Original Article

Screening of Individuals with Type 2 Diabetes on Anti-Diabetic Agents for Probable Hypoglycaemia Using the Stanford Hypoglycemia Questionnaire (SHQ) in Outpatient Settings: A Cross-Sectional Study from Outpatient Diabetes Care Centres in North India

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Abstract

Introduction: The study was aimed at identifying the incidence of unreported probable hypoglycaemia in individuals with type 2 diabetes (T2DM) on anti-diabetic medications, using the screening Stanford Hypoglycemia Questionnaire (SHQ) in real-world situations. **Methods:** It was a multicentre cross-sectional study on consecutive individuals attending 10 diabetes care centres in Lucknow, Uttar Pradesh, India. The inclusion criteria were as follows: known individuals with T2DM, literate, age greater than or equal to 18 years, on at least one anti-diabetic agent for more than a month and not engaged in regular self-monitoring of blood glucose (SMBG). **Results:** This study was conducted from August 2017 to April 2018, involving 1198 participants. The mean age of the individuals enrolled was 53.45 years (±10.83), with males comprising 55.3% of the population. It was found that 63.6% of patients were on sulphonylurea (SU), 14.5% were on pioglitazone, 92.2% on metformin, 62.3% on Dipeptidyl peptidase (DPP4i) and 12.8% on Sodium-glucose cotransporter (SGLT2i). The mean SHQ score was 1.81 (±1.59). Probable hypoglycaemia was mild in 57.59%, moderate in 14.69% and severe in 1.41%. Those with diabetic neuropathy (P = <0.001), retinopathy (P = <0.001) and nephropathy (P = <0.001) had significantly higher SHQ scores. Insulin or SU use was associated with a significantly higher SHQ score. Concomitant statin use was associated with a lower incidence of mild, moderate and severe hypoglycaemia (P = 0.01). On multivariate analysis, we found that age, sex, systolic blood pressure (SBP), insulin use and fasting blood sugar were the most important factors associated with an increased risk of hypoglycaemia with an R^2 cut-off of 0.7. **Conclusion:** SHQ was discovered to be a simple and cost-effective screening tool for outpatient detection of hypoglycaemia in an Indian setting, and it can add value to management.

Keywords: Hypoglycaemia, insulin, Stanford Hypoglycemia Questionnaire (SHQ), sulphonylurea

Introduction

In pursuit of achieving glycaemic targets recommended by various societies in the management of type 2 diabetes (T2DM), hypoglycaemia appears as a natural consequence. Increased hypoglycaemia is limited not only to insulin and

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sulphonylurea (SU) use but also occurs with other drugs alone or in combination.[1] Hypoglycaemia becomes more challenging in the presence of renal, cardiac or neurocognitive co-morbidities and special populations such as the elderly.[1] It is well known that even a single episode of hypoglycaemia does increase mortality and morbidity in people with diabetes, especially in the elderly and those with organ dysfunction.[1]

Unreported hypoglycaemia creates a hidden burden of complications over reported ones. Mild-to-moderate hypoglycaemia is particularly under-reported as patients infrequently associate the symptoms with low blood glucose levels.[2] Additionally, defective glucose counter-regulation may lead to an impaired response to hypoglycaemia or may present with inappropriately milder symptoms.[3]

As per the Centre for Disease Control and Prevention (CDC), the daily self-monitoring of blood glucose (SMBG) among persons with diabetes in the United States has increased over the past several decades. The International Federation of Diabetes (IDF) advised against using SMBG unless both the diabetic patient and their healthcare provider had the knowledge, expertise and commitment to go above the standard of care.[4] Lack of resources may make it difficult for many regions of the world to implement the numerous SMBG-related recommendations.[4] The majority of T2DM patients who are not using insulin do not benefit from routine SMBG, and evidence from clinical trials indicates neither glycaemic control nor hypoglycaemia improves.[5]

A large number of patients do not practice SMBG and therefore are unable to correlate their symptoms with mild-to-moderate hypoglycaemia.[6] This issue is more relevant in countries such as India, where the quality of care is not uniform and more than three-fourths of health care is provided by non-government-funded organizations. The service distribution is skewed towards urban and semi-urban areas, while three-fourths of the Indian population live in rural areas.[7] Hence, this study was planned to find the prevalence of symptoms of probable hypoglycaemia among people with T2DM on anti-diabetic medications using the Stanford Hypoglycemia Questionnaire (SHQ).

Material and Methods

This was a multicentre cross-sectional study on 1198 individuals at 10 diabetes clinics in Lucknow, Uttar Pradesh, India.

Written informed consent was obtained for participation in the study.

The inclusion criteria were as follows: known individuals with T2DM, literate, age ≥18 years, on at least one anti-diabetic agent for more than a month and not engaged in regular SMBG.

The exclusion criteria were as follows: pregnancy, use of herbal or alternative medications and recent acute illness within a month requiring hospitalization.

The SHQ is a well-validated questionnaire initially developed in Spanish and later translated into English.

With a desired precision of 5% (two-tailed), a 95% confidence interval and a power of 80%, the estimated sample size required was 984, assuming an expected portion of the population of 20% ($P = 0.2$). Considering an anticipated non-response rate of 10%, the minimum sample size needed was 1093. In this study, 1198 individuals were screened using the SHQ.

The study was conducted by Good Clinical Practice and the Declaration of Helsinki (2000). Ordinal regression or the proportional odds algorithm is used to model the relationship between hypoglycaemia symptoms with studied parameters.

Table 1: Comprehensive table for all the factors modelled with hypoglycaemia

	Male (663)			Female (535)			Total		
	Mean	*n*	SD	Mean	*n*	SD	Mean	*n*	SD
Age (years)	53.9	663	11.79	52.9	535	10.28	52.8	1198	11.15
Weight (Kg)	71.6	663	13.32	65.7	535	12.48	68.9	1198	13.27
Height (cm)	165.0	663	7.45	153.5	535	6.88	159.8	1198	9.19
*BMI (kg/m^2)	26.3	663	4.42	27.9	535	5.10	27.0	1198	4.80
Pulse (bpm)	86.1	662	11.96	90.4	534	12.83	88.0	1195	12.53
Abdomen circumference (cm)	96.0	661	11.20	97.7	535	12.51	96.8	1196	11.83
SBP (mmHg)	131.8	663	15.81	132.3	535	17.88	131.9	1197	16.77
DBP (mmHg)	80.4	663	8.94	80.1	535	9.84	80.3	1197	9.35
FBS (mg/dl)	139.7	583	55.14	148.7	454	59.30	143.6	1037	57.14
PPBS (mg/dl)	203.9	585	75.83	213.5	449	85.39	208.1	1034	80.22
HbA1c (%)	8.0	547	34.22	8.12	416	5.75	8.96	964	26.06
Serum creatinine (mg/dL)	1.1	504	0.66	0.9	377	0.56	1.11	880	0.63
UACR (mcg/mg)	58.8	43	75.78	356.9	22	875.52	159.7	65	524.88
eGFR (mL/min/1.73m^2)	91.5	505	37.86	82.1	376	29.18	87.5	880	34.72
SHQ score	1.5	663	1.45	2.2	535	1.64	1.82	1198	1.57

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, FBS: fasting blood sugar, PPBS: postprandial blood sugar, UACR: urine albumin-creatinine ratio, eGFR: estimated glomerular filtration rate, SHQ: Stanford Hypoglycemia Questionnaire

In ordinal logistic regression, the event of interest is observing a particular score. Multivariate analysis was applied to all the factors that were significantly associated with hypoglycaemia. In this study, the scores are defined as follows: A score of 0 indicates no symptoms, 1 to 3 indicates mild, 4 to 5 indicates moderate and 6+ indicates severe (hierarchy scoring: mild >moderate >severe), and more than 50 parameters [Table S6] were assessed.

Ethical aspect

The informed written consent was taken from each participants for the study and the ethics committee approval for the study was obtained from the Sanjivani Lung Centre Ethics Committee (approval reference—ECR/963/Inst/UP/2017), dated July 14, 2017.

Results

During the study period of August 2017 to April 2018, 1198 patients were included. Of these, 55.3% were males. The mean age was 53.45 (±10.83). SU was prescribed to 63.6%, pioglitazone to 14.5%, metformin to 92.2%, Dipeptidyl peptidase (DPP4i) to 62.3% and Sodium-glucose cotransporter (SGLT2i) to 12.8% of the study population. The mean SHQ score was 1.81 (±1.59) [Table 1].

The overall incidence of hypoglycaemia was 73.62% of participants, and it was symptomatically mild in 57.6%, moderate in 14.7% and severe in 1.4% [Tables S2-S4 and Figures S5-S7]. Mild symptoms were more common among males (55% vs. 45%), but there was a reversal of the ratio observed with an increase in severity with females numerically having severe symptoms twice in comparison with males [Table S9].

The respective log odds go up for individuals with neuropathy (0.839) ($P<0.001$), retinopathy (1.111) ($P<0.001$), nephropathy (0.796) ($P = 0.004$), insulin use (0.483) ($P = 0.009$) and SU use (0.321) ($P = 0.02$) [Figures S2 and S3], hence increasing the likelihood of scoring higher on SHQ. Individuals who use metformin ($P = 0.004$) and statin ($P = 0.01$) tend to fall into lower categories of hypoglycaemia symptoms depicting an inverse relationship [Figure 1, Table S5 and Figure S4].

The respective log odds decrease with metformin use (-0.625) and statin use (-0.339), increasing the likelihood of falling into lower levels of hypoglycaemia symptom, viz. severe <moderate <mild.

With incremental fasting blood sugar (FBS) (mg/dl) ($P=<0.001$), postprandial blood sugar (PPBS) (mg/dl) ($P = <0.001$), systolic blood pressure (SBP) (mm/Hg) ($P = <0.001$) and age (years) ($P = <0.001$), the log odds increase the SHQ score, hence the more severe degree of hypoglycaemia [Figure S1 and Table S1]. For falling into higher levels of hypoglycaemia, viz. mild >moderate >severe [Figure 2], respective proportional odds confirm the same.

With incremental estimated glomerular filtration rate (eGFR) (mL/min/1.73 m2), the log odds decrease for falling into higher levels of hypoglycaemia indicating an inverse relationship.

The proportional odds go down by (-0.006) for eGFR (mL/min/1.73 m2), hence increasing the likelihood of a lower SHQ score.

On a multivariate analysis taking into account all the factors that were significantly associated with hypoglycaemia, such as age, weight, sex, FBS, PPBS, SBP, eGFR, neuropathy, retinopathy, nephropathy, metformin, insulin, statin and SU, we found that age, sex, SBP, insulin use and fasting blood sugar were the most important factors associated with an increased risk of hypoglycaemia with R^2 cut-off of 0.7 [Supplementary Figure S5 and Tables 2, S7, S8].

Discussion

We found nearly three-fourths of individuals had some form of hypoglycaemia, of which one of every six individuals had moderate-to-severe hypoglycaemia [Figure S3]. Hypoglycaemia was found to be associated with the use of SU and insulin. Complications such as retinopathy, neuropathy and nephropathy were found to be associated with higher SHQ

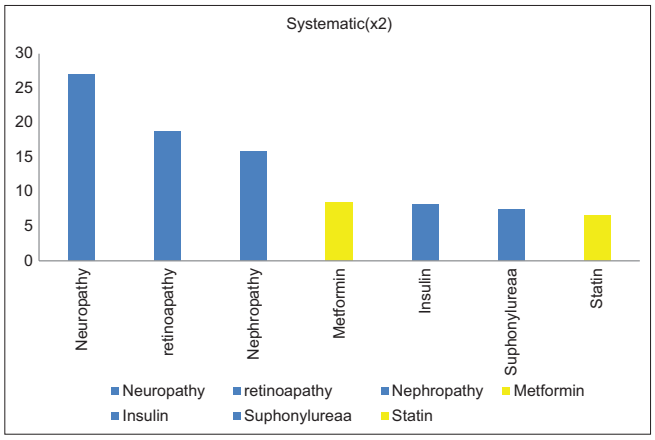

Figure 1: Association of Various Binary Significant Factors with the hypoglycemia symptom

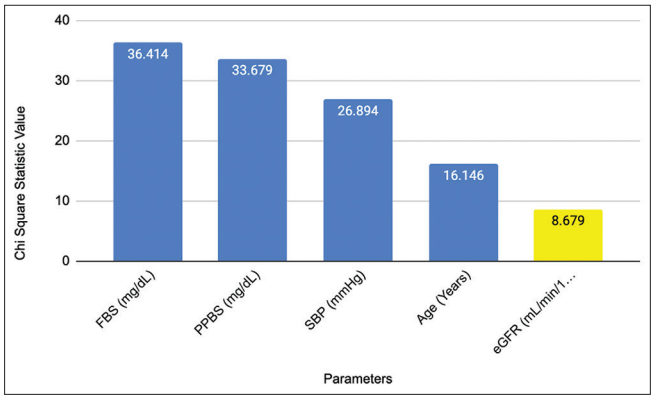

Figure 2: Association of various continuous significant factors with the hypoglycaemia symptoms

Table 2: Multivariate analysis with various parameters, which was significantly associated with hypoglycaemia

Variable(s)	Unstandardised beta	Standard error	Degree of freedom	Level of significance	Odds ratio
Age in Years	0.017	0.007	1	0.010	1.017
Sex	0.492	0.148	1	0.001	1.636
SBP (mmHg)	0.013	0.005	1	0.006	1.013
Any insulin use	-0.659	0.251	1	0.009	0.517
FBS (mg/dl)	0.009	0.002	1	<0.001	1.009
Constant	-2.392	0.717	1	0.001	0.091

a. Variable(s): Age in Years, Sex, SBP (mmHg)—systolic blood pressure, ANY INSULIN USE, FBS (mg/dl)—fasting blood sugar, constant.
b. B- Unstandardised beta, S.E.—standard error, df—degree of freedom, Sig.—level of significance, Exp.(B)—odds ratio. The probability of experiencing at least one symptom of hypoglycaemia can be calculated using the following formula: Probability=exp (-2.392+0.17 * Age in Years + 0.492 * 1 (for male) + 0.13 *SBP mmHg - 659 *ANY INSULIN USE (Yes) + 0.009 * FBS mg/dl)/(1+ exp (-2.392+0.17 * Age in Years + 0.492 * 1 (for male) + 0.13 * SBP mmHg - 659 * ANY INSULIN USE (Yes) + 0.009 * FBS mg/dl))

scores. Metformin and statin use was associated with a reduced probability of hypoglycaemia. Increasing age and SBP were more associated with hypoglycaemia. As the eGFR reduced, the probability of having hypoglycaemia increased.

Hypoglycaemia was found to be multifactorial, implying the need for a multimodal approach to mitigate the risk of hypoglycaemia.

Similar to our study, Edridge *et al*.[8] reported that the incidence of mild-to-moderate and serious hypoglycaemia is approximately 45% and 6%, respectively, with oral anti-diabetic agents, and 50% and 21%, respectively, in people using insulin.

The Hypoglycemia Assessment Tool (HAT) study, which is a large non-interventional real-world study of hypoglycaemia, assessed hypoglycaemia in 27 585 individuals across 24 countries and concluded that hypoglycaemia episodes are often unrecognised or unrecorded by patients.[9] Our study is unique for the evaluation of hypoglycaemia based on a validated questionnaire and correlated important parameters, which may directly or indirectly have an impact on glycaemic control.[10]

Furthermore, SU and insulin use had been associated with a higher risk of hypoglycaemia, which had been a focus of intense discussion after Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE), Veterans Affairs Diabetes Trial (VADT) and Action to Control Cardiovascular Risk in Diabetes (ACCORD) trials, suggesting adverse cardiovascular events linked with hypoglycaemia.[11-13] A recent study from North India quantified the burden of hypoglycaemia using the SHQ score and showed a positive correlation between hypoglycaemia using the SHQ score and glycaemic control, when SUs were used to achieve glycaemic control after the failure of another antihyperglycaemic regimen.[14] Patients in India lack the necessary structured education towards the recognition and prevention of hypoglycaemia, which is a cornerstone in the management of diabetes. The association between higher SHQ scores and higher SBP observed in this study could be attributed to an exaggerated blood pressure response, which persists for hours even after a single episode of hypoglycaemia.[15]

There are a paucity of data about the prevalence, impact, assessment and management of hypoglycaemia in this susceptible and high-risk population that commonly uses SU and also has limited access to SMBG devices.[16] Interestingly, apart from the expected correlation of hypoglycaemia with SU and insulin drug class and chronic kidney disease, we found that statin use reduces the risk of hypoglycaemia of all degrees. In the Jupiter trial, there was an increased number of physicians reporting diabetes (270 reports of diabetes in the rosuvastatin group vs 216 in the placebo group ($P = 0.01$)).[17] The hypothesis suggested is that statins cause hyperglycaemia by increasing calcium concentration in the islet cells, leading to a decrease in insulin release or by decreasing glucose transporter type (GLUT)-4-mediated peripheral glucose uptake.[18] This corroborates with the findings of our study that a lesser incidence of hypoglycaemia in statin users might be secondary to statin-induced hyperglycaemia.

Long-term statin use is associated with a reduced risk of anxiety, depression and hostility.[19] Many of the components of SHQ overlap with the symptoms of these conditions. Our finding may be due to the pleiotropic effects of the use of statin.

The study's strength is the ease with which this well-validated questionnaire can be used in clinical settings. This questionnaire has limitations because it provides a probability but does not objectively measure hypoglycaemia. Because of the low cost of this questionnaire, it can be used to screen people with diabetes in communities with poor healthcare resources.

Hypoglycaemia statistics derived from the SHQ score can be used as an educational tool for people with diabetes and their caregivers to develop insight into the magnitude of the problem and to encourage individuals at high risk to perform SMBG regularly.

Studies have indicated that the appropriate use of statins among people with diabetes is lower than expected.[20] The findings of this study reciprocate the same and could be an additional motivation for the use of statin in people with diabetes, especially with increasing evidence of hypoglycaemia being linked to mortality. Further studies are warranted in this direction, focusing on hypoglycaemia episodes in statin users and their protective role in mortality.

Conclusion

As the incidence of probable hypoglycaemia is very high in T2D not doing SMBG, it seems that SHQ may identify the people at risk who can be offered appropriate management. This SHQ method was found to be a simple and cost-effective screening tool in an Indian setup and can be used in outpatient settings after trailing it at a wider scale and translating and validating it into various regional languages to benefit the linguistically diverse non-English-speaking population of India.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Objective / AIM

To study the factors responsible to affect / influence Hypoglycaemia amongst patients.

Ho: Null Hypothesis: Various factors studied are not responsible to influence Hypoglycaemia or said another way various factors are not statistically influencing Hypoglycaemia.

Ha: Alternate Hypothesis: Various factors studied are statistically related to the Hypoglycaemia symptom amongst patients.

Research Methodology

Ordinal Regression / The Proportional Odds algorithm is used to model the relationship of how Hypoglycemia symptom is affected. In ordinal logistic regression, the event of interest is observing a particular score or less hence for Hypoglycemia Study the scores are defined as follows:-score is 0 = No symptom, 1 to 3 = Mild, 4 to 5 Moderate and 6+ Severe (Hierarchy scoring Mild > Moderate > Severe). Ordinal Regression ensures each logit has its own αj term but the same coefficient β. This means that the effect of the independent variable is the same for different logit functions.

Model Fit

Goodness of Fit - Statistics signifying predicted values from the model do not differ from the observed values hence the model is a Good Fit. Table 1* (p value > .05) is shown where all the significant factors are suggesting that observed data is a good fit of the model representing the population under study.

As the p-value/significance is greater than 0.05, the chosen model rightly predicts the data. Moreover, stating the sample is representative of the population.

Moreover reasonable scenario that observed data will reproduce consistent findings if they were repeated on another occasion and by other researcher.

Testing Parallel Lines

When one fits an ordinal regression one assumes that the relationship between the independent variables and the logits are the same for all the logits. That means that the results are a set of parallel lines or planes, one for each category of the outcome variable.

Null Hypothesis: Model assumes that the lines are parallel Table 1* (p value > .05).

Alternate Hypothesis: It is possible that the link function selected is incorrect for the data or that the relationship between the independent variables and logits are not the same for all logits.

Research Findings

Individuals who report Neuropathy, Retinopathy, Nephropathy, Insulin use and Sulfonylurea use tend to fall into higher categories of Mild, Moderate and Severe Hypoglycaemia as opposed to the lower categories.

The respective log odds goes up for Neuropathy (.839), Retinopathy (1.111), Nephropathy (.796), Insulin use (.483) and Sulfonylurea use (.321) hence increasing the likelihood of falling into higher levels of Hypoglycemia Symptom vis. Mild > Moderate > Severe (more probable category)

Individuals who report Metformin and Statin use tend to fall into lower categories of Hypoglycemia Symptom depicting an inverse relationship.

The respective log odds decreases by Metformin (-.625) and Statin (-.339) hence increasing the likelihood of falling into lower levels of Hypoglycemia Symptom vis. Severe < Moderate < Mild (more probable category)

With incremental FBS mgdl, PPBS mgdl, SBP mmHg and Age the log odds increase for falling into higher levels of Hypoglycaemia vis. Mild > Moderate > Severe (Increasing the likelihood to fall this direction)

Respective proportional odds are found to be FBS mgdl (0.006), PPBS mgdl (0.004), SBP mmHg (.018) and Age (.020) hence such factors tend to fall individuals with increasing chances of Hypoglycaemia i.e. Mild > Moderate > Severe.

However Severe Hypoglycaemia was seen to be absent (no relationship – basically no effect on Severe but before that the log odds are increasing for Mild and Moderate) apparently for FBSmgdl, PPBSmgdl and Age.

With incremental eGFR the log odds decreases for falling into higher levels of Hypoglycaemia indicating inverse relationship.

The proportional odds goes down by -.006 for eGFR hence increasing the likelihood of falling into lower levels of Hypoglycaemia Symptom vis. Severe < Moderate < Mild (more probable category)

Factors such as Pioglitazone, Weight, SGLT2, Abdominal Circumference and GLP1RA have shown no statistical relationship to Hypoglycaemia since all the respective p values are >.05

Multivariate analysis

Objective: Building a predictive model to estimate the probability of experiencing at least one symptom of hypoglycaemia.

"We have determined the definitions for 'No symptoms' and 'At least one symptom' based on the Stanford Hypoglycaemia Questionnaire (SHQ)."

Independent variables Considered

- AgeinYrs
- Sex
- WeightinKg
- Heightcm
- BMI
- Pulseperminute
- AbdominalCircumferencecm
- SBPmmHg
- DBPmmHg
- DurationofDiabetes
- SUPHONYLYUREAUSE
- AGIUSE
- PIOGLITAZONEUSE
- METFORMINUSE
- DPP4iUSE
- SGLT2iUSE
- ANYINSULINUSE
- BASALONLY
- FBSmgdl
- PPBSmgdl
- HbA1c
- SCreatininemgdl

Modelling Approach: Binary Logistic regression

"We used the forward conditional method to identify the key variables, and the following variables were selected."

"The threshold values were determined using the Receiver Operating Characteristic (ROC) curve."

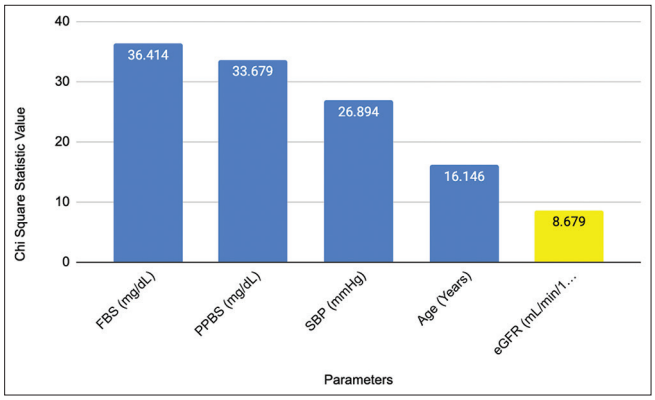

Figure S1: Association of Various Continuous Significant Factors with the hypoglycemia symptoms (*Severe Absent). This figure shows the systematic chi-square test value for different parameters. FBS: Fasting Blood Sugar, PPBS: Post Prandial Blood Sugar, SBP: Systolic Blood Pressure, eGFR: Estimated Glomerular Filtration Rate (blue signifies positive association and yellow signifies negative)

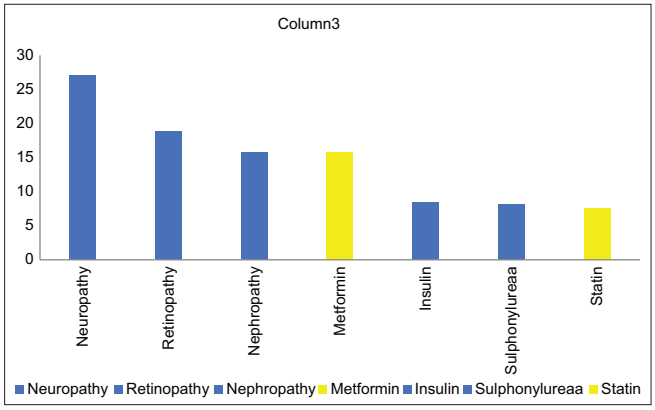

Figure S3: Association of Various Binary Significant Factors with the hypoglycemia symptom. This figure shows the systematic chi-square test value for different parameters

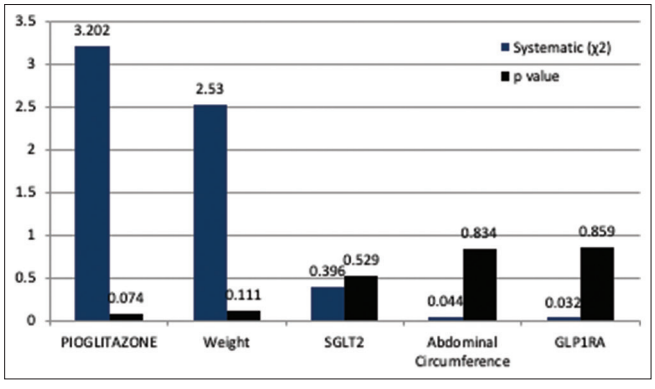

Figure S5: Various factors found to be statistically non significant while exploring the relationship to Hypoglycaemia

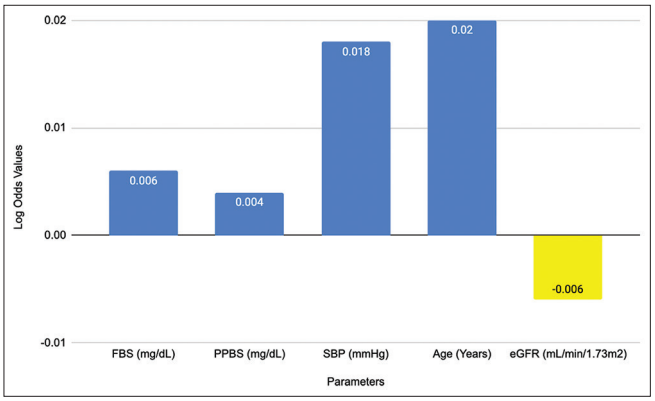

Figure S2: This figure shows log Odds of different continuous parameters of whose p values was significant i.e., is less than 0.05

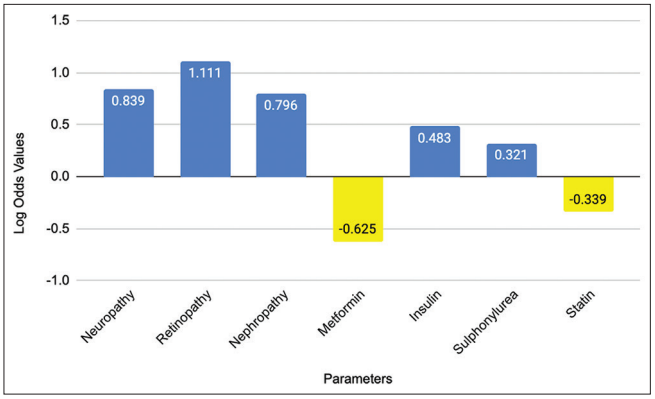

Figure S4: This figure shows log Odds of different continuous parameters of whose p values was significant i.e., is less than 0.05

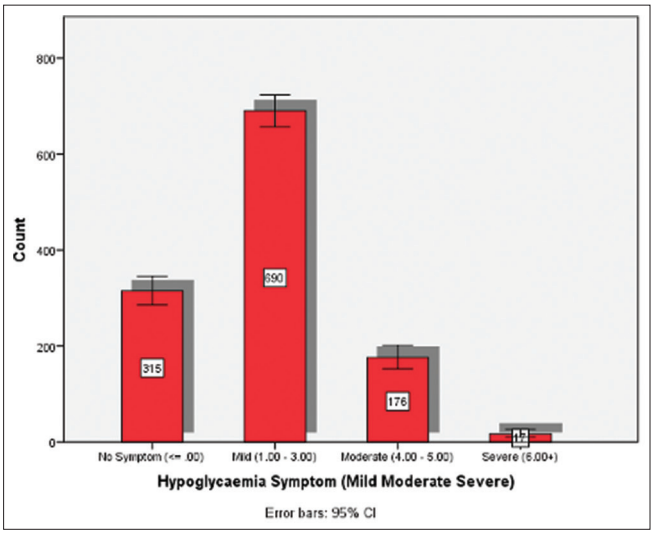

Figure S6: Graphical representation of table S4

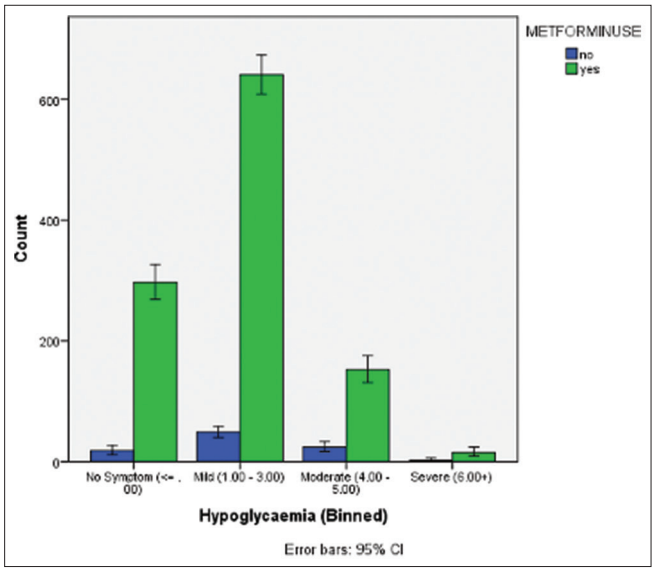

Figure S7: Graphical representation of Table S5s

Table S1: Table above justifies the same scenario (one more probable reason is that only a few individuals are present in such a case with Frequency=17* out of total patients)

Mean	Age in Years Mean	FBSmgdl Mean	PPBSmgdl Mean	SBPmmHg
Hypoglycaemia (Binned)				
No Symptom (<= 0.00)	51.8	128.32	190.73	128.5
Mild (1.00-3.00)	53.5	146.52	207.82	132.4
Moderate (4.00-5.00)	56.1	160.29	239.41	135.8
Severe (6.00+)	55.0	161.96	213.51	140.4
	*Absent	*Absent	*Absent	Impact is Present

Table S2: Comprehensive Table for all the factors modelled with Hypoglycaemia

Parameter	Chi – Square χ^2	Sig. *P*	Log Odds	Goodness-of-Fit (*P*)	Test of Parallel Lines (*P*)
Age	16.146	0.000	0.020	0.272	0.540
Weight	2.53	0.111			
SBP	26.894	0.000	0.018	0.923	0.791
FBS	36.414	0.000	0.006	1.0	0.225
PPBS	33.679	0.000	0.004	0.995	0.267
eGFR	8.679	0.003	-0.006	1.0	0.592
Negative Abdominal Circumference	0.044	0.834			
Nephropathy	15.794	0.000	0.796	0.979	0.979
Insulin Use	8.196	0.004	0.483	0.119	0.090
SGLT2i Use	0.396	0.529			
GLP1RA Use	0.032	0.859			
Metformin use	8.435	0.004	-0.625	0.499	0.499
PIOGLITAZONE Use	3.202	0.074			
Sulfonylurea Use	7.481	0.006	0.321	0.477	0.450
History* Hypoglycaemia	*Assumption not met though highly significant *P*<0.05				
Neuropathy	27.007	0.000	0.839	0.611	0.611
Retinopathy	18.782	0.000	1.111	0.559	0.504
Statin	6.576	0.010	-0.339	0.083	0.083
Premix* Use	*Assumption not met though highly significant *P*<0.05				

Table S3: Comprehensive table indicating the *effect size* in terms of *Log odds and Odds ratio* (EXP Beta) for factors modelled with Hypoglycaemia with 95% *Confidence Interval* (of these ratios)

Factors Modelled with Hypoglycaemia	Log Odds with 95% CI Proportional Odds			Odds Ratio with 95% CI (EXP β)		
	Log Odds ln(Θj)	Lower	Upper	Odds *P* (Y)	Lower	Upper
Age	0.020	0.010	0.030	1.020201	1.01005	1.030455
Weight	Non Significant *P*=0.111					
SBP	0.018	0.011	0.024	1.018163	1.011061	1.02429
FBS	0.006	0.004	0.009	1.006018	1.004008	1.009041
PPBS	0.004	0.003	0.006	1.004008	1.003005	1.006018
eGFR	-0.006	-0.010	-0.002	0.994018	0.99005	0.998002
Abdominal Circumference	Non Significant *P*=0.834					
Nephropathy	0.796	0.402	1.189	2.216657	1.494811	3.283796
Insulin Use	0.483	0.145	0.820	1.62093	1.15604	2.2705
SGLT2iuse	Non Significant *P*=0.529					
GLP1RAuse	Non Significant *P*=0.859					
Metformin Use	-0.625	-1.040	-0.209	0.535261	0.353455	0.811395
PIOGLITAZONE Use	Non Significant *P*=0.074					
Sulfonylurea Use	0.321	0.091	0.551	1.378506	1.095269	1.734987
History* Hypoglycaemia	*Assumption not met though highly significant *P*<0.05					
Neuropathy	0.839	0.522	1.156	2.314052	1.685395	3.177199
Retinopathy	1.111	0.609	1.613	3.037394	1.838592	5.017842
Statin	-0.339	-0.599	-0.080	0.712482	0.549361	0.923116
Premix* Use	*Assumption not met though highly significant *P*<0.05					

Table S4: Shows number of individual falling in the groups based on SHQ score

		Hypoglycaemia (Binned)			
Counts	Types of Hypoglycaemia	Frequency	Percent	Valid Percent	Cumulative Percent
Valid	No Symptom (<=0.00)	315	26.3	26.3	26.3
	Mild (1.00-3.00)	690	57.5	57.6	83.9
	Moderate (4.00-5.00)	176	14.7	14.7	98.6
	Severe (6.00+)	17	1.4	1.4	100.0
	Total	1198	99.9	100.0	
Missing	System	1	0.1		
Total		1199	100.0		

Table S5: Shows metformin use in various group based on SHQ score

Hypoglycaemia	Types of hypoglycaemia	Metformin use	Yes/No	Count
Hypoglycaemia (Binned)	No Symptom (<=0.00)	Metformin use	No	18
			Yes	297
	Mild (1.00-3.00)	Metformin use	No	49
			Yes	641
	Moderate (4.00-5.00)	Metformin use	No	24
			Yes	152
	Severe (6.00+)	Metformin use	No	2
			Yes	15

Table S6: Parameters Tested

	Parameters Tested
1	Weight
2	Height
3	Abdomen circumference
4	BMI
5	Age
6	Sex
7	Duration of Diabetes
8	Type Of Diabetes
9	Sulfonylurea Use
10	Sulfonylurea Type Name
11	Sulfonylurea total dose
12	Alpha Glucosidase Inhibitors Use (Voglibose)
13	Pioglitazone Use
14	Pioglitazone Type Name
15	Pioglitazone Total Dose
16	Metformin Use
17	Metformin Total dose
18	DPP4i Use
19	DPP4i Total Dose
20	SGLT2i Use
21	SGLT2i Name
22	SGLT2i Total Dose
23	GLP1 RA Use
24	GLP1 RA Name
25	GLP1 RA Total Dose
26	Any Insulin Use
27	Basal Insulin
28	Bolus Insulin
29	Basal Insulin Dose
30	Bolus Insulin Dose
31	Basal plus Insulin (1,2)
32	Basal Bolus Total Dose
33	Intermediate Acting NPH Name
34	Intermediate Acting NPH Total Dose
35	Premix Insulin Name
36	Premix Insulin Dose
37	Coformulation Name
38	Coformulation Total Dose
39	Statin Details
40	Systolic Blood Pressure
41	Diastolic Blood Pressure
42	Pulse
43	Fasting Blood Sugar
44	Post Prandial Blood Sugar
45	HbA1c
46	Serum Creatinine
47	Egfr
48	UACR
49	Retinopathy
50	Neuropathy
51	Nephropathy
52	Cardiovascular Events
53	Past History of Hypoglycemia

Table S7: StanfordquestionnaireSCORE *severity_coded2 Crosstabulation

Count			
	severity_coded2		Total
	0 No Symptoms	1 Some Symptoms	
StanfordquestionnaireSCORE			
0	316	0	316
1	0	253	253
2	0	255	255
3	0	179	179
4	0	120	120
5	0	59	59
6	0	11	11
7	0	5	5
Total	316	882	1198

Table S8: Classification Table[a]

Observed	Predicted		
	severity_coded2		Percentage Correct
	0 No Symptoms	1 Some Symptoms	
Step 1			
severity_coded2			
0 No Symptoms	179	111	61.7
1 Some Symptoms	264	482	64.6
Overall Percentage			63.8

a. The cut value is 0.700

Table S9: Frequency of various drugs used by the study participants

n	Male	Female	Overall	*P*
Sex, *n* (%)	663 (55.3)	535 (44.6)	1198	<0.001
SUPHONYLYUREAUSE, *n* (%)	416 (62.7)	346 (64.7)	762 (63.6)	0.529
AGIUSE, *n* (%)	76 (11.5)	43 (8.0)	119 (9.9)	0.061
PIOGLITAZONEUSE, *n* (%)	102 (15.4)	72 (13.5)	174 (14.5)	0.391
METFORMINUSE, *n* (%)	617 (93.1)	488 (91.2)	1105 (92.2)	0.281
DPP4iUSE, *n* (%)	412 (62.1)	335 (62.6)	747 (62.4)	0.913
SGLT2iUSE, *n* (%)	83 (12.5)	70 (13.5)	153 (12.8)	0.838
GLP1RAUSE, *n* (%)	0	1 (0.2)	1 (0.1)	0.447
ANYINSULINUSE, *n* (%)	78 (11.8)	71 (13.3)	149 (12.4)	0.486
STATIN, *n* (%)	284 (42.8)	242 (45.2)	526 (43.9)	0.572
PASTHISTORYOFHYPOGLYCEMIA, *n* (%)	129 (19.5)	126 (23.6)	255 (21.3)	0.076
RETINOPATHY, *n* (%)	33 (5.0)	29 (5.4)	62 (5.2)	0.579
NEPHROPATHY, *n* (%)	65 (9.8)	43 (8.0)	108 (9.0)	0.500
NEUROPATHY, *n* (%)	97 (14.6)	90 (16.8)	187 (15.6)	0.28
CVEVENTS, *n* (%)	27 (4.1)	20 (3.7)	47 (3.9)	0.612