Predictors of Diabetes-related Distress (DRD) before and after FreeStyle Libre-1 use:

Lessons from Association of British Clinical Diabetologists (ABCD) nationwide study

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Abstract

Aim

The objective of this study was to identify the baseline demographic and clinical characteristics associated with Diabetes-related Distress (DRD) and factors associated with improvement in DRD with the use of FreeStyle Libre-1 (FSL) in people living withT1D.

Methods

The study was performed using baseline and follow up data from the ABCD nationwide audit of people with diabetes initiated on the FSL in the United Kingdom. DRD was assessed using the two-item diabetes-related distress score (DDS) (defined as the average of the two-item score ≥3). People living with T1D were categorised into two groups, a high DRD was defined as average DDS greater than or equal to 3 and lower DRD as DDS less than three. We used an unsupervised gradient boosting machine learning model (GBM) to identify the relative influence (RI) of baseline parameters on average DDS score.

Results

The study population consisted of 9,159 patients,96.6% of which had Type 1 diabetes, with a median age of 45.1 years (IQR=32-56), with 50.1% females with a median baseline BMI of 26.1 (IQR=23.2-29.6) and median duration of diabetes 20 (IQR=11-32) years. The two components of the DDS were significantly correlated (r2=0.73 P<0.0001). Higher DRD was prevalent in 53% (n=4879 of 9159) of people living with T1D at baseline. In the GBM model, the top baseline variables associated with average DDS were baseline HbA1c (RI=51.1), baseline GOLD score (RI=23.3), gender (RI=7.05) and fear of hypoglycaemia (RI=4.96). Follow up data were available for 3312 participants. The top factors associated with improvement

in DDS following use of FSL were change in GOLD score (RI=28.2) and change in baseline HbA1c (RI=19.3)

Conclusions

In this large UK cohort of people living with T1D, diabetes distress was prevalent and associated with higher HbA1c, impaired awareness of hypoglycaemia and female gender. Improvement in glycaemic control and hypoglycaemia unawareness with the use of FSL was associated with improvement in DRD in people living with T1D.

Introduction

Diabetes-related distress (DRD) is increasingly recognized as an important determinant of suboptimal glycaemic control and complication risk in people living with T1D [1-6]. DRD is distinct from depression and anxiety and is a product of dealing with the unrelenting demands and limitations that diabetes inflicts on the life of the person with diabetes[1, 7-9]. DRD arises from the demands of self-care associated with diabetes and is the product of emotional adjustments [1]. DRD in Type 1 Diabetes (T1D) is also distinct from diabetes-related distress score (DDS) in Type 2 diabetes given the demands of doing multiple daily insulin injections, frequent blood glucose monitoring, hypoglycaemia, and general burnout due to incessant management needs of T1D [2-5, 9].

There are minimal population-based studies looking at the prevalence of DRD in people living with T1D. Most of the data are reported from small cross-sectional studies, which are not representative of the whole population of people with T1D and report a prevalence of up to 40%[3-5, 10-13]. We [14] and others [15-17] have recently shown significant improvement in DRD with the use of Freestyle Libre (FSL). FSL is a novel method for glucose monitoring for people living with diabetes. It consists of a sensor, the size of a £2 coin, is worn on the arm and has a very fine sensing electrode, which is automatically inserted just under the skin when the user applies the sensor to the skin. It measures blood sugar readings in the subcutaneous fluid. In 2017, the FreeStyle Libre flash glucose monitor became available on the NHS Drug Tariff and is used by approximately 40% of people living with Type 1 diabetes in the United Kingdom. There are no data looking at factors associated with improvement in DRD with the use of FSL. It is important to identify the risk factors associated with DRD and the factors which influence the reduction in DRD with the use of

FSL. This can enhance the understating of the potential causes of DRD in people living withT1Dand thereby suggest strategies to alleviate it. The objective of this study was to identify the baseline demographic and clinical characteristics associated with DRD and the factors which are associated with improvement in DRD with the use of FSL.

Methods

Ethical Approval

The ABCD nationwide audit program has Caldicott Guardian approval. The program is an audit program, not research. The NHS encourages audit of clinical practice, and there are guidelines, which were followed, in particular, that contributing centres only collect data from routine clinical practice, and all data collected are anonymized at the point of submission to the central database.

Data collection

Data for this study were obtained from the nationwide audit of FSL conducted by ABCD (http://www.diabetologists-abcd.org.uk/n3/FreeStyle_Libre_Audit.htm). This nationwide audit commenced in November 2017 using paper forms to collect data, which were then entered onto a secure online tool on the NHS IT network. This network provides maximum security and allows the analysis of anonymized national audit data. The tool has the facility to detect data from the same patient entered in two sites (e.g., hospital and primary care) and to merge the data when exported. Data were collected at baseline and follow-up during routine clinical care. Baseline pre-FSL data included demographics, source of FSL funding, previous structured diabetes education completion, HbA1c values from the previous 12 months, Gold

score (15) (to assess hypoglycaemia awareness), severe hypoglycaemia, paramedic callouts, and hospital admissions due to hypoglycaemia, hyperglycaemia and DKA over the previous 12 months. We also collected diabetes-related distress scores at baseline and follow-up using the two-item diabetes distress screening instrument (DDS2)[18]. The DDS2 is a 2-item diabetes distress screening instrument asking respondents to rate on a 6-point scale the degree to which the following items caused distress: (1) feeling overwhelmed by the demands of living with diabetes, and (2) feeling that I am often failing with my diabetes regimen. DDS2 refers to a 2-item diabetes screening instrument, and DDS-1 and DDS-2 represent the two components of the instrument. A score of ≥3 (moderate distress) discriminated high- from low-distressed subgroups and provided the highest sensitivity and specificity for this cut-off [18]. Hence, we have used the cut-off of ≥3 (moderate distress) to discriminate high-distress from low distress. At follow-up, we collected data on DDS, HbA1c, GOLD score along with FSL-specific measures, such as the number of scans per day and time in range (TIR). The baseline DDS and variables relating to resource utilization such as episodes of severe hypoglycaemia, episodes of hypoglycaemia and hyperglycaemia requiring hospital admissions and paramedic callouts were measured at the first visit at the initiation of FSL. The follow-up variables were collected at the first follow-up visit after initiating the patients on FSL.

Statistical methods

For reporting all of the study outcomes, including HbA_{1c}, Gold score, paramedic outcalls, and hospital admissions, we restricted the statistical analysis to those with at least one follow-up data entry. The χ^2 test of association was used to compare categorical variables. The

Mann-Whitney *U* test or *t*-tests were used to compare continuous variables associated with improvement in DDS following the use of FSL.

Machine learning methods

For identifying risk factors for DDS and predictors of change in DDS following the use of FreeStyle Libre (FSL) we used a gradient boosting machine (GBM) learning model. Based on the input predictor variables, this machine learning algorithm consecutively fits new decision trees to provide a more accurate prediction of response. The primary idea of this algorithm is the learning procedure that results in consecutive error fitting, with each decision tree chosen to minimize the loss function [19, 20]. The GBM model generates the relative importance (RI) of each variable in the model by identifying if that variable was selected to split on during the tree building process and how much the squared error (overall trees) decreased as a result of this variable. Results from the GBM model are presented as variable importance for each reported as relative importance (RI). All analyses were conducted in R4.0.2 with library *GBM* and *CARET* (http://www.r-project.org/). For identifying the association with baseline DDS, we included 14 variables (supplementary table 1) in the GBM model, and for identifying variables associated with post FSL improvement in DDS, 24 variables were used in the GBM model. The post-FSL model had included a larger number of variables as it consisted of the derived variables from follow-up data with variables such as change in HbA1c (delta HbA1c) and Gold score (delta Gold). An average item score of ≥3 (high and moderate distress) discriminated high from the low-distressed subgroup, and a categorical variable was created to be used for GBM model at baseline and at the follow-up. In the GBM model, the data were divided into training (2/3 of the data) and testing set and the results from the training set were used in the testing set to calculate the

model accuracy. The model accuracy and the area under the curve (AUC) was evaluated using the testing dataset. The hyperparameters were selected using a grid search and are described in the supplementary material. We selected all the baseline and follow-up variables for the model building, which could affect DRD. This was based on both the clinical understanding of factors that can influence DRD and prior literature. We reported all RI of all the variables included in the model in supplementary materials. An essential advantage of using GBM models is that it deals with missing values as containing information rather than missing at random. During tree building, split decisions for every node are found by minimizing the loss function and treating missing values as a separate category. Although there were 3.4%, missing data for HbA1c and 14% missing data for Gold score, it is likely to have a minimal effect on prediction modelling.

Although GBM models have several advantages as compared to traditional regression analysis, the impurity-based feature importance in the GBM model has two disadvantages a) it calculates the variable importance based on training data, and b) it tends to favour high cardinality features. Permutation feature importance (PIMP) [21] is an alternative to impurity-based feature importance that does not suffer from these flaws. The permutation feature importance model ranks the variables in the model based on the increase in the model's prediction error after permuting the variable. If shuffling the variable values in the model increases the model error, then the variable is classed as "important" as the model relied on the feature for its prediction, whereas the variable is "unimportant" if shuffling its values leaves the model error unchanged. We have also used the random forest model as an alternative method of feature selection to confirm the results of GBM models. The random

forest can be used to find a set of predictors that best explains the variance in the response variable. This analysis was performed with R-packages "randomForest"," vita", and "varImp

The results of the machine-learning algorithm were examined using logistic regression analysis to understand the direction of the effect. The top predictors from the GBM model were included in the logistic regression model to understand the directionality of the effect estimate. For the baseline analysis, the DDS2 was converted into a categorical variable with of average (average of DDS-1 and DDS-2) DDS2 ≥3 (high and moderate distress) discriminated high from low distress. In the post-FSL follow-up model, those with average DDS2 ≥3 (high and moderate distress) at baseline and follow-up DDS2 of less than three were classed as having transitioned to lower DRD.

Results

Table 1 shows the baseline demographic and clinical characteristics of the study population. The study population consisted of 9,159 patients,96.6% of which had Type 1 diabetes, and the rest consisted of patients using FSL for other indications such as pregnancy, poorly controlled Type 2 diabetes, and renal dialysis. The median age of the study population was 45.1 years (IQR=32-56) and 50.1% females with a median baseline BMI of 26.1 (IQR=23.2-29.6)and median duration of diabetes 20 (IQR=11-32)years. The majority of the study participants had T1D (96.6%), with 23% using insulin pump therapy. The median baseline HbA1c was 67.5(IQR=58-79.3) mmol/mol and median GOLD score 2 (1-4). The mean DDS-1 and DDS-2 across the baseline study population were 3 (2-4). The overall prevalence of DRD (mean of DDS-1 and DDS-2 ≥3) was 53% (n=4879 of 9159). Of the 9,159 study participants, 3,312 had at least one follow-up DDS with a mean follow-up period of

7.2(±6.3) months. The baseline demographic and clinical characteristics of those with and without follow-up were similar.

Factors associated with baseline DDS

Figure 1 shows the results of the GBM model with the top 6 baseline variables associated with baseline average DDS. In the GBM model, the top baseline variables associated with average DDS were baseline HbA1c (RI=51.1), baseline GOLD score (RI=23.3), gender (RI=7.05) and fear of hypoglycaemia (RI=4.96). **Supplementary Table 1** shows the results of linear regression analysis and shows a statistically significant association of higher baseline HbA1c, higher baseline Gold Score and female gender with baseline DDS.

Supplementary Figure 1 and shows the results of the GBM model with top variables associated with DDS-1 and DDS-2. In the GBM model, the top baseline variables associated with DDS-1 were HbA1c (RI= 35.5), GOLD score (RI=22.5) and glucose variability as an indication for starting FSL (RI=15.02). The top baseline variables associated with DDS-2 were HbA1c (RI=48.7), GOLD score (RI=20.9) and female gender (RI= 5.6). The model accuracy was 0.44(0.42-0.47) for DDS-1 and 0.44 (0.42-0.46) for DDS-2. The AUC of the baseline DRD model was 0.69 (0.62-0.76). The findings of the machine-learning model were confirmed by using the top six variables in a logistic regression model, and these were significantly associated with DDS at $P<0.05$.

Figure 2a shows the mean DDS in those with hypoglycaemia awareness and hypoglycaemia unawareness at baseline. The DDS was significantly higher in those with hypoglycaemia unawareness (GOLD score >= four at baseline) (P-Anova<0.0001). **Figure 2b** shows three strata of baseline HbA1c and baseline DDS in each category. The mean DDS was lowest in those with baseline HbA1c <47.5 mmol/mol compared to those with HbA1c between 47.5 –

69.4 mmol/mol and highest in those with baseline HbA1c >69.4 mmol/mol (P-Anova<0.0001).

Supplementary figures 5A and 5B show the top variables associated with DRD using the random forest model and the Permutation feature importance model (PIMP). Both the models show results comparable to the GBM models with baseline HbA1c, Gold score, glucose variability and gender as important predictors of DRD

Factors associated with improvement in DDS following FSL use

In those with paired data, DDS-1 reduced from 2.4(±1.3) to 2.2(±1.2) (P<0.0001) while the DDS-2 reduced from 2.4(±1.3) to 2.2(±1.3) (P<0.0001). In those with paired data, following the use of FSL, the prevalence of moderate to severe distress on DDS2 reduced from 50% to 26%.

Table 2 shows the results of univariate analysis of those with and without improvement in DDS following the use of FSL. Improvement in DDS at follow-up was associated with lower follow up HbA1c and lower follow-up Gold score, higher baseline GOLD score.

Figure 3 shows the results of the GBM model with top variables associated with improvement in average DDS score with the use of FSL at follow-up. The top factors associated with improvement in DDS following use of FSL were change in GOLD score (RI=28.2) and change in baseline HbA1c (RI=19.3). **Supplementary Table 4** shows the results of linear regression analysis and shows a statistically significant association of reduction in GOLD score drop in baseline HbA1c with improvement with DDS.

Supplementary figure 2 shows the results of the GBM model with top variables associated with improvement in DDS score following the use of FSL. For the DDS-1 lower GOLD score at

follow-up (RI=39.8), lower follow up HbA1c (RI=18.3) and GOLD score (RI=11.58), and a higher number of FSL scans per day (RI= 8.65) were top factors associated with transitioning to a low DDS1 at follow-up. For DDS-2 absolute change in GOLD score (RI=38.2) and HbA1c (RI=32.5), follow-up GOLD score (RI=12.6) and a higher number of FSL scans per day (RI= 4.7) were top factors associated with transitioning to a low DDS-2 at follow-up. A reduction in HbA1c at follow-up had a higher influence on the change in DDS-2- failing' as compared to change in DDS-1 'overwhelmed' at follow-up. The model accuracy for DDS-1 model was 0.84 (0.81-0.86) and 0.80 (0.78-0.82) for the DDS-2 model. The AUC for the follow-up DRD model was 0.82 (0.71-0.86). The findings of the machine-learning model were confirmed by using the top six variables in a logistic regression model and these were significantly associated with DDS at $P<0.05$.

Supplementary figures 6A and 6B show the top variables associated with improvement in DRD using the random forest model and the Permutation feature importance model (PIMP). Both the models show results comparable to the GBM models with change in HbA1c and Gold score and time in target HbA1c over 14 days as top predictors of improvement in DRD.

Discussion

We present the results of the largest study looking at the factors associated with DDS in people with TID before and after the use of FSL in the United Kingdom. The prevalence of DRD is high. We show that improvement in HbA1c and hypoglycaemia awareness is associated with DRD in FSL eligible people with T1D in the UK population. We also show that improvements in HbA1c, hypoglycaemia awareness and a higher number of scans per day are associated with improvements in DRD in people living with TID.

Longitudinal population-based and cross-sectional studies in people living with T1D have demonstrated excess rates of depression compared to the non-diabetes population[1, 5-7]. However, numerous studies have shown that diabetes-related distress is often misinterpreted as depression in the T1D population [7-9]. There have been several small cross-sectional studies [5, 10, 13, 22]looking at DDS in TID, which have used several scales to measure DDS. The Diabetes Distress Scale (DDS17), a 17-item self-report measure [23] of overall diabetes distress, is the most commonly used measure to identify DRD. This score is used in assessing emotional burden, physical-related distress, regimen-related distress, and interpersonal distress associated with T1D. DDS17 [23] has been used in the USA and European populations to understand and quantify DDS. However, this is a long questionnaire and can be challenging to use in clinical settings and to screen for DRD in large population-based studies. As an alternative to DDS17, Lawrence et al. [18] developed a Brief Diabetes Distress Screening (DDS2) Instrument with two question screening instrument. The sensitivity and specificity of this composite instrument is 95% and 85%, respectively and can be used easily in clinical settings. In our nationwide study, we utilized this 2-point composite

instrument to understand the prevalence of DRD in T1D and the factors which affect it at baseline and predictors of improvement following flash glucose monitoring.

The baseline prevalence of DRD was high in our cohort, with 53% patients with moderate to severe distress as compared to previous studies, which have reported a prevalence of 40% [24, 25]. This is likely to reflect our study population, which was mostly restricted to those who fulfilled the criteria set for National Health Service (NHS) funding in the UK, limiting the generalisability of the conclusions. However, these access criteria have now resulted in more than 40% of people living with diabetes being reimbursed for the FSL, which indicates that the selection criterion will encompass a substantial proportion of people with T1D.

The association of DDS with baseline clinical and demographic characteristics in people with T1D is complicated by the hidden and complex correlation between the baseline clinical and demographic variables. We utilized GBM, a machine learning algorithm that has better efficiency in accounting for correlation, missing data, and outliers as compared to a standard regression analysis approach [20]. We show improvement in HbA1c has the largest relative influence on DDS1 (feeling overwhelmed with demands of living with diabetes), while the degree of hypoglycaemia unawareness (GOLD score) had the largest relative association with DDS2 (feeling that I am failing with my diabetes routine). Our study is in agreement with previous studies, which have shown the detrimental effect of higher HbA1c and hypoglycaemia unawareness in people with T1D[4, 13, 22, 24]. For example, a longitudinal study of 280 consecutive T1D patients in the UK population showed that DRD showed a significant correlation with HbA1c and Gold score independently and with synergistic effect[13]. Another study[4] in 450 adolescents with T1D in Australia showed a significant positive correlation between HbA1c and diabetes distress and showed that this correlation

was stronger than the relationship between HbA1c and depressive symptoms. Interestingly, the female gender was associated with DRD at baseline, which is in agreement with a previous study[13]. It is possible that the females have additional blood glucose variations during menstruation, pregnancy, and post-gestational period [26, 27]. These variations are more likely to cause hypoglycaemia unawareness and poor glycaemic control and can contribute to DRD. However, interestingly female gender was not the top predictors of the improvement in DRD following the use of FSL. This suggests that glucose monitoring is associated with improvement in DRD irrespective of gender. Further studies are needed to investigate the gender-specific causes of DRD in people with diabetes. Our data also shows that baseline BMI, the absolute value of HbA1c following the use of FSL, number of FSL scans per day and time in the range were associated with improved DRD with the use of FSL. It is possible that those with a higher baseline BMI, also had a higher baseline HbA1c [28] and hence had a larger improvement glycaemic control and hence it was associated with improvement in DRD. Interestingly BMI was not the top predictors of baseline DRD and agrees with the previous study in people living with T1D [29]. Our study also showed that engagement with FSL and improved time in range and HbA1c were amongst the top factors associated with improvement in DRD. Interestingly Polonsky et al. [30] recently described an association between better time in range with better mood. We are only starting to understand the relationship between time in range and psychological outcomes, and further analyses will be welcome [30].

We have recently shown that the use of FSL significantly improved glycaemic control, hypoglycaemia awareness and DRD in people living withT1D [14]. This cohort gave us a unique opportunity to assess the effects of baseline clinical and demographic features in FSL users and the associated changes in DRD in people living with T1D using the FSL. We showed

that improvements in hypoglycaemia awareness and glycaemic control had the largest influence on improvement in DRD when patients living with T1D used FSL. We also showed that engagement with FSL as evidenced by the number of FSL scans performed per day was associated with ad improvement in DRD. Higher HbA1c and impaired awareness of hypoglycaemia are associated with DRD , can have a negative impact on self-management, resulting in further DRD [1, 2, 10].

Our study had several limitations. The major limitations include the lack of a comparator arm and, being a real-world observational cohort study as opposed to a randomised controlled trial, opportunistic rather than systematically organised data collection. Furthermore, socioeconomic status has shown to be an important predictor of DRD and this variable was not captured in our nationwide dataset. Despite these limitations, the strength of our study was that these data represent the largest UK-wide, real-world data on looking at the baseline association of DRD and the effect of flash glucose monitoring on it. Further, our GBM models for baseline DRD had a moderate accuracy indicating that our models do not fully capture all the sources of DRD in this population. For the first time, we have shown that the use of flash glucose monitoring can improve diabetes-related distress by improving hypoglycaemia awareness and glycaemic control.

In summary, this real-world study demonstrates that high HbA1c and impaired awareness of hypoglycaemia are important risk factors for DRD. Our study shows that the use of the FSL, particularly with frequent scanning, can improve both glycaemic control and DRD in people living with T1D.

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The FSL audit was independently initiated and performed by ABCD, and the authors remain independent in the analysis and preparation of this report.

Author Contributions. E.G.W., C.W., R.E.J.R., and T.S. conceived the presented idea. H.D., E.G.W., C.W., R.E.J.R., and T.S. contributed to the data analysis. H.D. wrote the first draft of the manuscript. All of the authors contributed to the writing of the manuscript and made

extensive comments, criticism, and changes in the final draft of the paper. All of the authors saw the final version of the manuscript. H.D. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Table 1: Baseline demographic and clinical characteristics of the study population

	Baseline (n=915)	Follow-up(n=3312)
Age (years) (median IQR)	45.1 (32-56)	47 (34-58)
Sex, % females	4573 (50.1%)	2230(50.2%)
Baseline BMI (kg/m2) (median IQR)	26.1 (23.2-29.6)	26 (12-35)
Duration of diabetes (years) (median IQR)	20 (11-32)	22 (43.8)
Type 1 diabetes	8816 (96%)	4259 (96%)
Insulin pump	2157 (23%)	1020 (23%)
White Caucasians	7303 (80%)	3549 (80%)
pre-FSL HbA1c (mmol/mol) (median IQR)	67.5 (58-79.3)	66 (57-76.5)
Baseline Gold score (median IQR)	2 (1-4)	2 (1-4)
Mean DDS1 (median IQR)	3 (2-4)	3 (2-4)
Mean DDS2 (median IQR)	3 (2-4)	3 (2-4)

Table 2: Comparison of Demographic and clinical characteristics in those with and without improvement in DDS score following FSL

	Improvement in DDS following FSL use (970)	No change in DDS with FSL use (2342)	P-value
Age (years) mean (SD)	47.3(±15.3)	46.6(±15.2)	0.22
Sex, females	519 (53%)	1211 (51%)	0.36
Baseline BMI (kg/m2)	26.8 (±5.3)	26.6(±5.1)	0.96
Duration of diabetes (years)	25.4(±14.9)	25.6 (±14.8)	0.9
pre-FSL HbA1c (mmol/mol)	69.0 (±16.3)	67.9(16.2)	0.07
post FSL HbA1c (mmol/mol)	62.2 (±12.5)	63.6 (±14.5)	0.004
Baseline Gold score	2.7 (±1.7)	2.5 (±1.6)	0.0004
Post FSL Gold score	2.1(±1.3)	2.3 (±1.5)	0.01
Average number of FSL Scan in 14 days	12.5 (±13.8)	12.3(±12.4)	0.72

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Figure 1: GBM model with top 6 baseline variables associated with baseline Diabetes Related Distress (DRD)

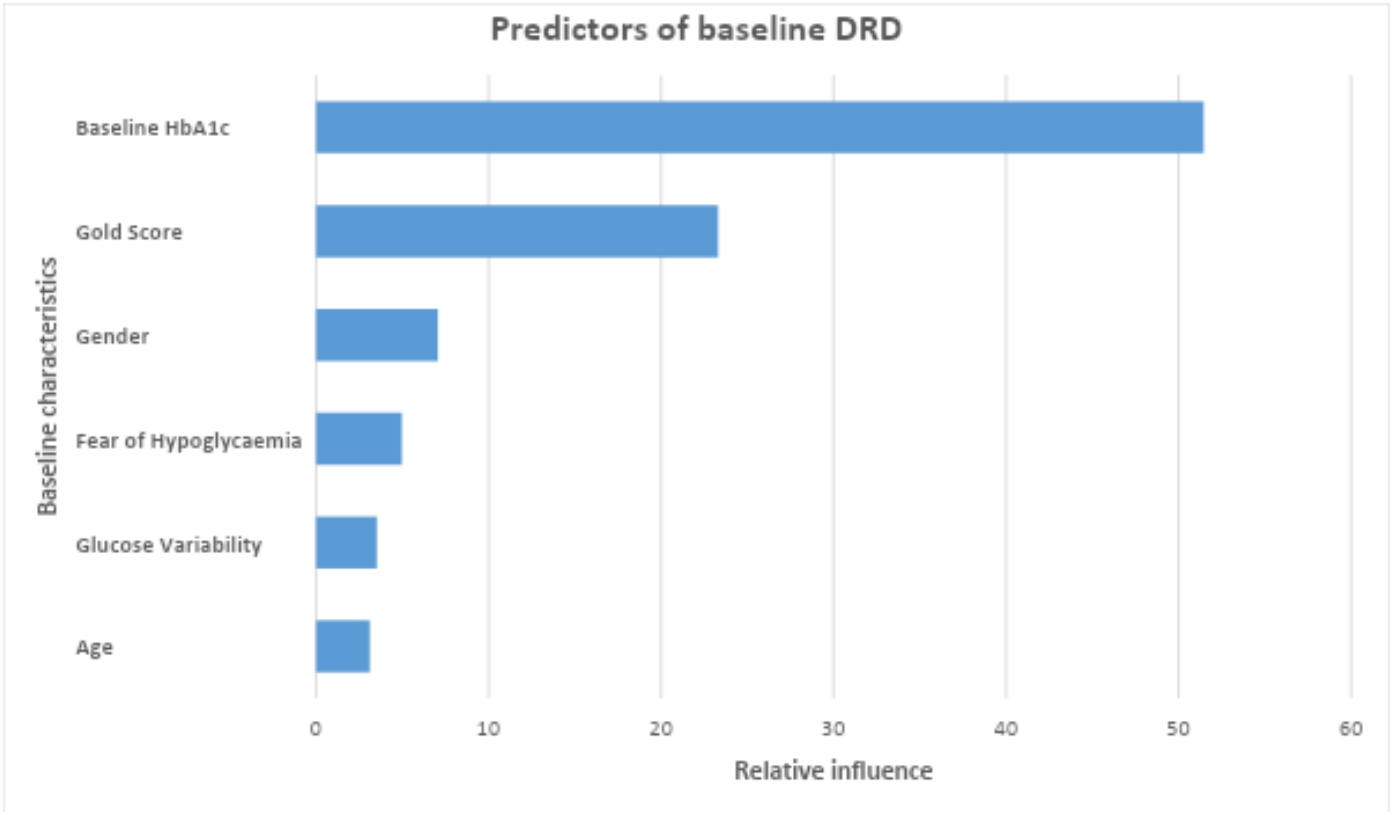
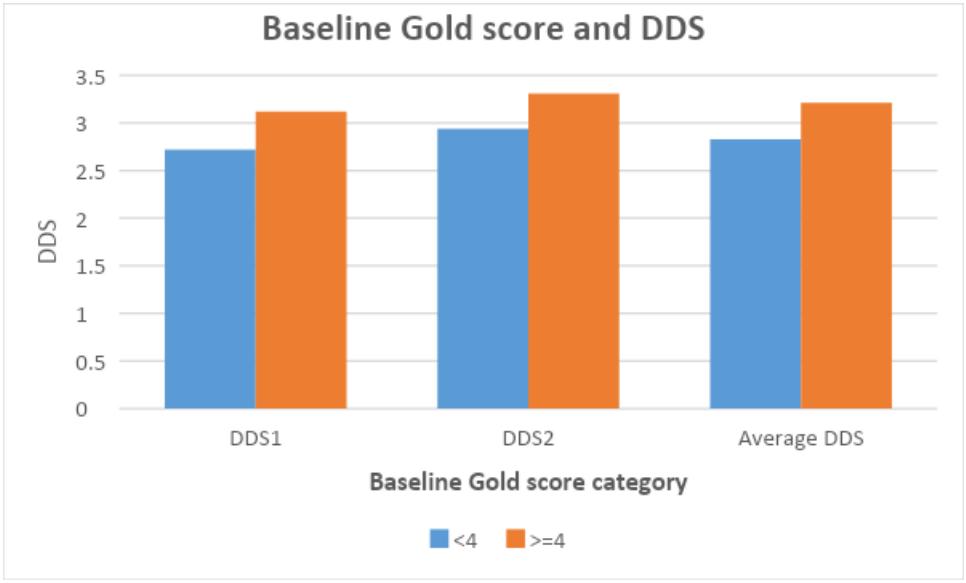


Figure 2a and 2b : Association of baseline Gold score and HbA1c with DRD



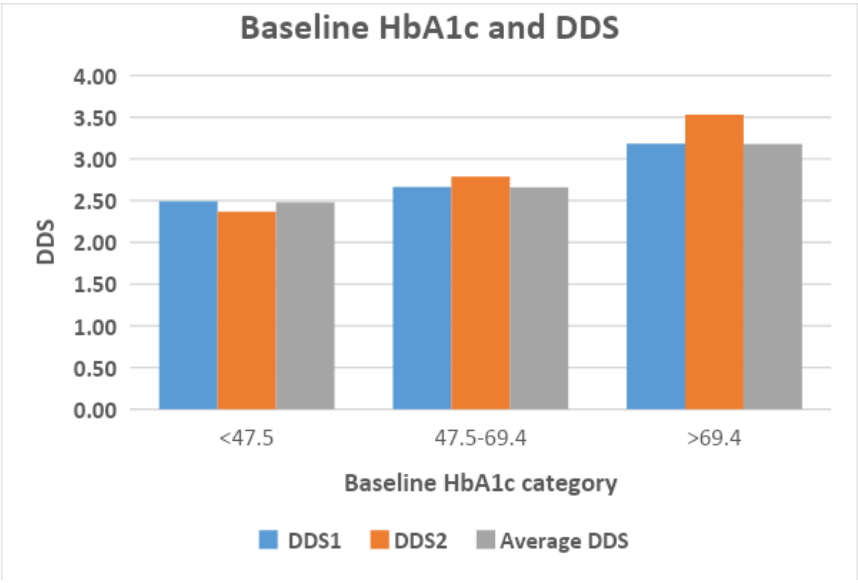
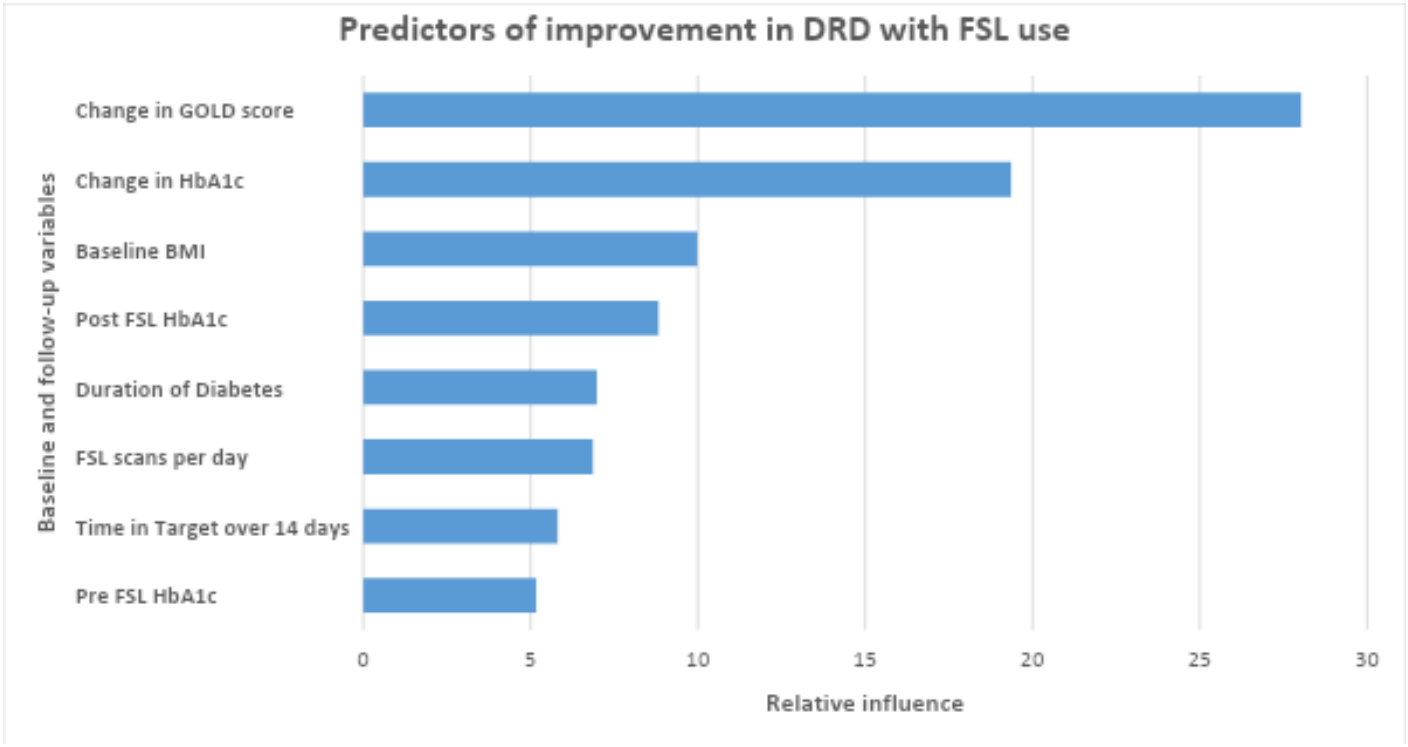


Figure 2a shows three strata of baseline HbA1c and baseline DDS in each category and **Figure 2b** shows three strata of baseline HbA1c and baseline DDS in each category

Figure 3: GBM model with top variables associated with improvement in average DDS score with use of FSL at follow-up



References

1. Berry E, Lockhart S, Davies M, Lindsay JR, Dempster M: **Diabetes distress: understanding the hidden struggles of living with diabetes and exploring intervention strategies**. *Postgrad Med J* 2015, **91**(1075):278-283.
2. Dennick K, Sturt J, Speight J: **What is diabetes distress and how can we measure it? A narrative review and conceptual model**. *J Diabetes Complications* 2017, **31**(5):898-911.
3. Hagger V, Hendrieckx C, Cameron F, Pouwer F, Skinner TC, Speight J: **Cut Points for Identifying Clinically Significant Diabetes Distress in Adolescents With Type 1 Diabetes Using the PAID-T: Results From Diabetes MILES Youth-Australia**. *Diabetes Care* 2017, **40**(11):1462-1468.
4. Hagger V, Hendrieckx C, Cameron F, Pouwer F, Skinner TC, Speight J: **Diabetes distress is more strongly associated with HbA1c than depressive symptoms in adolescents with type 1 diabetes: Results from Diabetes MILES Youth-Australia**. *Pediatr Diabetes* 2018, **19**(4):840-847.
5. Hagger V, Hendrieckx C, Sturt J, Skinner TC, Speight J: **Diabetes Distress Among Adolescents with Type 1 Diabetes: a Systematic Review**. *Curr Diab Rep* 2016, **16**(1):9.
6. Powers MA, Richter SA, Ackard DM, Craft C: **Diabetes Distress Among Persons With Type 1 Diabetes**. *Diabetes Educ* 2017, **43**(1):105-113.
7. Fisher L, Gonzalez JS, Polonsky WH: **The confusing tale of depression and distress in patients with diabetes: a call for greater clarity and precision**. *Diabet Med* 2014, **31**(7):764-772.
8. Fisher L, Polonsky WH, Hessler D: **Addressing diabetes distress in clinical care: a practical guide**. *Diabet Med* 2019, **36**(7):803-812.
9. Fisher L, Polonsky WH, Hessler DM, Masharani U, Blumer I, Peters AL, Strycker LA, Bowyer V: **Understanding the sources of diabetes distress in adults with type 1 diabetes**. *J Diabetes Complications* 2015, **29**(4):572-577.
10. Boden MT, Gala S: **Exploring correlates of diabetes-related stress among adults with Type 1 diabetes in the T1D exchange clinic registry**. *Diabetes Res Clin Pract* 2018, **138**:211-219.
11. Eilander MMA, Snoek FJ, Rotteveel J, Aanstoot HJ, Bakker-van Waarde WM, Houdijk E, Nuboer R, Winterdijk P, de Wit M: **Parental Diabetes Behaviors and Distress Are Related to Glycemic Control in Youth with Type 1 Diabetes: Longitudinal Data from the DINO Study**. *J Diabetes Res* 2017, **2017**:1462064.
12. Hood KK, Iturralde E, Rausch J, Weissberg-Benchell J: **Preventing Diabetes Distress in Adolescents With Type 1 Diabetes: Results 1 Year After Participation in the STePS Program**. *Diabetes Care* 2018, **41**(8):1623-1630.
13. Todd PJ, Edwards F, Spratling L, Patel NH, Amiel SA, Sturt J, Choudhary P: **Evaluating the relationships of hypoglycaemia and HbA1c with screening-detected diabetes distress in type 1 diabetes**. *Endocrinol Diabetes Metab* 2018, **1**(1):e00003.
14. Deshmukh H, Wilmot EG, Gregory R, Barnes D, Narendran P, Saunders S, Furlong N, Kamaruddin S, Banatwalla R, Herring R *et al*: **Effect of Flash Glucose Monitoring on Glycemic Control, Hypoglycemia, Diabetes-Related Distress, and Resource Utilization in the Association of British Clinical Diabetologists (ABCD) Nationwide Audit**. *Diabetes Care* 2020, **43**(9):2153-2160.
15. Nana M, Moore SL, Ang E, Lee ZX, Bondugulapati LNR: **Flash glucose monitoring: Impact on markers of glycaemic control and patient-reported outcomes in individuals with type 1 diabetes mellitus in the real-world setting**. *Diabetes Res Clin Pract* 2019, **157**:107893.
16. Pintus D, Ng SM: **Freestyle libre flash glucose monitoring improves patient quality of life measures in children with Type 1 diabetes mellitus (T1DM) with appropriate provision of education and support by healthcare professionals**. *Diabetes Metab Syndr* 2019, **13**(5):2923-2926.

17. Tyndall V, Stimson RH, Zammitt NN, Ritchie SA, McKnight JA, Dover AR, Gibb FW: **Marked improvement in HbA1c following commencement of flash glucose monitoring in people with type 1 diabetes**. *Diabetologia* 2019, **62**(8):1349-1356.
18. Fisher L, Glasgow RE, Mullan JT, Skaff MM, Polonsky WH: **Development of a brief diabetes distress screening instrument**. *Ann Fam Med* 2008, **6**(3):246-252.
19. Fukaya E, Flores AM, Lindholm D, Gustafsson S, Zanetti D, Ingelsson E, Leeper NJ: **Clinical and Genetic Determinants of Varicose Veins**. *Circulation* 2018, **138**(25):2869-2880.
20. Natekin A, Knoll A: **Gradient boosting machines, a tutorial**. *Front Neurorobot* 2013, **7**:21.
21. Altmann A, Tolosi L, Sander O, Lengauer T: **Permutation importance: a corrected feature importance measure**. *Bioinformatics* 2010, **26**(10):1340-1347.
22. Hessler DM, Fisher L, Polonsky WH, Masharani U, Strycker LA, Peters AL, Blumer I, Bowyer V: **Diabetes distress is linked with worsening diabetes management over time in adults with Type 1 diabetes**. *Diabet Med* 2017, **34**(9):1228-1234.
23. Polonsky WH, Fisher L, Earles J, Dudl RJ, Lees J, Mullan J, Jackson RA: **Assessing psychosocial distress in diabetes: development of the diabetes distress scale**. *Diabetes Care* 2005, **28**(3):626-631.
24. Nicolucci A, Kovacs Burns K, Holt RI, Comaschi M, Hermanns N, Ishii H, Kokoszka A, Pouwer F, Skovlund SE, Stuckey H *et al*: **Diabetes Attitudes, Wishes and Needs second study (DAWN2): cross-national benchmarking of diabetes-related psychosocial outcomes for people with diabetes**. *Diabet Med* 2013, **30**(7):767-777.
25. Perrin NE, Davies MJ, Robertson N, Snoek FJ, Khunti K: **The prevalence of diabetes-specific emotional distress in people with Type 2 diabetes: a systematic review and meta-analysis**. *Diabet Med* 2017, **34**(11):1508-1520.
26. Barata DS, Adan LF, Netto EM, Ramalho AC: **The effect of the menstrual cycle on glucose control in women with type 1 diabetes evaluated using a continuous glucose monitoring system**. *Diabetes Care* 2013, **36**(5):e70.
27. Goldner WS, Kraus VL, Sivitz WI, Hunter SK, Dillon JS: **Cyclic changes in glycemia assessed by continuous glucose monitoring system during multiple complete menstrual cycles in women with type 1 diabetes**. *Diabetes Technol Ther* 2004, **6**(4):473-480.
28. Phelan H, Foster NC, Schwandt A, Couper JJ, Willi S, Kroschwald P, Jones TW, Wu M, Steigleder-Schweiger C, Craig ME *et al*: **Longitudinal trajectories of BMI z-score: an international comparison of 11,513 Australian, American and German/Austrian/Luxembourgian youth with type 1 diabetes**. *Pediatr Obes* 2020, **15**(2):e12582.
29. Wardian JL, True MW, Folaron I, Colburn J, Tate JM, Beckman DJ: **The Choice Should Be Yours: Diabetes-Related Distress by Insulin Delivery Method for People with Type 1 Diabetes**. *Diabetes Technol Ther* 2020, **22**(1):42-47.
30. Polonsky WH, Fortmann AL: **The influence of time in range on daily mood in adults with type 1 diabetes**. *J Diabetes Complications* 2020, **34**(12):107746.