEP as well as staff, and administrators that worked at the center before and after implementation of IPEP, it was noted that several important changes occurred as a result of IPEP included: 1) the establishment of a Diabetes Education Department as a sub-department of the Nursing Department, 2) the employment and assignment of certified diabetes educators (CDE) to each diabetes clinic, 3) the assignment of a room within each clinic specifically designated for patient counseling by CDEs. In addition to providing patients with educational material that included booklets prepared in Arabic, CDEs showed patients how to use their medication, advised them on when to take their medication, and provided patients the opportunity to purchase a subsidized glucose monitor for 10 Jordanian Dinars (14 USD) from the NCDEG's pharmacy. If patients purchased the glucose monitor, had one available, or planned to purchase one, the CDEs provided patients with a chart to be filled out by patients. The chart asked patients to take readings of their blood

glucose levels throughout the day for one week – asking patients to take a reading before and after every meal, before they sleep, and once they wake up. After the first week of readings, patients were asked to come back to the clinic and provide the completed chart to the CDEs. CDEs were empowered by the NCDEG administration to adjust diabetes medication dosages and time of diabetes medications administration based on their analysis of the chart. After the second meeting with the CDE, patients were asked to continue monitoring their blood glucose and fill out a subsequent chart that only required three daily measures. In subsequent visits with the CDEs, usually when patients came to the center for follow-up with a physician, patients were asked to provide their charts to the CDEs at which point CDEs would review the chart and ensure patients were using their medication properly and that their questions were answered. The most extensive meeting with the CDEs occurred at the first visit (right after first physician visit) and second visit (1 week after first physician visit), with briefer meetings afterwards during subsequent physician follow-up visits. As of 2012, NCDEG did not have a feedback mechanism in place to assess the success of IPEP.

To understand the effectiveness of IPEP and provide NCDEG with an assessment of the programs efficacy, we retrospectively studied HbA1c control in patients treated in NCDEG during 2006-07 and 2010-11, before and after implementation of the program.

OBJECTIVE

The primary objective of the study was to compare the diabetes treatment outcomes of diabetic patients in two time periods as assessed by change in HbA1c levels, before and after implementation of a health worker-led patient support program, in a public diabetes treatment center in Amman Jordan. We hypothesized that patients treated in IPEP would achieve greater

decreases in HbA1c compared to patients not treated in the program. Our secondary objective was to understand whether males and females responded differently to diabetes treatment offered at the NCDEG, and in what way did responses differ. Finally, we aimed to gain a snap shot of patient characteristics upon first being treated at the center, to better understand the characteristics of patients with diabetes being served by Jordan's NCDEG.

METHODS

Study Location

The NCDEG was established in Amman, the capital of Jordan, for comprehensive preventative and clinical services in the fields of diabetes, endocrinology and genetic disorders. NCDEG receives patients from every governorate of the country through both physician-referral and self-referral. The center is composed of 13 clinics, the three largest primarily treat diabetes. All the patients with diabetes seen by the center are treated in the diabetes clinics. Each diabetes clinic is composed of an endocrinologist, an endocrinologist fellow, a team of primary care physicians, a nursing staff, a nutritionist, and a laboratory technician. Patients are first assessed by a nurse who takes anthropometric measures and records all current medications. A patient then has their HbA1c measured, and is then seen by a primary care physician who records a full patient history, assesses the patient's status, and prescribes necessary medications. Either the head endocrinologist or the endocrinologist fellow approves the prescribed treatment after meeting with the patient and primary care doctor. After 2008, after meeting with a physician patients would be able to discuss their treatment and received advice and educational material from a CDE.

Study Design

We conducted a retrospective cohort records-based study within NCDEG, a public T2DM treatment center located in Amman, Jordan. T2DM treatment outcomes were compared between patients treated in Period 1 (P1) (01Jan2006 to 31Dec2007) and Period 2 (P2) (01Jan2010 to 31Dec2011) to assess whether the implementation of an IPEP that occurred between the two periods improved T2DM treatment. The outcome of interest was change in HbA1c levels after three visits to NCDEG. Data was collected for a minimum of three visits and a maximum of six visits to the center. For this study, only data for the first three visits were used and associated lab results. Remaining data will be used for subsequent studies.

Eligibility Criteria

Subjects needed to be new patients within each respective time period – we achieved this goal using NCDEG's file numbering system which allowed us to only include newly opened files within each respective time period. Patients needed to have had a minimum of three visits to the center within each respective time period to be included. Subjects needed to be at least 25 years of age, and have T2DM as either defined by an HbA1c of 6.5% or above at first visit or indicated by the physician in the medical record. Patients who were pregnant were excluded from the study.

Selection of Study Sample Data Collection

To identify and collect data, we utilized NCDEG's records numbering system to identify when a patient's first visit occurred. Records numbered between 5,681 and 18,832 were opened in P1 and records numbered between 42,244 and 10,7387 were opened in P2. Using

the SAS Proc ILM, a list of numbers was randomly generated, between 5,681 and 18,832 for P1 and between 42,244 and 107,387 for P2 (Figure 1). All P1 records were in paper form, while a proportion of P2 records were electronic. Within each period, some of the files were inactive and stored in an inaccessible location, which prevented the team from collecting data on those records. Inactive files were of patients who only came to NCDEG once, and subsequently did not come back for retreatment. Inactive files were identified as inactive by the team through NCDEG system for tracking inactive files – in the place of an inactive file within the NCDEG filing system would be a form indicating that file was inactive. Files were inactivated after two years of the first visit if the patient had not returned. Since five years elapsed since the end of P1, all files that were eligible to be inactivated in P1 were inactivated by the time the study was initiated. However, when we initiated the study in 2012, only files opened in the beginning of P2 were eligible for inactivation, where as the remaining files that would have been inactivated had the study been conducted later would have been excluded in our study as the patient would have only had one visit to the center and not met minimum eligibility criteria.

Based on preliminary record pulls as well as applying exclusion and inclusion criteria, we recognized the eligibility rate would be relatively low –2% to 15%, primarily due to the requirement that patients have a minimum of three visits within each period. We aimed for a final sample size of 1000 patients, 500 within each time period. To avoid the possibility of not reaching the target sample, we included more than 70% of the available records within each respective period in the randomly generated list. For P1 located records, a physician assessed whether each record met the inclusion criteria. For P2 records, a proportion of records were captured electronically, which allowed inclusion to occur in two phases – a first inclusion/exclusion phase based on the electronic data available, and a second inclusion/exclusion phase based on a physician assessment of the physical record.

Data Collection

OZ developed an iPad App Survey (IAS) to collect the data for the study (Illustrations A.1-A.7). When assessing potential strategies for data collection, we recognized that developing an IAS would reduce costs and save time during the data collection process by eliminating the need to transfer data collected from paper to electronic forms necessary to conduct analysis. It would also allow us to scale up the effort and recruit physicians from NCDEG to join the project effort. The IAS was installed on each iPad purchased for the study and distributed to each member of the research team. The IAS was iteratively tested with the team, using feedback on design and functionality to improve the IAS's performance. Security features in the IAS included data encryption, team member specific usernames, and password protected entry. Performance monitoring features included timestamps that were automatically generated at the beginning and end of each data entry. Data quality features included forced data entry feature (record could not be saved when the minimum data fields for three visits were filled), range limits on continuous variables, and verification algorithms for specified variables. We paid particular attention to ease of use of the IAS by keeping data fields large, and ensuring that colors and designs contrasted well to allow for ease of visualization and handling. To ensure integrity of an inputted record, various levels of IAS of privileges were developed. The administrator account (for OZ access) had privileges to view, edit, and delete inputted records as well as access to improve IAE performance if errors arose during data collection. The coordinator account (for ML and MA) had privileges to view and delete inputted records as was needed for the development of input of Quality Control files (see *Data Quality*). The standard accounts had the privileges to create records (ML, MA, AA, BM, AA, LH, MJ). Standard accounts

were made for each member of the team with individualized passwords and usernames. Finally, each inputted record was associated with a particular username, which allowed for performance feedback used for quality control calibrations of data entry.

The IAS was used to collect data on a minimum of 258 data fields and a maximum of 537 data fields based on how many visits a patient had to NCDEG and how many lab results they had. We collected data on gender, age, height, duration of T2DM upon visit, insurance coverage, and copay percent for each subject. We collected data on date of visit, weight, waist, diastolic blood pressure, systolic blood pressure, HbA1c, family history of T2DM, smoking status, 19 comorbidities, and 57 medication/supplements for each visit for a minimum of three and a maximum of six. We collected data on dates and values of lab tests: LDL cholesterol, HDL cholesterol, total cholesterol, and triglycerides for maximum of six lab tests. Data on only the first three visits where used for this study, while remaining data will be used for future studies.

Data Collection Team

The team was composed of six primary care physicians representing the three diabetes clinics within NCDEG. OZ initiated the project, founded the team, and led the research effort. OZ also organized tutorial sessions, led team meetings, developed protocols for distribution, and developed IAS. Upon joining the team and receiving the study protocol, the physicians were provided with a tutorial on how to use the application via videoconference. Topics of the tutorial included best practices for data entry, security, and maintenance. The tutorial also included an overview of variable definitions and criteria. Finally, one of the physicians received extensive training through additional videoconference meetings so as to have the capacity to address data entry issues as they arose. Weekly videoconference meetings were held to

address major issues, and issues that required immediate attention between meetings were either handled via email or via phone call with OZ.

Quality Control Measures

Quality control measures were carried out during data collection to ensure that the final dataset accurately reflected information that was present in the medical records. Before data collection began, all physicians inputting data and determining exclusion/inclusion of files were provided with a detailed study protocol. All the physicians participating in the study underwent training on data input and exclusion/inclusion criteria. Before physicians could begin data entry, they had to demonstrate their ability to use the iPad application developed for the project by OZ and input a standard file with 100% accuracy as compared to a previous entry of that file that was prepared by the two lead doctors within the NCDEG, with any differences resolved through agreement. Once all six team members began to enter patient records into the database, 55 randomly selected records from the records that were included in the study were selected as quality control records (QC). Two physicians independently entered the data from the QCs and their independent entries were consolidated into one – any differences before consolidation were resolved by physician agreement. The 55 QCs were used to measure an inter-rater reliability for each categorical collected variable and correlations for continuous variables. The record entries were compared to QCs in real-time via percent agreement, which allowed us to assess the quality of record entries and take corrective action if any data entry problems were identified.

Table A.1 and Table A.2 (Appendix) present measurements on the quality of the data collected as compared to 55 QC input. In Table A.1 the correlation between selected

continuous variables in the original input and the QC input are presented. The correlation for HbA1c V1, HbA1c V2, and HbA1c V3 between original input and QC input is 1.0000 ($p<0.0001$), 1.0000 ($p<0.0001$), and 1.0000 ($p=0.0016$) respectively. Table A.2 presents the inter-rater reliability Kappa coefficients (IRRC) for several comorbidities and medication variables of interest. All comorbidity and medication variables included in the finale model had high IRRC: Sulfonylurea (IRRC=0.9242), NPH (IRRC=1.0000), Metformin (IRRC=1.000), CKD (1.000), and Hyperthyroidism (IRRC=1.0000).

Statistical Analyses

Baseline variables were compared between P1 and P2, as well as between genders within each period using t-tests for continuous variables, and χ^2 test for categorical variables and Fischer's exact tests when appropriate. To assess baseline characteristics and changes in baseline characteristics with important covariates, categorical variables were created for BMI (Normal: $18.5\leq BMI<25.0$; Overweight: $25.0\leq BMI<30.0$; Obese Class 1: $30.0\leq BMI<34.9$; Obese Class 2: $35.0\leq BMI<40$; Obese Class 3: $40\leq BMI$), blood pressure (Normal: Systolic< 120 and Diastolic<80; Prehypertension: $120\leq$Systolic<140 or $80\leq$Diastolic<90; Stage 1 – High: $140\leq$Systolic<160 or $90\leq$Diastolic<100; Stage 2 – High: $160\leq$Systolic or $100\leq$Diastolic). All study subjects were diabetics, so they need to meet two of the following criteria to be considered to have metabolic syndrome: Antihypertensive medication and/or high blood pressure (≥140 mm Hg systolic or ≥90 mm Hg diastolic), Plasma triglycerides ≥150 mg/dL, HDL cholesterol <35 mg/dL in males or <39 mg/dL in females, or BMI >30 kg/m^2Improvement of diabetes status was categorized into four categories. The first category was composed of patients who at the first visit had an HbA1c

level greater than or equal to 6.5%, and after three visits to NCDEG had dropped below the 6.5% threshold. The second category was composed of subjects who at the first clinical visit had an HbA1c level greater than or equal to 6.5%, and after three visits to NCDEG had reduced their HbA1c levels, but not below the 6.5% threshold. The third group was composed of those whose HbA1c% increased in the span of three visits with a final HbA1c% of higher or equal to 6.5% - this group was composed of both those who at the first visit had an HbA1c above and below 6.5%. The final category was composed of those who had an HbA1c of below 6.5% at first visit, and maintained that status after three visits. These categories were chosen for their clinical relevance. The baseline variables were compared across the four categories using an analysis of variance for continuous variables, a χ^2 test for categorical variables, and Fischer's exact tests when appropriate

The main outcome variable was the difference in HbA1c level between the first visit and the third visit and the primary exposure variable of interest was the period in which treatment was sought. We determined that the main outcome variable was normally distributed. Using Proc GLM, a linear model was created by including all baseline measures available, including comorbidities and medications used. Using the Partial F-test, variables were removed from the model in descending (i.e. following a backward stepwise approach) based on the highest non-significant p-value until the removal of a variable significantly affected the fit of the model. The main predictor of interest, period of treatment, was not eligible to be removed regardless of p-value. The p-value of dummy variables was assessed to be the lowest p-value within the group. Dummy variables for a given categorical variable were removed from the model together.

Quality of data collected was assessed in real-time via percent agreement. Proc Corr was used to measure the correlation between inputted files and QC files. Proc Freq with the Agree Option was used to measure the simple Kappa coefficient for each categorical variable to assess intra-rater reliability.

All analyses were conducted using SAS statistical software (version 9.2 SAS Institute Inc., Cary, NC, USA).

RESULTS

Selected baseline characteristics of the 765 participants are presented in Table 1. There were 323 subjects in P1 and 442 subjects in P2. The average age at first visit for P1 was 55.46 years (SD=9.78), which was statistically the same as the average age at first visit for P2 56.24 years (SD=10.39) (p=0.295). The HbA1c reading at V1 of 9.35(%) (SD=2.15) was statistically the same in P1 and P2 9.28(%) (SD=2.10), (p=0.611). There was a difference in LDL cholesterol levels (p=0.043): 131.80 mg/dL (SD=34.70) for P1, and 123.10 mg/dL (SD=43.74) for P2. There was also a difference in baseline systolic blood pressure: 129.60 mmHg (SD 19.47) for P1, and 137.50 mmHg (SD 21.23) for P2. The distribution of blood pressure in categories of Normal, Prehypertension, High Blood Pressure Stage 1 and High Blood Pressure Stage 2 was different between P1 and P2 (p=0.004). A greater proportion of the patients had High Blood Pressure Stage 1 and Stage 2 in P2 compared to P1. The distribution of smoking status categories was different between P1 and P2 (p<0.001), with a larger proportion in P2 having never been smokers (35.52%) compared to P1 (20.12%), and as well a higher proportion in P2 being current smokers (19.91%) compared to P1 (13.93%). More subjects in P1 had an unknown smoking status (58.51%) compared to P2 (36.20%). Similarly, the distribution of patient family history of

diabetes was different between P1 and P2 (p<0.001). A far greater proportion of the patients had P1 (44.89%) had a no family history of diabetes compared to P2 (27.50%). For those with enough data to assess metabolic syndrome, the distribution of with metabolic syndrome in P1 and P2 was similar (p=0.724). The distribution of insurance copay amount was different between P1 and P2 (p<0.001), with a larger proportion in P2 having to pay a 20% copay (79.95%) compared to P1 (71.88%), and a far lower proportion in P2 paying a 12% copay (0.91%) compared to P1 (13.44%). Baseline characteristics that were equivalent between periods included BMI by category (Normal, Overweight, Obese Class 1, Obese Class 2, and Obese Class 3), and insurance type categories (Governmental, Private, No Insurance, and Unknown).

Table 2 presents change in selected baseline characteristics between the first and third NCDEG visit by period. The change in Hba1c was similar in both P1 and P2. In P1 the drop in HbA1c was -1.54(%) (SD=1.81), while in P2 it was -1.52(%) (SD=1.85) (p=0.894). Change in diastolic and systolic blood pressure were also not significantly different between periods. However, while the BMI of patients in P1 decreased after 3 visits (-0.10(%), SD=1.69), it increased in P2 after 3 visits (0.19(%), SD 1.52) (p=0.013). Another statistically significant change in baseline variable different between P1 and P2 was time elapsed between V1 and V3. While the average time elapsed between V2 and V3 in P1 was 145.90 days (SD=82.69), it was 157.70 days (SD=77.89) for P2.

Table 3 presents selected baseline characteristics of the study sample across gender. Several baseline characteristics differed between males and females. Most important, males had a higher baseline Hba1c of 9.49(%) (SD=2.16), compared to females who had an average

baseline HbA1c of 9.13(%) (SD=0.018). Females at baseline were older than males, (57.15 years, SD=9.68) versus (54.67 years, SD=10.45) (p=<0.001). Females had a higher baseline HDL level compared to males (p<0.001). Similarly, females had a higher Total Cholesterol (TC) compared to males (p=0.013). Females also had a higher Body Mass Index (BMI) (p<0.001) and a higher systolic blood pressure at baseline (p<0.001) compared to males. As indicated by chi-square tests, the distribution of BMI categories, blood pressure categories, smoking status, and metabolic syndrome status differed between genders.

Table 4 presents changes in selected baseline characteristics of males and females after three visits to the center. There were several differences of interest. Notably, male HbA1c dropped by a larger degree (-1.77(%) (SD 1.84)) compared to female HbA1c change (-1.30(%) (SD 1.80)) (p<0.001). The BMI of males also dropped by a greater degree compared to females (p<0.001), and among males less time elapsed between V1 and V3 compared to females (p=0.025). Whereas males come in for V3 appointment after 146.20 (SD=75.04) days, females come in after 159.20 days (SD=84.49).

Table 5 presents baseline characteristics stratified by period and gender. It is interesting to note that the differences between males and females with regards to baseline characteristics also existed within each period. In some cases differences in baseline characteristics between males and females differed only within one of the periods. Females had higher HDL levels compared to males in both P1 (p<0.001) and P2 (p<0.001) and higher TC compared to males in P2 (p=0.042). In both P1 and P2, females had a higher (p<0.001) BMI compared to males and a higher (p<0.005) systolic blood pressure. Smoking status differed between males and females,

with higher proportion of males being smokers compared to females ($p<0.001$) in both time periods. Gender differences were also identified for copay categories ($p=0.081$), family history of diabetes ($p<0.001$), and metabolic syndrome status ($p<0.003$) but only in P2.

Table 6 presents changes in selected baseline characteristics stratified by gender and period. It is interesting to note that in both P1 and P2 the HbA1c of males decreased by a greater amount compared to females. While in P1, the HbA1c of males decreased by 1.80(%) (SD=1.81), in the same period the HbA1c of females decreased by 1.26(%) (SD=1.77) ($p=0.007$). Similarly in P2, while the HbA1c of males decreased by 1.74(%) (SD 1.81), the HbA1c of females decreased by 1.32(%) (SD 1.77) ($p=0.019$). While in P1, the BMI of males decreased (-0.14 kg/m^2 (SD=1.35), it increased for females (0.38 kg/m^2 (SD=1.99)).

Table 7 presents clinically relevant glucose control outcomes after three visits to NCDEG. Subjects were categorized into one of four mutually exclusive categories: a) improve (decrease) to an HbA1c below 6.5(%) (N=103), b) improve (decrease) to an HbA1c above 6.5(%) (N=504), c) maintain an HbA1c below 6.5(%) (N=27), or d) experience an HbA1c increase to above 6.5(%) (N=145). The distribution across these categories by period was borderline significant ($p=0.056$). More patients improved to below 6.5(%) in P1 (14.86%) compared to P2 (12.44%), while more patients HbA1c increased in P1 (17.03%) compared to P2 (20.36%). Most patients in both periods improved their HbA1c, but did not pass the 6.5(%) HbA1c threshold: P1 (65.02%) and P2 (63.35%). The distribution glucose control outcome by gender was significant ($p=0.013$). More males were represented in the improved categories compared to females. For males,

15.67% improved to below 6.5(%) compared 11.26% for females. For males, 66.32% improved to below 6.5(%) compared to 61.78% for females.

Table 8 presents the adjusted and unadjusted parameter estimates for the final linear regression model predicting **Δ**HbA1c (V1-V3) (R-square=0.612). The key independent variables were period and gender (differential response to integrated patient education program), and the model was adjusted for the following covariates: duration of diabetes, HbA1c at first visit, time elapsed between V2-V3, change in BMI between V1-V3, chronic kidney disease status, hyperthyroidism status, and medication status for metformin, sulfonylurea, Mix Insulin and neutral protamine Hagedorn (NPH) Insulin.HbA1c decreased by 0.177(%) more in P2 than in P1 (p=0.043). Gender was significantly associated with decrease in HbA1c. Males decreased their HbA1c levels by 0.222(%) more compared to females (p=0.012).

To assess which covariates contributed to the confounding of the primary exposure of interest (period) toward the null, the unadjusted β estimate of period was compared the to the β estimate of period when each covariate of the final model was added to the model one at a time. Table 9 presents how the β estimate of the primary exposure of interest (period) is affected by including the covariates in the final model one at a time. The β estimate for period without controlling for any covariates is 0.0180 (p=0.894), while in the final model it is -0.1770 (p=0.044). The changes in the β estimate range from 0.0750 when age is included to a change of -0.0529 when Metformin is included.

DISCUSSION

As hypothesized before undertaking the study, period of treatment was associated with improved blood glucose control (as assessed by **Δ**HbA1c (V1-V3)) among patients treated in the center after the introduction of the IPEP compared to those treated before its introduction. This finding supports NCDEG's initiative to invest time and resources into establishing a diabetes education program that covers correct use of medication as well as provides dietary and lifestyle guidance for patients and offers them support in monitoring their blood glucose levels.

Univariate estimates ΔHbA1c (V1-V3) between periods were confounded towards the null, as indicated by a significant difference in ΔHbA1c (V1-V3) in the adjusted model, but a non-significant difference in ΔHbA1c (V1-V3) in the univariate analysis. An analysis to identify the major cofounding covariate did not indicate which covariate was the major confounder. The univariate ΔHbA1c (V1-V3) between genders was confounded away from the null, as the difference in response between genders decreased, but remained significant in the adjusted model.

An interesting outcome to note was the differential T2DM status response between males and females. Males consistently performed better in reducing their HbA1c – their response to treatment was better in both periods, and better when combining all males in P1 and P2 to compare with all females in P1 and P2. It is unclear why male diabetes treatment response is better in this sample. Studies conducted on different samples outside of Jordan have shown that females respond differently to diabetes and diabetes treatment compared to males (*32*, *33*).

While we do not know why male response to treatment of diabetes is better compared to female response, both overall and within each period – we can speculate that it may have to do with differential patient-physician relationships across gender (*34*). Males may respond more positively when treated by a male physician compared to females (*34*). Within the center, there were 2 male physicians for every female physician treating T2DM. It is also possible that males receive more family support when they are diagnosed with diabetes (*35*). Culture could also play a major role in the physician patient dynamic. While observing physician-patient interaction at NCDEG, we noticed that male diabetic patients often came with their wife or daughter. While meeting with the physician, the wife or daughter would ask the physicians very specific questions regarding the appropriate diet for the father or husband as they would usually prepare the meals. It is possible that since males primarily rely on their wives or daughters for their diet selection, they may likely adhere to a recommended diet. Whereas females would not have that advantage – as they would prepare the food, they may be less likely to stop preparing specific foods on account of their diabetes. Perhaps the greater decrease in HbA1c of males could be attributed to the fact that males had higher baseline HbA1c levels, however in the multivariate linear model, the effect of gender remained statistically significant even after adjusting for variables that were differential between males and females at baseline, including HbA1c at visit 1. Another potential explanation is that females had a higher BMI at baseline, which could make achieving lower HbA1c more difficult (*36*).

We also collected compressive data on baseline characteristics that will provide NCDEG with an improved understanding of incoming patient characteristics. It is interesting to note

that at baseline, patients came to the center with an HbA1c nearly 3.0(%) higher than the threshold for diabetes diagnosis at 6.5(%). The HbA1c of patients was beyond unsatisfactory control of blood glucose, which would suggest that mechanisms should be developed for identifying diabetes in patients earlier.

Finally, as Table 7 presents, we were able to show that nearly two-thirds of all diabetes patients improved their HbA1c after three visits, but did not pass the 6.5(%) threshold. There was also a large proportion of the patients whose diabetes status worsened as indicated by a higher HbA1c after three visits. This was particularly pronounced in females.

There are several important study limitations and strengths that are worth mentioning. Because this was a records review study we needed to rely on the assessment of physicians in recording medication use and the presence of chronic conditions. However, because the chronic conditions we were interested in would have an impact on diabetes treatment, if they were present, they were likely to be present within the chart. The same reasoning applies for data on medications – because we were interested in looking at medications associated with diabetes, if they were not present within the chart, then the patient was likely not taking these medications. Physicians at NCDEG suggested that because various diabetes medications are contraindicated for specific comorbidities that several layers of comorbidity assessment and medication assessment are in place within the center to avoid prescribing a medication that is contraindicated. For example, patients with chronic kidney disease cannot be prescribed Metformin as the Glucophage will deposit within the poorly functioning kidneys as they cannot excrete it properly. Furthermore, when prescribing medications, physicians recorded a list of

medications on the chart, and then transferred to prescription pads. Patients first meet with a nurse that records all medications used and comorbidities present within the chart.

Another potential weakness of the study is the possibility that other unidentified changes in treatment of diabetes at NCDEG contributed to the effect observed. This was addressed by conducting comprehensive interviews with nursing staff, medical staff, as well as administrators who were employed at the center during P1 and P2. They confirmed that the only other major difference experienced between P1 and P2 was increase in patients treated, which they speculated could be detrimental to the quality of patient care. Seeing as how patients in P2 experience a greater adjusted improvement in HbA1c compared to P1, we can assume that the intervention may have had an even greater impact had patients had as much time with physicians as in P1.

The major strengths of the study include the comprehensive nature of the data collected. In addition to being able to collect data on anthropometric measures, we were able to collect data on medications used, chronic conditions present, as well as lipid profiles.

This study brings up interesting questions that we would like to address in future studies, including why treatment response is differential. As we have collected data on the first 6 visits, it would be interesting to see whether the P2 advantage persists past the third visit. It would also be interesting to conduct a survival analysis to understand whether time to blood glucose control is significantly different between each period (*37*). Finally, while we have noted in the study the differential response between males and females, the reasons are not clear. Future work should try to address this question in the context of the Jordanian population.

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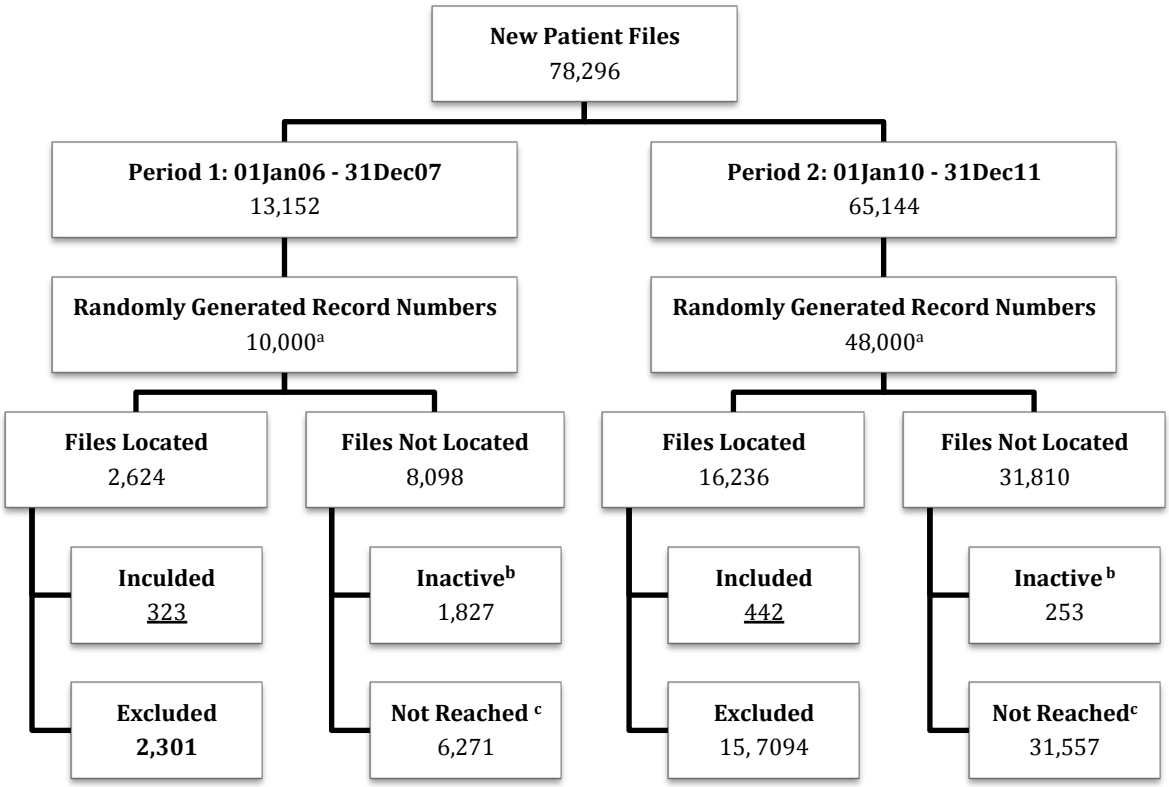
TABLES AND FIGURES

Figure 1 Process of Randomization and Applying of Exclusion and inclusion criteria.



a. The number of randomly generated number was higher than the number of files we aimed to collect because the inclusion rate was highly variable in a pilot run for determining the amount of file numbers we need to generate. As a result, more than 70% of available numbers were generated, and records were sequentially pulled based on the order of the generated numbers.

b. There were more inactivated files in Period 1 (P1) versus Period 2 (P2) because files are inactivated every two years based on whether a patient only had one visit to the center. Since five years elapsed since the end of P1, all files that needed to be inactivated were. However, when we initiated the study in 2012, only files opened in the beginning of P2 were eligible for inactivation, where as the remaining files that would have been inactivated had the study been conducted later would have been excluded in our study as the patient would have only had one visit to the center and not met minimum eligibility criteria.

c. We did not reach all the randomly generated file numbers due to time constraints. Had we continued going through the randomly generated file numbers we would have stopped once we reached our target sample

Table 1: Selected Baseline Characteristics by Period (Visit 1)

Characteristic	Period 1 (N=323)[b]	Period 2 (N=442)[b]	p[c]
HbA1c (%)	9.35 ± 2.15 (323)	9.28 ± 2.10 (442)	0.611
Age (year)	55.46 ± 9.78 (323)	56.24 ± 10.39 (442)	0.295
Cholesterol (mg/dL)			
LDL	131.80 ± 34.70 (111)	123.10 ± 43.74 (251)	**0.043**[d]
HDL	43.65 ± 10.73 (109)	43.34 ± 13.30 (252)	0.815[d]
TC	195.4 ± 40.77 (113)	198.50 ± 49.56 (231)	0.537[d]
TG (mg/dL)	182.9 ± 108.5 (114)	199.80 ± 154.70 (257)	0.228[d]
BMI (kg/m^2)	32.47 ± 7.58 (308)	32.66 ± 9.05 (436)	0.765[d]
BMI by Category[e]			0.862
Normal	23 (7.47%)	30 (6.88%)	
Overweight	103 (33.44%)	141 (32.34%)	
Obese Class 1	101 (32.79%)	142 (32.57%)	
Obese Class 2	48 (15.58%)	81 (18.58%)	
Obese Class 3	33 (10.71%)	42 (9.63%)	
Blood Pressure (mmHg)			
Diastolic	78.37 ± 12.67 (322)	78.08 ± 13.40 (442)	0.761
Systolic	129.60 ± 19.47 (323)	137.50 ± 21.23 (442)	**<0.001**
Blood Pressure by Category[f]			**0.004**
Normal	53 (16.46 %)	57 (12.90%)	
Prehypertension	199 (61.80%)	236 (53.39%)	
High – Stage 1	57 (17.70%)	121 (27.38%)	
High – Stage 2	13 (4.04%)	28 (6.33%)	
Smoking Status			**<0.001**
Never	65 (20.12%)	157 (35.52%)	
Current	45 (13.93%)	88 (19.91%)	
Former	24 (7.43%)	37 (8.37%)	
Unknown	189 (58.51%)	160 (36.20%)	
Family History of DM			**<0.001**
Yes	29 (8.98%)	24 (5.45%)	
No	145 (44.89%)	121 (27.50%)	
Unknown	149 (46.13%)	295 (67.05%)	
Metabolic Syndrome[g]			0.724
Yes	37 (48.68%)	93 (51.10%)	
No	39 (51.32%)	89 (48.90%)	
Insurance Type			0.359
Governmental	298 (92.26%)	413 (93.44%)	
Private	7 (2.17%)	10 (2.26%)	
No Insurance	11 (3.41%)	16 (3.62%)	
Unknown	7 (2.17%)	3 (0.68%)	
Copay (%)			**<0.001**
0	34 (10.63%)	67 (15.26%)	
12	43 (13.44%)	4 (0.91%)	
20	230 (71.88%)	351 (79.95%)	
100	13 (4.06%)	17 (3.87%)	

Abbreviations: HbA1c, Glycosylated Hemoglobin; LDL, Low-density Lipoprotein; HDL, High-density Lipoprotein; TC, Total Cholesterol; TG, Triglycerides; BMI, Body Mass Index; DM, Type 2 Diabetes Mellitus

a. Table values are mean ± SD (number) for continuous variables and n (column %) for categorical variables.

b. Numbers may not sum to total due to missing data, and percentages may not sum to 100% due to rounding.

c. p-value is for student t-test (continuous variables) or $\chi 2$ test (categorical variables).

d. Variances not equal.

e. Normal: 18.5≤BMI<25.0; Overweight: 25.0≤BMI<30.0; Obese Class 1: 30.0≤BMI<34.9; Obese Class 2: 35.0≤BMI<40; Obese Class 3: 40≤BMI

f. Normal: Systolic< 120 and Diastolic<80; Prehypertension: 120≤Systolic<140 or 80≤Diastolic<90; Stage 1 – High: 140≤Systolic<160 or 90≤Diastolic<100; Stage 2 – High: 160≤Systolic or 100≤Diastolic.

American Heart Association definition for metabolic syndrome was used. All study subjects were diabetics, so they need to meet two of the following criteria to be considered to have metabolic syndrome: Antihypertensive medication and/or high blood pressure (≥140 mm Hg systolic or ≥90 mm Hg diastolic), Plasma triglycerides ≥150 mg/dL, HDL cholesterol <35 mg/dL in males or <39 mg/dL in females, or BMI >30 kg/m^2

Table 2: Change in Selected Baseline Characteristics by Period (Visit 1 – Visit3)

Characteristic	Period 1(N=323) [b]	Period 2(N=442)[b]	p [c]
Δ HbA1c			
Absolute (%)	-1.54 ± 1.81 (323)	-1.52 ± 1.85 (442)	0.894
Percent (Δ%)	-14.39 ± 16.19 (323)	-13.92 ± 16.58 (442)	0.700
Δ BMI (kg/m^2)	-0.10 ± 1.69 (308)	0.19 ± 1.52 (436)	**0.013**[d]
Δ Blood Pressure (mmHg)			
Diastolic	1.21 ± 17.23 (322)	-2.91 ± 16.76 (442)	0.173
Systolic	-2.16 ± 20.42 (323)	-3.79 21 ± 20.42 (442)	0.259
Time (days)			
V1 and V3	145.90 ± 82.69 (323)	157.70 ± 77.89 (442)	**0.043**
V1 and V2	58.63 ± 51.34 (323)	61.81 ± 47.25 (442)	0.375
V2 and V3	87.24 ± 57.02 (323)	95.89 ± 61.39 (442)	**0.048**

Abbreviations: HbA1c, Glycosylated Hemoglobin; BMI, Body Mass Index

[a.] Table values are mean ± SD (number) for continuous variables and n (column %) for categorical variables.

[b.] Numbers may not sum to total due to missing data, and percentages may not sum to 100% due to rounding.

[c.] p-value is for student t-test (continuous variables) or $\chi 2$ test (categorical variables).

[d.] Variances were not equal.

Table 3: Selected Baseline Characteristics by Gender (Visit 1)

Characteristic	Female (N=382) [b]	Male (N=383) [b]	p [c]
HbA1c (%)	9.13 ± 2.16 (382)	9.49 ± 2.07 (383)	**0.018**
Age (year)	57.15 ± 9.68 (383)	54.67 ± 10.45 (383)	**<0.001**
Cholesterol (mg/dL)			
LDL	127.70 ± 43.13 (183)	123.7.10 ± 39.42 (179)	0.356
HDL	47.60 ± 12.75 (182)	39.20 ± 10.88 (179)	**<0.001** [d]
TC	203.60 ± 48.54 (175)	191.10 ± 44.31 (169)	**0.013**
TG (mg/dL)	197.20 ± 174.60 (184)	199.80 ± 154.70 (257)	0.228 [d]
BMI (kg/m^2)	34.98 ± 8.73 (368)	30.23 ± 7.51 (376)	**<0.001** [d]
BMI by Category [e]			**<0.001**
Normal	10 (2.72%)	43 (11.44%)	
Overweight	73 (19.84%)	171 (45.48%)	
Obese Class 1	131 (35.60%)	112 (29.79%)	
Obese Class 2	91 (24.73%)	38 (10.11%)	
Obese Class 3	63 (17.12%)	12 (3.19%)	
Blood Pressure (mmHg)			
Diastolic	78.73 ± 12.78 (382)	77.67 ± 13.38 (382)	0.263
Systolic	137.30 ± 21.77 (382)	131.10 ± 19.47 (383)	**<0.001** [d]
Blood Pressure by Category [f]			**0.018**
Normal	47 (12.30 %)	63 (16.49%)	
Prehypertension	207 (54.19%)	228 (59.69%)	
High – Stage 1	102 (26.70%)	76 (19.90%)	
High – Stage 2	26 (6.81%)	15 (3.93%)	
Smoking Status			**<0.001**
Never	136 (35.60%)	86 (22.45%)	
Current	18 (4.71%)	115 (30.03%)	
Former	9 (2.36%)	52 (13.58%)	
Unknown	219 (57.33%)	130 (33.94%)	
Family History of T2DM			0.272
Yes	21 (5.50%)	32 (8.40%)	
No	133 (34.82%)	133 (34.91%)	
Unknown	228 (59.63%)	216 (56.69%)	
Metabolic Syndrome [g]			**0.003**
Yes	61 (42.07%)	69 (61.06%)	
No	84 (57.93%)	44 (38.94%)	
Insurance Type			0.902
Governmental	357 (93.46%)	354 (92.43%)	
Private	7 (1.83%)	10 (2.61%)	
No Insurance	13 (3.40%)	14 (3.66%)	
Unknown	5 (1.31%)	5 (1.31%)	
Copay (%)			0.396
0	45 (11.81%)	56 (14.81%)	
12	27 (7.09%)	20 (5.29%)	
20	296 (77.69%)	285 (75.40%)	
100	13 (3.41%)	17 (4.50%)	

Abbreviations: HbA1c, Glycosylated Hemoglobin; LDL, Low-density Lipoprotein; HDL, High-density Lipoprotein; TC, Total Cholesterol; TG, Triglycerides; BMI, Body Mass Index; DM, Type 2 Diabetes Mellitus

a. Table values are mean ± SD (number) for continuous variables and n (column %) for categorical variables.

b. Numbers may not sum to total due to missing data, and percentages may not sum to 100% due to rounding.

c. p-value is for student t-test (continuous variables) or $\chi 2$ test (categorical variables).

d. Variances not equal.

e. Normal: 18.5≤BMI<25.0; Overweight: 25.0≤BMI<30.0; Obese Class 1: 30.0≤BMI<34.9; Obese Class 2: 35.0≤BMI<40; Obese Class 3: 40≤BMI

f. Normal: Systolic< 120 and Diastolic<80; Prehypertension: 120≤Systolic<140 or 80≤Diastolic<90; Stage 1 – High: 140≤Systolic<160 or 90≤Diastolic<100; Stage 2 – High: 160≤Systolic or 100≤Diastolic.

g. American Heart Association definition for metabolic syndrome was used. All study subjects were diabetics, so they need to meet two of the following criteria to be considered to have metabolic syndrome: Antihypertensive medication and/or high blood pressure (≥140 mm Hg systolic or ≥90 mm Hg diastolic), Plasma triglycerides ≥150 mg/dL, HDL cholesterol <35 mg/dL in males or <39 mg/dL in females, or BMI >30 kg/m^2

Table 4: Change in Selected Baseline Characteristics by Gender (Visit 1 – Visit 3)

Characteristic	Female 1(N=382) [b]	Male 2(N=383) [b]	p [c]
Δ HbA1c			
Absolute (%)	-1.30 ± 1.80 (382)	-1.77 ± 1.84 (383)	**<0.001**
Percent (%Δ)	-11.78 ± 15.94 (383)	-16.44 ± 16.89 (383)	**<0.001**
Δ BMI (kg/m^2)	-0.10 ± 1.75 (368)	-0.24 ± 1.42 (383)	**<0.001 ***
Δ Blood Pressure (mmHg)			0.128
Diastolic	-2.71 ± 17.00 (382)	-1.68 ± 16.98 (382)	
Systolic	-4.20 ± 21.09 (382)	-1.99 ± 18.87 (383)	
Δ Time (day)			
V1 and V3	159.20 ± 84.49 (382)	146.20 ± 75.04 (383)	**0.025***
V1 and V2	64.76 ± 50.81 (382)	56.19 ± 46.82 (383)	**0.015**
V2 and V3	94.44 ± 55.24 (383)	90.03 ± 55.24 (383)	0.308

Abbreviations: HbA1c, Glycosylated Hemoglobin; BMI, Body Mass Index

[a.] Table values are mean ± SD (number) for continuous variables and n (column %) for categorical variables.

[b.] Numbers may not sum to total due to missing data, and percentages may not sum to 100% due to rounding.

[c.] p-value is for student t-test (continuous variables) or $\chi 2$ test (categorical variables).

[d.] Variances were not equal.

Table 5: Selected Baseline Characteristics by Period and Gender (Visit 1)

	Period 1			Period 2		
Characteristic	**Female (N=154)[b]**	**Male (N=169)[b]**	**p[c]**	**Female (N=228)[b]**	**Male (N=214)[b]**	**p[c]**
HbA1c (%)	9.10 ± 2.19 (154)	9.59 ± 2.10 (169)	**0.041**	9.15 ± 2.14 (228)	9.41 ± 2.05 (214)	0.185
Age (year)	56.34 ± 9.73 (154)	54.66 ± 9.79 (169)	0.123	57.70 ± 9.62 (228)	54.68 ± 10.97 (214)	**0.002**
Cholesterol (mg/dL)						
LDL	133.70 ± 38.07 (56)	129.90 ± 31.13 (55)	0.561	125.10 ± 45.07 (127)	121.00 ± 42.41 (124)	0.459
HDL	47.13 ± 11.36 (56)	39.98 ± 8.69 (53)	**<0.001**	47.81 ± 13.35 (126)	38.88 ± 11.70 (126)	**<0.001**
TC	200.70 ± 43.71 (59)	189.60 ± 36.81 (54)	0.149	205.10 ± 50.94 (116)	191.80 ± 47.43 (115)	**0.042**
TG (mg/dL)	186.80 ± 109.20 (58)	178.90 ± 108.70 (56)	0.700	201.90 ± 171.60 (129)	197.80 ± 133.20 (128)	0.830*
BMI (kg/m^2)	35.72 ± 8.97 (143)	29.66 ± 4.56 (165)	**<0.001**	34.51 ± 8.56 (225)	30.68 ± 9.17 (211)	**<0.001**
BMI by Category[f]			**<0.001**			**<0.001**
Underweight	0 (0.00%)	0 (0.00%)		1 (0.44%)	0 (0.00%)	
Normal	3 (2.10%)	20 (12.12%)		6 (2.67%)	23 (10.90%)	
Overweight	27 (18.88%)	76 (46.06%)		46(20.440%)	95(45.020%)	
Obese Class 1	49(34.27%)	52(31.52%)		82 (36.44%)	60 (28.44%)	
Obese Class 2	35(24.48%)	13(7.88%)		56(24.89%)	25(11.85%)	
Obese Class 3	29(20.28%)	4(2.42%)		34(15.11%)	8(3.79%)	
Blood Pressure (mmHg)						
Diastolic	79.25 ± 12.48 (154)	77.56 ± 12.82 (168)	0.231	78.38 ± 13.00 (228)	77.76 ± 13.84 (214)	0.627
Systolic	132.8x ± 21.00 (154)	126.6x ± 17.52 (168)	**0.005***	140.3x ± 21.81 (228)	134.6x ± 20.24 (20.24)	**0.005**
Blood Pressure by Category[g]			0.056			0.368
Normal	21 (13.64%)	32(19.05%)		26 (11.40%)	31(14.49%)	
Prehypertension	90(58.44%)	109(64.88%)		117 (51.32%)	119(55.61%)	
High – Stage 1	34(22.08%)	23(13.69%)		68(29.82%)	53(24.77%)	
High – Stage 2	9 (5.84%)	4(2.38%)		17(7.46%)	11(5.14%)	
Smoking Status			**<0.001**			**<0.001**
Never	36 (23.38%)	29 (17.16%)		100 (43.86%)	57 (26.64%)	
Current	6 (3.90%)	39 (23.08%)		12 (5.26%)	76 (35.51%)	
Former	2 (1.30%)	22 (13.02%)		7 (3.07%)	30 (14.02%)	
Unknown	110 (71.43%)	79 (46.5%)		109 (47.81%)	51 (23.83%)	
Family History of T2DM			0.241			**<0.001**
Yes	18 (11.69%)	11 (6.51%)		3 (1.32%)	21 (9.91%)	
No	69 (44.81%)	76 (44.97%)		64 (28.07%)	57 (26.89%)	
Unknown	67 (43.51%)	82 (48.52%)		161 (70.61%)	134 (63.21%)	
Metabolic Syndromeh			0.373			**0.003**
Yes	20 (44.44%)	17 (54.84%)		41 (41.00%)	52 (63.41%)	
No	25 (55.56%)	14 (45.16%)		59 (59.00%)	30 (36.59%)	
Insurance Type			0.327			0.813
Governmental	144 (93.51%)	154 (91.12%)		213 (93.42%)	200 (93.46%)	
Private	1 (0.65%)	6 (3.55%)		6 (2.63%)	4 (1.87%)	
No Insurance	6 (3.90%)	5 (2.96%)		7 (3.07%)	9 (4.21%)	
Unknown	3 (1.95%)	4 (2.37%)		2 (0.88%)	1 (0.47%)	
Copay (%)			0.901			**0.081**
0	16 (10.39%)	18 (10.84%)		29 (12.78%)	38 (17.92%)	
12	23 (14.94%)	20 (12.05%)		4 (1.76%)	0 (0.00%)	
20	109 (70.78%)	121 (72.89%)		187 (82.38%)	164 (77.36%)	
100	6 (3.90%)	7 (4.22%)		7 (3.08%)	10 (4.72%)	

Abbreviations: HbA1c, Glycosylated Hemoglobin; LDL, Low-density Lipoprotein; HDL, High-density Lipoprotein; TC, Total Cholesterol; TG, Triglycerides; BMI, Body Mass Index; T2DM, Diabetes Mellitus

a. Table values are mean ± SD (number) for continuous variables and n (column %) for categorical variables.

b. Numbers may not sum to total due to missing data, and percentages may not sum to 100% due to rounding.

c. p-value is for student t-test (continuous variables) or $\chi 2$ test (categorical variables).

f. Normal: Systolic< 120 and Diastolic<80; Prehypertension: 120≤Systolic<140 or 80≤Diastolic<90; Stage 1 – High: 140≤Systolic<160 or 90≤Diastolic<100; Stage 2 – High: 160≤Systolic or 100≤Diastolic.

g. American Heart Association definition for metabolic syndrome was used. All study subjects were diabetics, so they need to meet two of the following criteria to be considered to have metabolic syndrome: Antihypertensive medication and/or high blood pressure (≥140 mm Hg systolic or ≥90 mm Hg diastolic), Plasma triglycerides ≥150 mg/dL, HDL cholesterol <35 mg/dL in males or <39 mg/dL in

Table 6: Change in Selected Baseline Characteristics by Period and Gender

	Period 1			Period 2		
Characteristic	**Female (N=154)[b]**	**Male (N=169)[b]**	**p[c]**	**Female (N=228)[b]**	**Male (N=214)[b]**	**p[c]**
Δ HbA1c						
Absolute (Δ)	-1.26 ± 1.77 (154)	-1.80 ± 1.81 (169)	**0.007**	-1.32 ± 1.82 (228)	-1.74 ± 1.87 (214)	**0.019**
Percent (%Δ)	-11.53 ± 15.75 (154)	-17.00 ±16.18 (169)	**0.002**	-11.95 ± 16.09 (228)	-16.01 ± 17.45 (214)	**0.011**
Δ BMI (kg/m^2)	0.38 ± 1.99 (143)	-0.14 ± 1.35 (165)	**0.008***	-0.08 ± 1.55 (225)	-0.32 ± 1.47 (211)	0.096
Δ Blood Pressure (mmHg)						
Diastolic	-1.36 ± 16.39 (154)	-1.08 ± 18.01 (168)	0.882	-3.62 ± 17.30 (228)	-2.15 ± 16.16 (214)	0.361
Systolic	-3.99 ± 20.98 (154)	-0.44 ± 17.86 (169)	0.102*	-4.33 ± 21.21 (228)	-3.22 ± 19.58 (214)	0.566
Δ Time (day)						
V1 and V3	149.30 ± 82.15 (154)	142.70 ± 83.30 (169)	0.473	165.90 ± 85.58 (228)	149.00 ± 67.88 (214)	**0.022***
V1 and V2	61.72 ± 48.85 (154)	55.81 ± 55.10 (169)	0.299*	66.82 ± 53.31 (228)	56.48 ± 39.23 (214)	**0.020***
V2 and V3	87.61 ± 57.21 (154)	86.89 ± 57.01 (169)	0.910	99.06 ± 67.72 (228)	92.51 ± 53.80 (214)	0.260*

Abbreviations: HbA1c, Glycosylated Hemoglobin; BMI, Body Mass Index; V(n), Visit (n)

[a.] Table values are mean ± SD (number) for continuous variables and n (column %) for categorical variables.

[b.] Numbers may not sum to total due to missing data, and percentages may not sum to 100% due to rounding.

[c.] p-value is for student t-test (continuous variables) or $\chi 2$ test (categorical variables).

[d.] Variances not equal.

Table 7: Clinically Relevant Diabetes Status Outcomes (Visit 1 – Visit 3)

Characteristic	**Improve[a] Below 6.5% (N = 103)**	**Improve[b] Above 6.5% (N= 504)**	**Maintain[c] Below 6.5% (N=27)**	**Worsen[d] Above 6.5% (N=145)**	**p[e]**
Period					0.056
2006-2007	48 (14.86%)	210 (65.02%)	10 (3.10%)	55 (17.03%)	
2010-2011	55 (12.44%)	289 (63.35%)	17 (3.85%)	90 (20.36%)	
Gender					**0.013**
Female	43 (11.26%)	236 (61.78%)	18 (4.71%)	85 (22.25%)	
Male	60 (15.67%)	254 (66.32%)	9 (2.35%)	60 (15.67%)	

[a.] Began with an HbA1c of above 6.5%. After three visits, HbA1c decreased and passed 6.5%.

[b.] Began with an HbA1c of above 6.5%. After three visits, HbA1c decreased, but did not pass 6.5%.

[c.] Began with an HbA1c of below 6.5%. After three visits, HbA1c remained 6.5%.

[d.] Began with an HbA1c of either above or below 6.5%. After three visits, if started with an HbA1c of above 6.5%, it increased. After three visits, if started with an HbA1c of below 6.5%, it increased and passed 6.5%.

[e.] p-value is for $\chi 2$ test.

Table 8: Multivariate Linear Regression Model of ΔHbA1c (V3-V1) Outcome

Model	Adjusted β Estimate (SE)	p	Unadjusted β Estimate (SE)	p
Period		**0.043**		**0.894**
Period 1	**Reference**		**Reference**	
Period 2	**-0.177 (0.089)**		**0.018 (0.134)**	
Gender		0.012		<0.001
Female	Reference		Reference	
Male	-0.222 (0.088)		-0.469 (0.132)	
Age (year)	0.002 (0.001)	0.048	0.024 (0.006)	<0.001
Duration of Diabetes (year)	0.037 (0.008)	<0.001	0.028 (0.010)	<0.006
HbA1c at First Visit (%)	-0.685 (0.023)	<0.001	-0.619 (0.022)	
Time (V3 – V2) (day)	0.002 (0.003)	0.002	0.004 (0.001)	<0.001
BMI (V3 – V1) (kg/m^2)	-0.079 (0.079)	0.008	-0.164 (0.042)	<0.001
Chronic Kidney Disease		0.025		0.019
No	Reference		Reference	
Yes	0.646 (0.646)		0.999 (0.425)	
Hyperthyroidism		<0.001		0.078
No	Reference		Reference	
Yes	5.696 (1.167)		3.236 (1.834)	
Metformin		0.004		<0.001
No	Reference		Reference	
Yes	0.029 (0.099)		0.586 (0.137)	
Sulfonylurea		0.002		0.323
Yes	Reference		Reference	
No	0.320 (0.104)		-0.131 (0.323)	
MIX Insulin		<0.001		0.028
No	Reference		Reference	
Yes	0.712 (0.154)		0.407 (0.185)	
NPH Insulin		0.002		0.626
Yes	Reference		Reference	
No	2.547 (0.830)		0.633 (1.300)	

Abbreviations: HbA1c, Glycosylated Hemoglobin; V(n), Visit (n); BMI, Body Mass Index

[a.] R-square for the model equals 0.612

[b.] Included baseline characteristics and reverse dropped based on whether dropping a variable would significantly affect t fit of the model as assessed by the Partial F-test.

[c.] A negative β Estimate signifies that with every increase in unit of the covariate, the decrease in HbA1c between visit 1 a visit 3 increases.

Table 9: Testing for Covariate Confounding of Primary Predictive Variable

Model	Period β Estimate	p	Change β
Period (Univariate)	**0.0180**	**0.894**	---
Period (Final Model)[a]	-0.1765	0.043	-0.1945
Period + Gender	-0.0003	0.998	-0.0183
Period + Age	-0.0008	0.995	-0.0188
Period + Duration of Diabetes	0.0038	0.977	-0.0142
Period + BMI (V3-V1)	0.0720	0.598	0.0540
Period + HbA1c V1	-0.0309	0.742	-0.0489
Period + Time (V3-V2)	-0.0299	0.823	-0.0479
Period + Chronic Kidney Disease	0.0072	0.957	-0.0108
Period + Hyperthyroidism	0.0281	0.835	0.0101
Period + Metformin	-0.0349	0.794	-0.0529
Period + Sulfonylurea	0.0268	0.842	0.0088
Period + Mix Insulin	0.0180	0.893	0.0000
Period + NPH Insulin	0.0185	0.891	0.0005

Abbreviations: HbA1c, Glycosylated Hemoglobin; V(n), Visit (n); BMI, Body Mass Index

[a.] The final model included the following covariates: gender, age, duration of diabetes, BMI (V3-V1), HbA1c V1, Time (V3 – V2), Chronic Kidney Disease, Hyperthyroidism, Metformin, Sulfonylurea, Mix Insulin, and NPH.

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APPENDIX

Table A1: Correlation of Selected Continuous Variables Between Gold Standard Quality Control File Inputs and Corresponding File Inputs [a]

Model	Pearson Correlation Coefficient
HbA1c (%)	
Visit 1	1.0000 (0.0000)
Visit 2	1.0000 (0.0000)
Visit 3	1.0000 (0.0016)
Weight (kg)	0.9996 (0.0040)
Height (cm)	0.9999 (0.0024)
Date (day)	
Visit 1	0.9886 (0.0205)
Visit 2	0.9998 (0.0028)
Visit 3	0.9914 (0.0187)
Duration of Diabetes (year)	0.9828 (0.0255)
Cholesterol (mg/dL)	
LDL	0.9784 (0.0450)
HDL	0.9997(0.0055)
TC	0.9808 (0.0423)
TG (mg/dL)	0.9985 (0.0115)
Copay (%)	0.9732 (0.0325)

Abbreviations: HbA1c, Glycosylated Hemoglobin; LDL, Low-density Lipoprotein; HDL, High-density Lipoprotein; TC, Total Cholesterol; TG, Triglycerides

[a.] Comparing entries of 55 QC file inputs and original input.

Table A2: Selected Inter-rater Reliability Coefficients for Comorbidity and Medication Variables [a]

Model	Inter-rater Reliability Kappa Coefficient
Sulfonylurea	0.9242
MIX Insulin	0.9128
NPH Insulin	1.0000
Metformin	1.0000
Beta-Blockers	0.9483
Hydrochlorothiazide	0.8991
Statin	0.9532
Chronic Kidney Disease	1.0000
Hyperthyroidism	1.0000
Osteoporosis	1.0000

[a.] Comparing entries of 55 QC file inputs and original input.

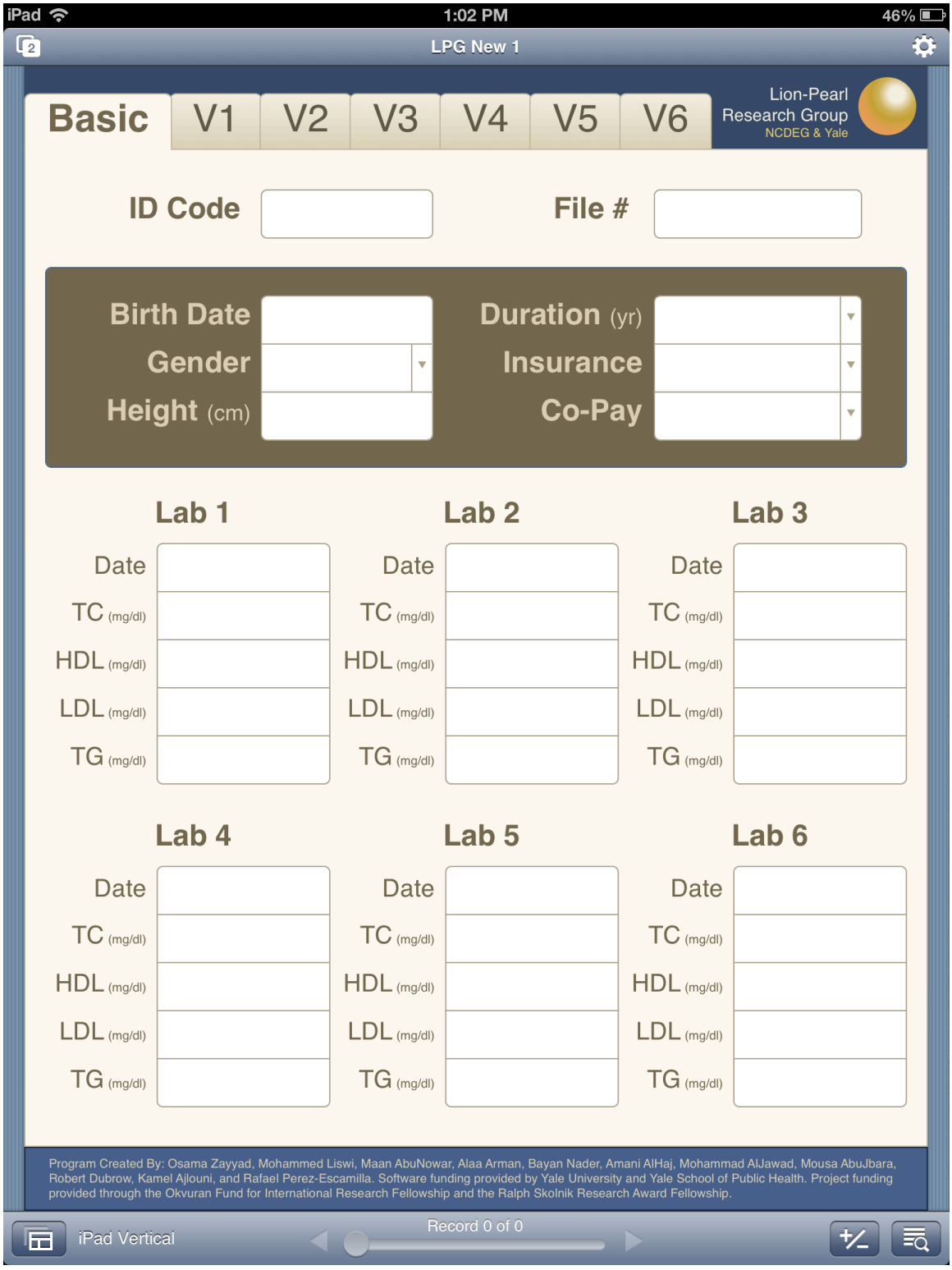

Illustration A.1: Screenshot of Basic Information and Lab Results Section of iPad Survey Application

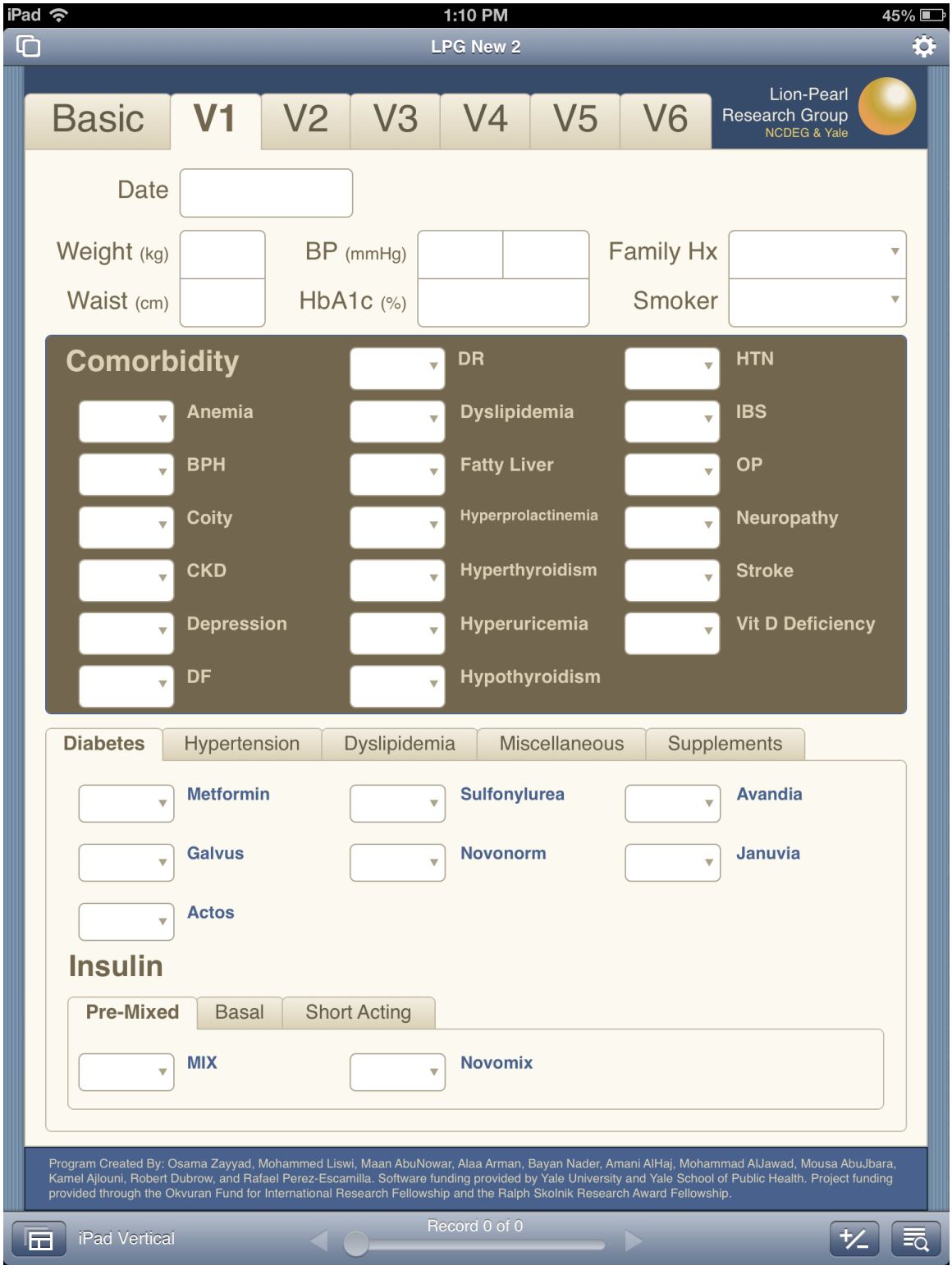

Illustration A.2: Screenshot of iPad Survey Application used to collect data for the study. Visit 1 with Diabetes Medication Section and Pre-mixed Insulin Subsection presented. All Visit pages include same data fields as Visit 1.

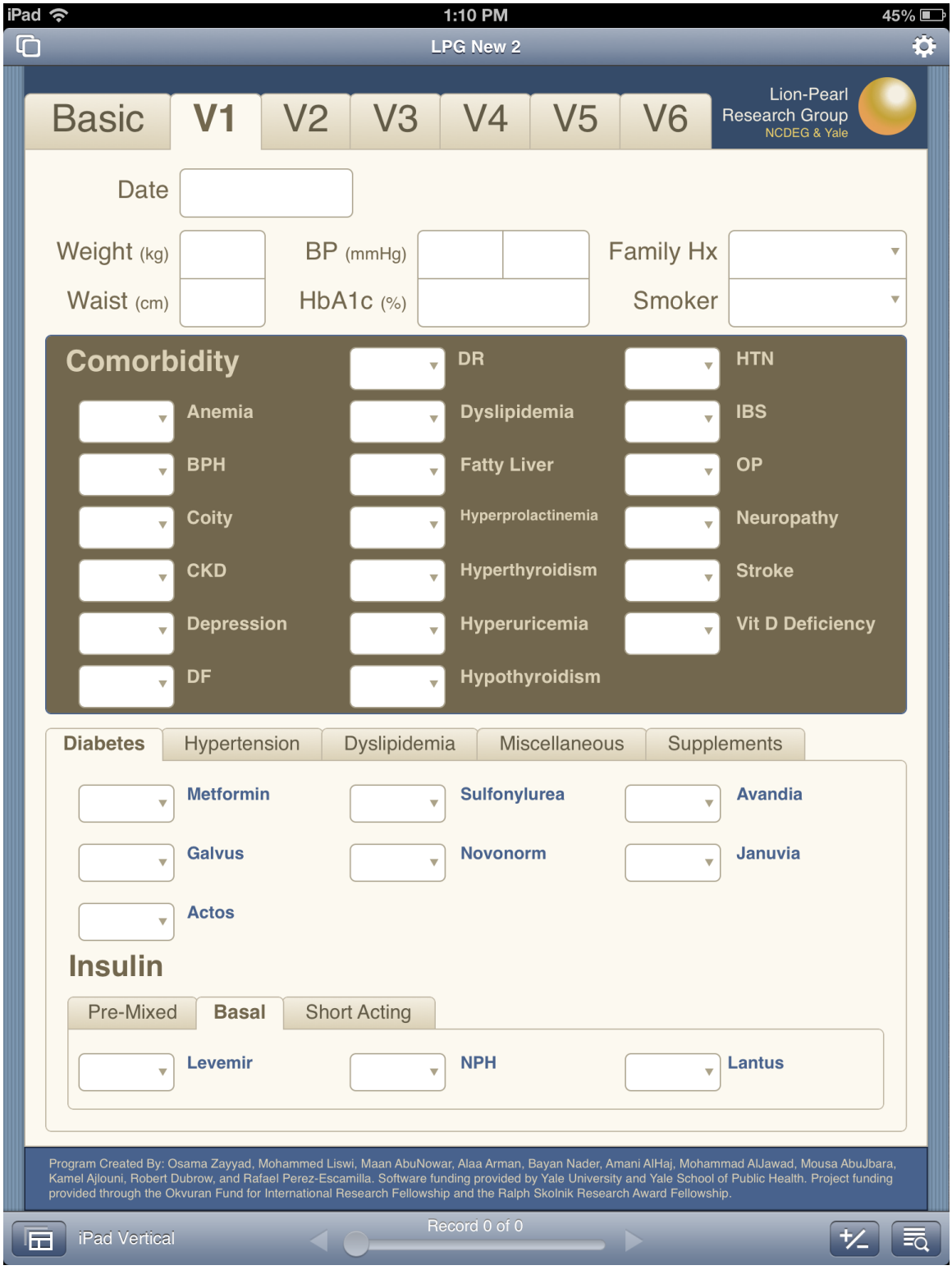

Illustration A.3: Screenshot of iPad Survey Application used to collect data for the study. Visit 1 with Diabetes Medication Section and Basal Insulin presented. All Visit pages include same data fields as Visit 1.

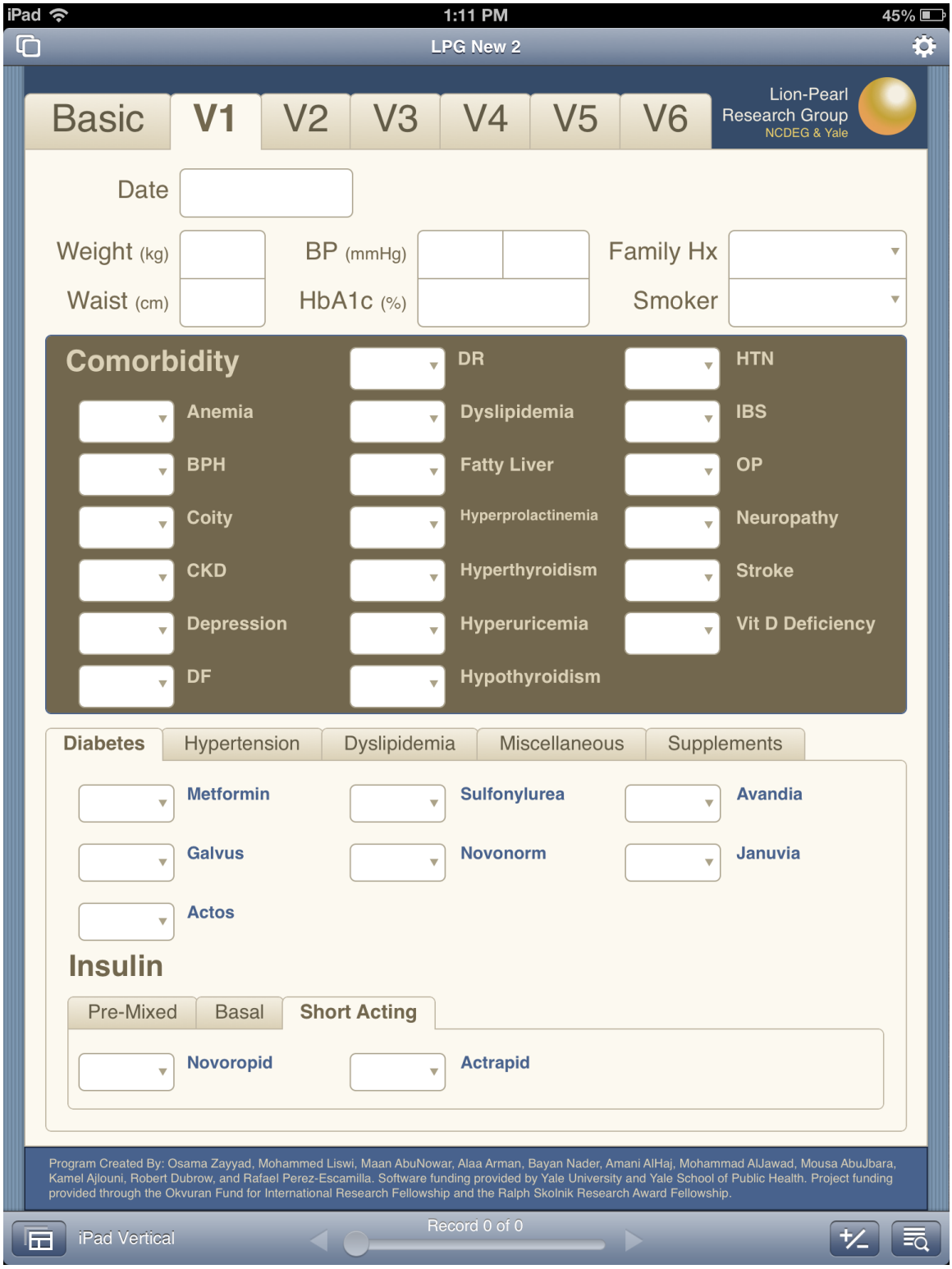

Illustration A.4: Screenshot of iPad Survey Application used to collect data for the study. Visit 1 with Diabetes Medication Section and Short Actin Insulin Subsection presented. All Visit pages include same data fields as Visit 1.

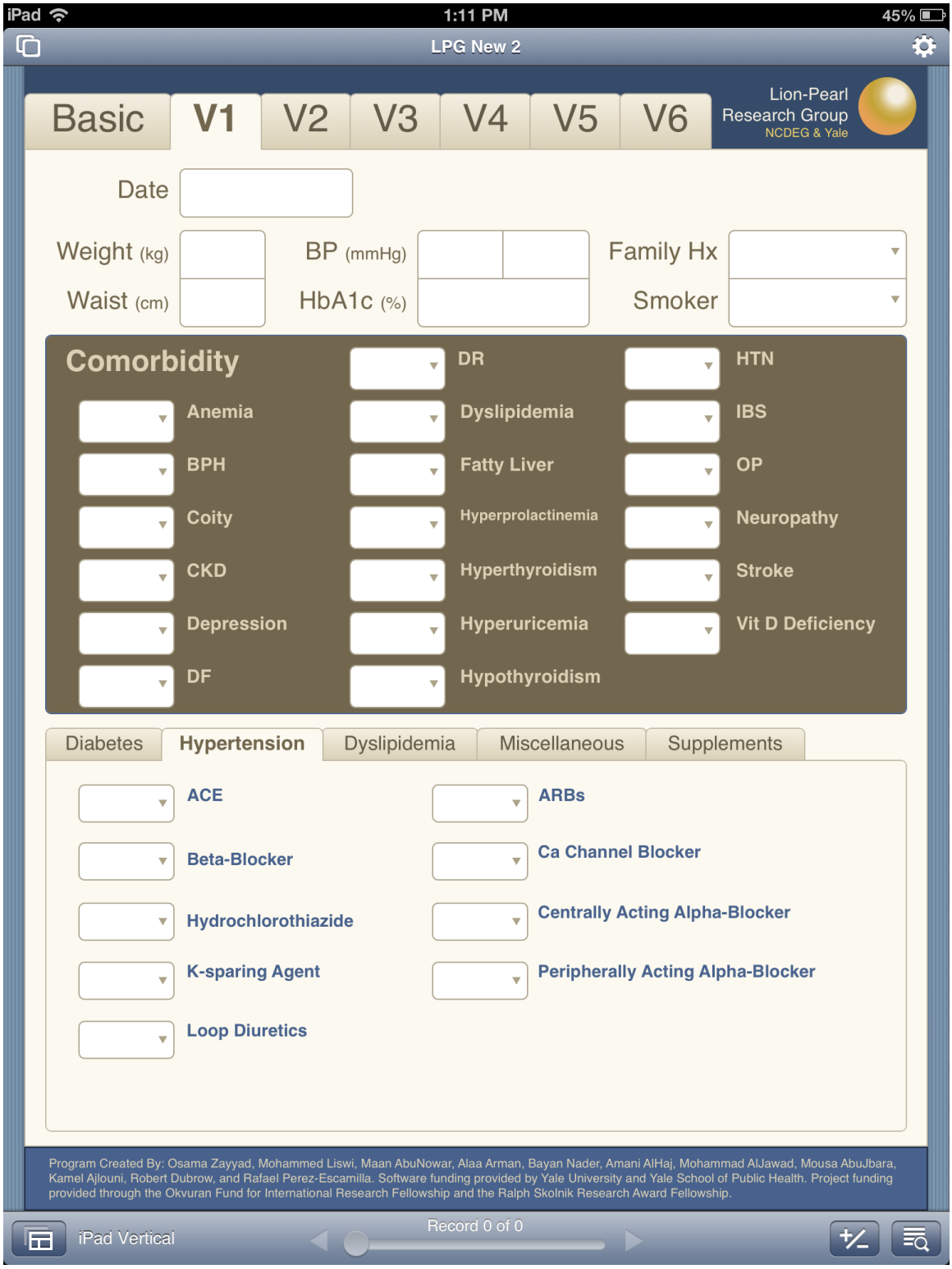

Illustration A.5: Screenshot of iPad Survey Application used to collect data for the study. Visit 1 with Hypertension Medication Section presented. All Visit pages include same data fields as Visit 1.

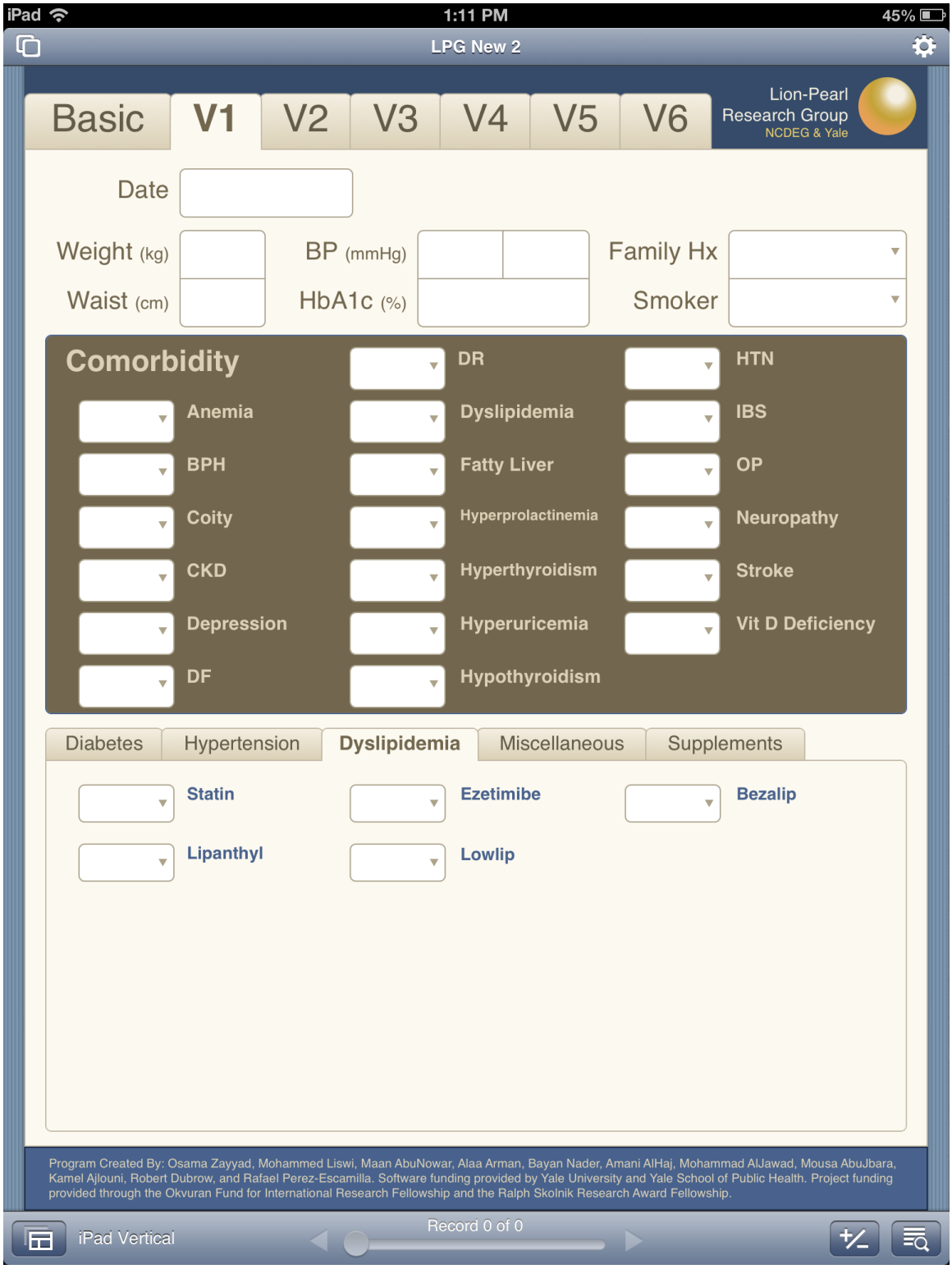

Illustration A.6: Screenshot of iPad Survey Application used to collect data for the study. Visit 1 with Dyslipidemia Medication Section presented. All Visit pages include same data fields as Visit 1.

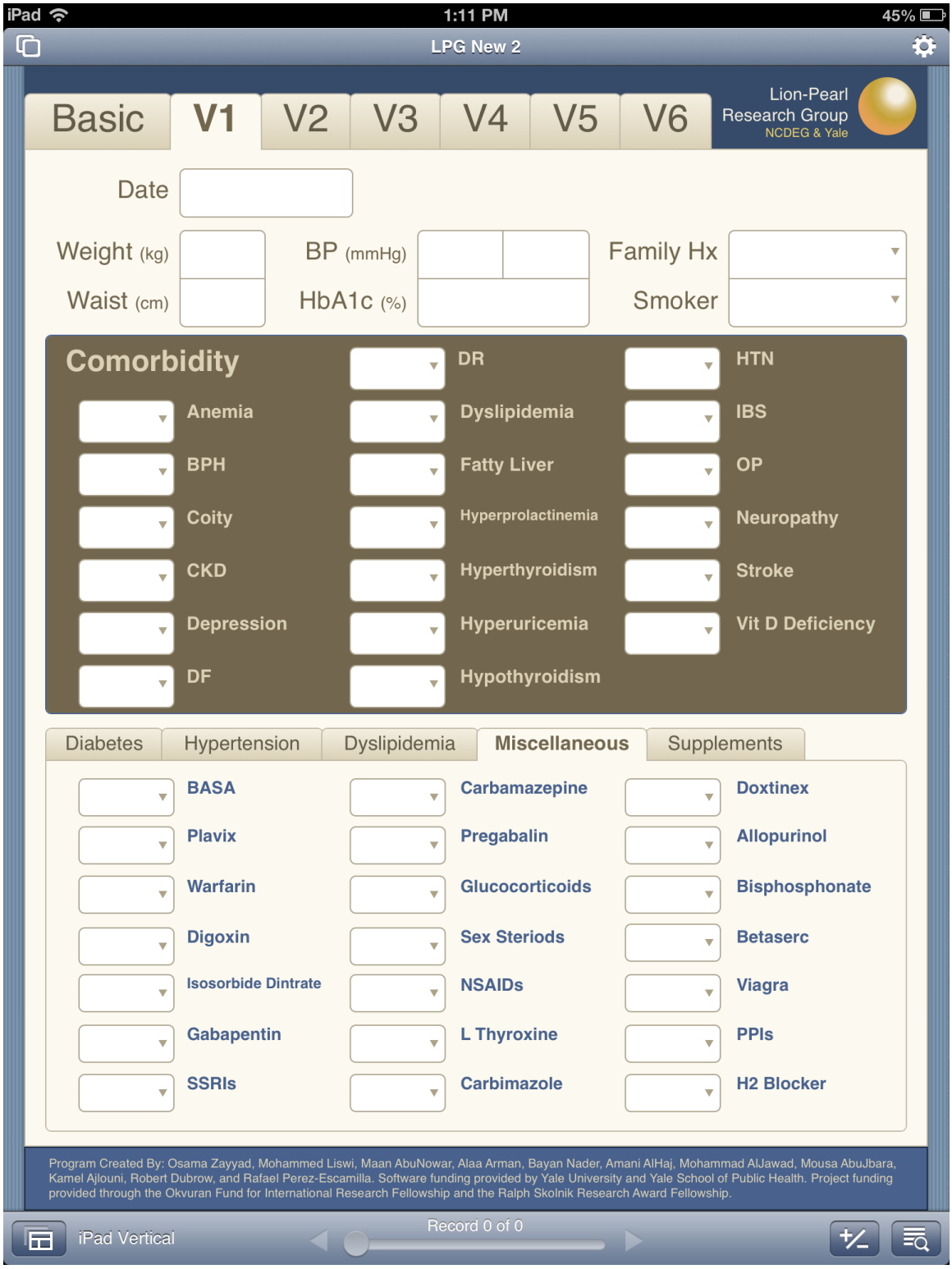

Illustration A.7: Screenshot of iPad Survey Application used to collect data for the study. Visit 1 with Miscellaneous Medication Section presented. All Visit pages include same data fields as Visit 1.

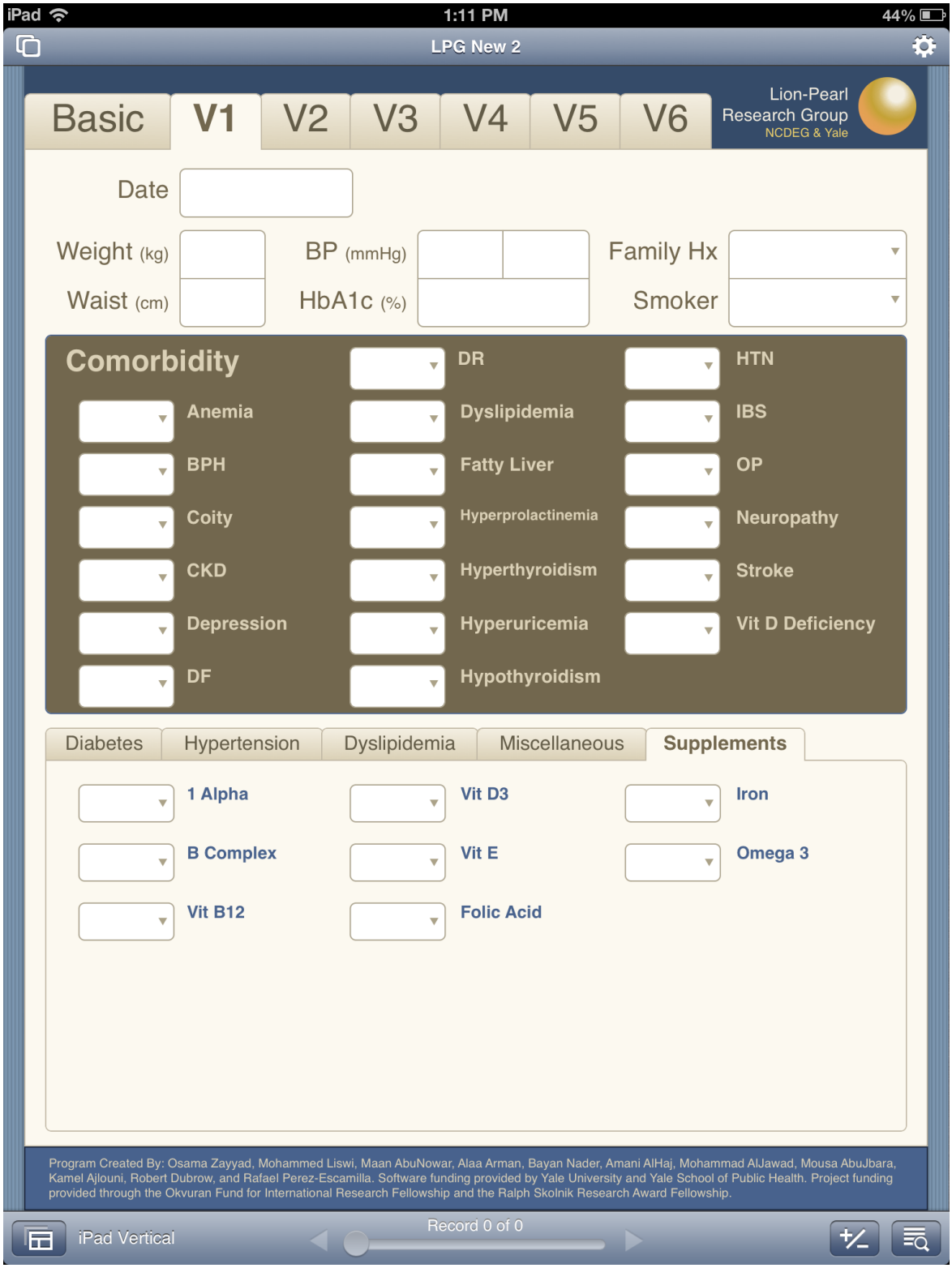

Illustration A.8: Screenshot of iPad Survey Application used to collect data for the study. Visit 1 with Supplements Section presented. All Visit pages include same data fields as Visit 1.