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Insulin Regimens and Clinical Covariates among Type 2 Diabetes patients

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ABSTRACT

Background: Different insulin regimens are used to manage poorly controlled diabetic patients. The variability in these regimens leads to differences in patients' experiences and clinical outcomes. Understanding the impact of different insulin regimens on patient outcomes is crucial for optimizing diabetes management.
Objective. This study compared insulin experiences and clinical outcomes in outpatient type 2 diabetic patients using two commonly prescribed insulin regimens.
Methods. In this comparative cross-sectional study, patients were divided into two groups, each comprising 25 individuals. The study was carried out at Zagazig University Hospital and Al Mabara Health Insurance Hospital in Zagazig, Egypt, for 6 months. The research utilized a validated questionnaire, the Insulin Treatment Experience Questionnaire (ITEQ), to assess patients' experiences with insulin treatment and explore various clinical covariates associated with diabetes in both groups.
Results: The findings revealed inadequate glycemic control in both insulin regimen groups, as indicated by elevated levels of glucose indices. Notably, three domains of ITEQ showed significant differences, with higher mean scores observed in the basal-bolus group (p-value < 0.05). A statistically significant positive correlation was found between total ITEQ scores and Insulin Therapy Related-Quality of Life (ITR-QoL) (r=* 0.607* and r= 0.749*, respectively).
Conclusion: Patients utilizing basal-bolus insulin analogs exhibited superior glycemic control and quality of life in comparison to individuals employing premixed human insulin. The study emphasizes the importance of incorporating patient-reported outcomes into healthcare provider follow-up, providing valuable insights to enhance the overall patient experience of treatment.

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1. Introduction:

Type 2 diabetes (T2D) is a significant public health concern worldwide and in Egypt, affecting a substantial portion of the population (10.9%). This percentage is anticipated to double within the next two decades, reaching approximately 20% (1). One of the notable characteristics of this disease is the progressive deterioration of B-cell function over time. Consequently, there is a need to incorporate insulin therapy into the treatment plans as the disease advances (2). According to the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) clinical guidelines, the initial step in incorporating insulin therapy usually involves basal insulin (3). However, due to the ongoing decline in B-cell function, many patients will require a gradual intensification of insulin therapy to achieve the desired glycemic control. This intensification can be achieved by either adding prandial (mealtime) insulin doses through separate injections (basal-plus approach), with a gradual increase in prandial doses until a full basal-bolus regimen is achieved or by using a combination of both basal and prandial insulin in a single vial (premixed), with stepwise increments in the number of doses (4).

Both premixed and basal-bolus insulin regimens have demonstrated effectiveness in achieving blood glucose control (5). Premixed formulations have been developed to reduce the required injections, enhancing patient adherence and compliance (6). However, the benefit of fewer injections may be accompanied by a more rigid regimen and an increased risk of side effects such as hypoglycemia, which can negatively impact patient compliance and treatment outcomes (7,8). Conversely, many healthcare professionals consider basal-bolus formulations the optimal approach for blood glucose control due to their flexibility in independently adjusting insulin doses and types (9). Nonetheless, the burden of multiple insulin injections and the need for regular dose calculations may present challenges that can affect patient experience and satisfaction with the treatment (10).

Previous research examining premixed and basal-bolus insulin regimens has produced inconsistent patient preferences and treatment satisfaction results. This study aimed to compare two commonly utilized insulin regimens among T2D patients in outpatient settings. To achieve this, a validated tool will be utilized to assess patients' experiences and gauge their satisfaction with the treatments. Additionally, clinical variables will be analyzed and compared between the two groups to gain a comprehensive understanding of the effectiveness of each regimen.

2. Materials and Methods

2.1. Study population

The comparative cross-sectional study was carried out at Zagazig University Hospital and Al Mabara Health Insurance Hospital in Zagazig, Egypt, between September 2021 and March 2022. The study focused on outpatients attending the internal medicine department who were diagnosed with T2D and receiving insulin therapy. The inclusion criteria for the study were as follows: being 35 years of age or older, undergoing insulin therapy for at least one year prior to the screening visit. Before recruiting patients, the study obtained approval from the Zagazig University Hospital Institutional Review Board (IRB) Committee under reference number #6864/11-4-2021. Patients with diabetes types other than T2D, individuals unable to complete the questionnaires based on self-ratings, those hospitalized within the past 30 days, individuals with visual or hearing impairments that could hinder communication, pregnant or breastfeeding females, and patients who declined to participate in the study were excluded. Patients were provided with a detailed explanation of the study's objectives and relevant information to ensure ethical considerations. They were subsequently requested to provide written informed consent indicating their willingness to participate in the study.

2.2. Data collection

The patients are divided into two groups, with 25 patients in each group. Each group comprised 25 patients, determined using the Open Epi I program with a 5% level of significance and a 5% estimate of error, As total Insulin therapy–related quality-of-life score was 103.08±9.83 in diabetics patients on premixed regimen vs 90.60± 19.42 among patients on Insulin analogs as basal bolus regimen (11). The classification was based on the type of insulin regimen they were using premixed or basal bolus. In the study, the premixed group pertains to the administration of premixed human insulin (specifically Mixtard®), whereas the basal-bolus group involves the utilization of a basal insulin analog (such as glargine or degludec) in combination with a mealtime insulin analog (such as aspart or glulisine). Additionally, official permission was obtained from the Faculty of

Medicine to conduct the study in outpatient clinics and health insurance hospitals. The data collection process included gathering patients' demographic information, as well as information regarding their diabetes diagnosis and insulin therapy. The participants' social class was determined using a validated questionnaire known as the Fahmy questionnaire (12). Additionally, blood and urine samples were collected to investigate various clinical factors such as glycemic control, lipid profile, and kidney function tests.

To assess the patients' experience with insulin treatment, the researchers employed a validated questionnaire, Insulin Treatment Experience Questionnaire (ITEQ). This questionnaire consisted of 27 questions, which were further divided into seven subscales covering different aspects of life related to insulin treatment. An additional question was included to evaluate overall satisfaction with the treatment. The subscales covered various topics such as leisure activities, psychological barriers, insulin handling, control of diabetes, dependence on insulin, control of weight, and sleep. Patients were asked to indicate their level of agreement with each item using a 5-point Likert scale. For the first seven subscales, the scale ranged from 1 (representing "totally agree") to 5 (representing "totally disagree"). The scale used to assess general treatment satisfaction ranged from 1 (very satisfied) to 5 (very dissatisfied). The questionnaire has been validated and proven effective in evaluating treatment satisfaction and everyday experiences in individuals with T2D undergoing insulin therapy (13).

2.3. Statistical analysis

The study uses the mean ± standard deviation (S.D.) as a descriptive statistic to represent the data. To assess differences between the two groups, appropriate statistical tests were conducted following an examination of the data distribution. The Mann-Whitney test was utilized to compare the various domains of the ITEQ questionnaire results. Furthermore, the study explored correlations between different variables and the total score of the ITEQ questionnaire. Additionally, previously collected data on the overall quality of life, as evaluated through the Insulin Therapy Related-Quality of Life (ITR-QoL) questionnaire for the same cohort of patients, were scrutinized for potential associations. The collected data will be analyzed using Statistical Package of Social Services version 25 (SPSS) software on a computer. A result will be considered statistically significant if the probability of significance ($p<0.05$) and considered highly statistical significant if (p value ≤ 0.001)

3. Results

Table 1 presents the demographic characteristics and clinical covariates of patients belonging to the premixed and basal-bolus groups. No statistically significant differences are observed between the two groups in terms of age, gender, body mass index, insulin doses, and duration of illness. However, the duration of using the insulin regimen differs significantly (p-value = 0.000), with the premixed group having a longer duration (mean ± SD: 7.52 ± 6.15) compared to the basal-bolus group (mean ± SD: 2.88 ± 2.46). The analysis of social class revealed that a high percentage of patients in the premixed group belonged to the low and middle social class (96%), while all patients in the basal-bolus group were either in the middle or high social class (100%).

Regarding the usage of oral antidiabetic drugs, 16 patients in the premixed group and 12 patients in the basal-bolus group are found to be using oral antidiabetic medications from various classes, and there is no significant difference observed between the two groups (p-value = 0.393).

Table 2 presents data pertaining to glycemic indices, lipid profile, and renal function for both groups. In term of glycemic indices, there is a significant difference observed in HbA1c levels (p-value = 0.000), with higher mean levels in the premixed group (mean ± SD: 10.86 ± 1.99) compared to the basal-bolus group (mean ± SD: 8.58 ± 1.51). Additionally, the lipid profile shows significant differences between the two groups in terms of total cholesterol and triglyceride levels (p-value = 0.011, p-value = 0.000, respectively), with higher mean levels observed in the premixed group.

In the assessment of renal functions, most tests exhibit significant differences between the two groups. This includes eGFR (p-value = 0.011), urea levels (p-value = 0.000), BUN (p-value = 0.000), and serum albumin to creatinine ratio (p-value = 0.000). The basal-bolus group shows higher mean eGFR values, while the premixed group exhibited higher mean levels of urea, BUN, and serum albumin to creatinine ratio.

Figure 1 displays the mean scores for all items within different domains of the ITEQ. The premixed and basal-bolus groups are compared, with specific questions outlined by Mook et al. (13).

Table 1. *Demographics and patient characteistics of both premixed and Basal-Bolus groups with 25 patients in each group*.

Variables	Premixed N (25)	Basal-bolus N (25)	P- value
Age (years)	55.4±9.412	55.16±9.869	0.929(N.S.)
Sex			
Male	7(28%)	9(36%)	0.544(N.S)
Female	18(72%)	16(64%)	
Social class			
Low social class	10 (40%)	0 (0%)	0.001**(HS)
Middle social class	14 (56%)	19 (76%)	
High social class	1 (4%)	6 (24%)	
Duration of diabetes (years)	14.36±9.591	13.54± 8.362	0.961(N.S)
Duration of using insulin regimen (years)	7.52±6.158	2.88±2.468	0.000*(HS)
Dose of insulin (units)	64.4±17.159	67.88±21.082	0.529(N.S)
Weight (Kg)	86.16±11.04	86.96± 13.66	0.821(N.S)
BMI	32.19± 4.46	30.91± 5.16	0.355(N.S)
Oral antidiabetic treatment:			
Insulin only	9 (36%)	13(52%)	0.393 (N.S)
Oral + insulin	16 (64%)	12 (48 %)	0.393 (N.S)
No. of injections per day			
1-2	25 (100%)	0 (0.0%)	0.000**
≥ 3	0 (0.0%)	25 (100%)	

BMI ; Body mass index. The data are presented in a standardized format, reporting means with corresponding standard deviations (SD) or percentages (n%) unless specified otherwise. **Independent t-test, Chi-square test**, **Mann-Whitney test**, **or Fisher's exact test** were employed to assess the significance between the two groups as appropriate. Significance was determined at a p-value less than 0.05, with not significant denoted as "N.S," highly significant as "HS," and significant as "S."

Among all the domains, three domains, namely diabetes control, sleep, and global satisfaction, exhibited significant differences, with higher mean scores observed in the basal-bolus group (Table 3). Specifically, out of the six items related to the investigation of the diabetes control domain of ITEQ, only three questions showed significant differences, indicating higher scores in the basal-bolus group. The three items denoted as (2, 5, 6) in Figure 1 are associated with pronounced fluctuations in blood glucose levels, expressing concerns regarding the potential occurrence of severe hypoglycemic events during nocturnal periods, as well as the manifestation of exceptionally severe hypoglycemic episodes in the context of insulin treatment. The 2 items related to the sleep domain also demonstrated significant differences, with higher scores observed in the basal-bolus group (Figure 1). The mean total scores for all domains were significantly higher in the basal-bolus group compared to the premixed group (p-value = 0.001).

In (Figure 2), it is shown that HbA1c has a statistically significant positive correlation with PPG in both the premixed and basal-bolus groups (r=0.799 and r=0.408, respectively), while only FBG for the premixed group (r=0.489). Furthermore, there is a statistically significant positive correlation between PPG and FBG in the premixed and basal-bolus groups (r=0.695 and r=0.736, respectively). Additionally, there is a statistically significant positive correlation between the total ITEQ scores and total ITR-QoL scores in both the premixed and basal-bolus groups (r=0.607 and r=0.749, respectively). Notably, the total ITEQ score demonstrates a statistically significant positive correlation with social class in the basal-bolus group (r=0.403)

Table 2. *Laboratory data of blood glucose measurements, lipid profile, and kidney function of the studied patients with 25 patients in each group.*

Variables	Premixed N (25)	Basal-bolus N (25)	P- value
Glycemic indices			
HbA1c	10.86±1.99	8.58±1.51	0.000* (HS)
FBG (mg/dl)	182.16±77.1	169.29±34.92	0.854 (N.S)
PPG (mg/dl)	274.63±88.08	232.12±71.04	0.064(N.S)
Lipid profile			
Total cholesterol (mg/dl)	194.04±16.88	169.2±39.05	0.011* (S)
Triglycerides (mg/dl)	141.16± 19.73	111.6±44	0.000* (HS)
HDL (mg/dl)	46.4± 5.96	45.84±3.95	0.266(N.S)
LDL (mg/dl)	115.33±24.81	102±34.03	0.088(N.S)
Renal functions			
eGFR:(ml/min/1.73m^2)	69.05±10.85	81.81±21.03	0.011** (HS)
Urea: (mg/dl)	39.48±5.64	30.04±9.85	0.000*** (HS)
BUN (mg/dl)	18.41±2.65	13.58±4.57	0.000*** (HS)
Serum creatinine (mg/dl)	0.95±0.13	0.9±0.23	0.081 (NS)
uACR (mg/g)	590.4±629.07	107.97±126.2	0.000*** (HS)

FBG; Fasting blood glucose, **PPG**; Postprandial glucose, **HDL**; High-density lipoprotein, **LDL**; Low-density lipoprotein, **BUN**; Blood urea nitrogen, **uACR**; Urinary albumin/creatinine ratio. The data are presented in a standardized format, reporting means with corresponding standard deviations (SD) or percentages (n%) unless specified otherwise. **The Mann-Whitney test** was employed to assess the significance between the two groups. Significance was determined at a p-value less than 0.05, with not significant denoted as "N.S," highly significant as "HS," and significant as "S."

Table 3. *Mean scores of different ITEQ domains for both groups with 25 patients in each group.*

Domains	Premixed N (25)	Basal-Bolus N (25)	p-value
leisure activities	3.24±0.90	3.53±0.79	0.281 (NS)
Psychological barriers	2.86±1.43	3.02±1.17	0.468 (NS)
Handling	3.96±0.68	3.80±0.71	0.446 (NS)
Diabetes control	2.52±0.76	3.28±0.92	0.008** (HS)
Dependence	3.38±0.98	3.58±1.11	0.335 (NS)
Weight control	2.90±1.10	2.85±1.02	0.922 (NS)
Sleep	1.72±1.08	3.02±1.55	0.002** (HS)
Global satisfaction	2.88±1.09	4.12±1.01	0.000*** (HS)
Total score	2.93±0.57	3.48±0.51	0.001*** (HS)

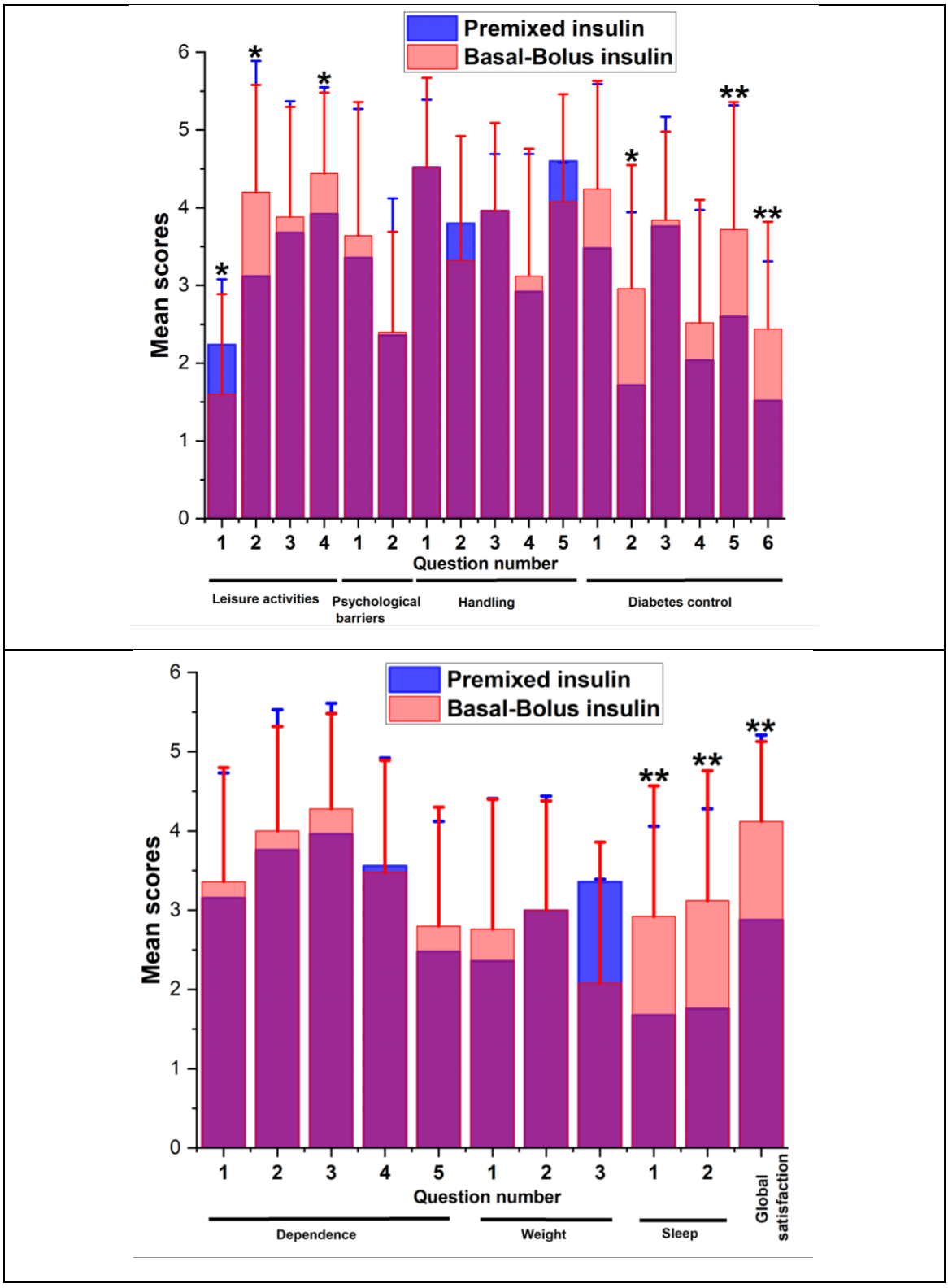

Figure 1. *Mean scores for all items of different ITEQ domains in both groups with 25 patients in each group. Whereas, *denotes p<0.05, ** p-value< 0.001.*

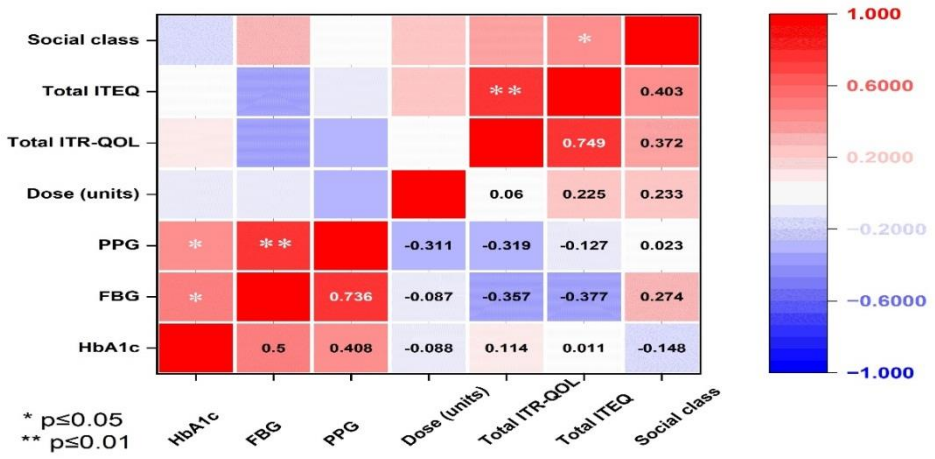

Figure 2. *Correlation matrices of glycemic laboratory data, insulin dose, social class, and total scores of ITEQ and ITR-QoL questionnaires for premixed insulin.*

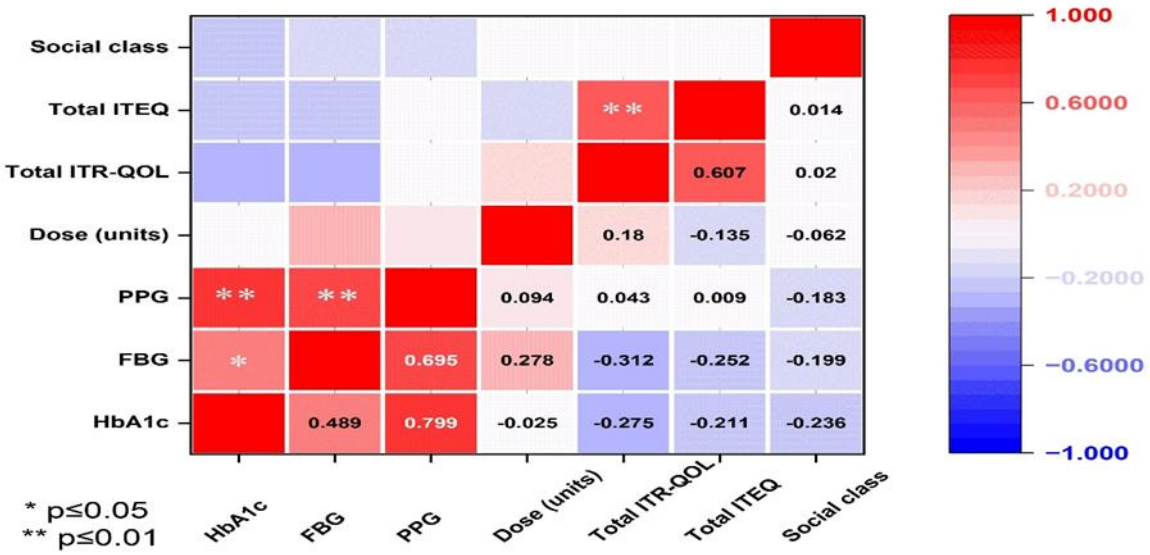

Figure 3. *Correlation matrices of glycemic laboratory data, insulin dose, social class, and total scores of both ITEQ and ITR-QoL questionnaires for Basal-Bolus insulin.*

4. Discussion

This cross-sectional study offers a comparative analysis of insulin administration experiences among T2D patients using two frequently prescribed insulin regimens in outpatient settings. The study employs a validated questionnaire to assess the insulin experience and investigated various clinical covariates associated with diabetes in both groups. The findings indicate that patients in both insulin regimen groups exhibit inadequate glycemic control, as demonstrated by elevated levels of HbA1c, FBG, and PPG. These results are consistent with previous studies conducted on Egyptian diabetic patients (14,15). However, it is observed that patients utilizing the basal-bolus insulin regimen demonstrated superior glycemic control compared to those using the premixed regimen, which aligns with several studies highlighting the benefits of basal-bolus insulin therapy in achieving optimal glycemic control compared to premixed insulin therapy (16–18).

The analysis of patients' characteristics revealed that there were no significant differences between the two groups in terms of age, gender, and duration of diabetes, except for the duration of using the insulin regimen, which was found to be longer in the premixed group. This observation can be explained by the fact that most of the diabetic patients in the basal-bolus group had previously been using a premixed insulin regimen before transitioning to the basal-bolus regimen. Furthermore, there was a significant difference in the social class between the two groups. The majority of patients in the premixed group belonged to the low and middle social class categories, while all patients in the basal-bolus group were classified as middle and high social class. This finding highlights the influence of socioeconomic disparities on the accessibility to intensive insulin regimens such as basal-bolus regimens. It suggests that individuals from lower social classes may face challenges in accessing and affording more advanced insulin therapies (19). This is further supported by the significant correlation observed between social class and the utilization of the basal-bolus insulin regimen in our study. The disparity in injection frequency between the two groups is attributed to the prescription regimen. The premixed group follows a twice-daily schedule, with two-thirds of the doses administered in the morning and the remaining one-third in the evening. In contrast, the basal-bolus group employs a regimen consisting of one basal injection per day and additional injections before each meal, resulting in a total of three to four injections per day.

The analysis of the lipid profile demonstrated that the mean values of various lipid parameters in both groups were within the normal range for diabetic patients, except for LDL, which exceeded the normal level in both groups. However, it was observed that the premixed group had significantly higher mean values of total cholesterol and triglycerides compared to the basal-bolus group. This finding can be attributed to the association between lower socioeconomic levels and a higher incidence of dyslipidemia, particularly in individuals with type 2 diabetes. Previous studies have indicated that socioeconomic factors can influence the prevalence and severity of dyslipidemia, with lower socioeconomic status being linked to unfavorable lipid profiles (20,21).Furthermore, it has been reported that the initiation of insulin analogs is associated with improvements in the lipid profile (22). This observation suggests the need for further research to compare the effects of both human and analog insulin types on lipid profiles. Exploring the differential impact of these insulin types on lipid parameters could provide valuable insights into optimizing diabetes management and addressing cardiovascular risk factors. In addition, the research findings revealed that patients in the premixed insulin group exhibited a more significant deterioration in kidney function, as indicated by a significantly lower mean estimated glomerular filtration rate (eGFR) and a significantly higher mean urine albumin-to-creatinine ratio (uACR), compared to those in the basal-bolus group. These findings can be explained by the significant association between higher glycated hemoglobin levels in the premixed group compared to the basal-bolus group and the significant deterioration of renal function. The higher glycated hemoglobin levels may contribute to the increased risk of nephropathy observed in the premixed insulin group (23,24).

When comparing the experience of insulin regimens, it was observed that patients in the basal-bolus group reported a significantly higher sense of control over their diabetes and improved sleep quality compared to those in the premixed group. The enhanced sense of diabetes control experienced by basal-bolus patients stemmed from the reduced fluctuations in blood glucose levels and fewer concerns about the occurrence of severe nocturnal hypoglycemic events. Furthermore, basal-bolus patients exhibited a lower incidence of severe hypoglycemic episodes

associated with insulin treatment. Additionally, the basal-bolus group demonstrated better sleep outcomes, as reflected by their ability to obtain a good night's sleep and go to bed with peace of mind in relation to their insulin treatment. The observed outcomes can be ascribed to the distinction between Neutral Protamine Hagedorn (NPH) insulin in the premixed insulin formulation (Mixtard®) and glargine, employed as the basal insulin component in a basal-bolus regimen. Numerous studies have indicated that NPH insulin is correlated with a heightened risk of both nocturnal and severe hypoglycemic events in comparison with the insulin analog glargine. (25–27).

Moreover, the findings of this study align with numerous other investigations that have compared various insulin regimens, consistently demonstrating that premixed insulin regimens are linked to a heightened risk of both nocturnal and severe hypoglycemic events when contrasted with the basal-bolus regimen (28–30). These findings provide a plausible explanation for the superior sleep outcomes reported by patients in the basal-bolus group compared to those in the premixed group. The reduced incidence of hypoglycemic events, particularly during nighttime periods, among basal-bolus patients may contribute to their enhanced ability to achieve restful sleep and approach bedtime with a sense of reassurance regarding their insulin treatment. Contrary to the aforementioned findings, individuals in the premixed insulin group reported higher levels of satisfaction with their treatment regimen. This discrepancy can be attributed to the complexity associated with the basal-bolus insulin regimen, which has been consistently highlighted as a potential barrier to convenience and adherence to insulin therapy in numerous studies (31,32). The intricate nature of the basal-bolus regimen, involving multiple injections and the need for frequent blood glucose monitoring, may pose challenges for patients, ultimately influencing their satisfaction levels with the treatment approach.

Moreover, the study shows significant positive correlation between the scores obtained from the Insulin Treatment Experience Questionnaire (ITEQ) and the Insulin Treatment Related Quality of Life Questionnaire (ITR-QoL), which serve as indicators of the patients' quality of life, particularly in the context of basal-bolus insulin regimens. This correlation suggests that a more positive insulin experience and higher satisfaction with basal-bolus insulin regimens are associated with improved outcomes in terms of quality of life (33,34). These findings align with previous research demonstrating the effectiveness of the basal-bolus insulin regimen in enhancing and improving Health-Related Quality of Life (HRQOL) when compared to other insulin regimens (35–37). Moreover, the notable correlation of postprandial glucose (PPG) with glycated hemoglobin (HbA1c) in both the premixed and basal-bolus cohorts suggests its efficacy as a superior indicator for assessing glycemic control when compared to fasting blood glucose (FBG), which exhibits significant correlation solely within the premixed group. This observation aligns with previous research affirming the superiority of PPG as an indicator over FBG in evaluating overall glycemic status (38).

There are several limitations to consider in this study. Firstly, the constrained sample size and the exclusive conduct of the study at a single institution introduce constraints to the generalizability of the findings. Another limitation pertains to the relatively limited exploration of the distinct types of oral antidiabetic medications administered, and the potential influence of these medications on participants' interactions with insulin remains insufficiently examined.

Furthermore, an investigation of diverse insulin delivery devices for both study groups is imperative for a comprehensive understanding of the observed outcomes.

In summary, this study elucidates the impacts of two prevalent insulin regimens on individuals with T2D. Recommendations underscore the importance of integrating patient-reported outcomes into healthcare provider follow-ups, offering valuable insights to enhance the patient treatment experience and, ultimately, optimize glycemic control. Additionally, there is a strong recommendation for fostering effective communication between patients and healthcare providers, especially concerning socio-economic factors and variations in insulin regimens, to better address individual patient requirements. Active solicitation of feedback from patients undergoing insulin therapy is encouraged, with the prospect of implementing modifications to align with patient needs, thereby augmenting the overall treatment experience and satisfaction.

5. Conclusion

The study provides insights into the effects of premixed human insulin and basal-bolus insulin analogs on the quality of life of patients in Egyptian teaching and insurance hospitals. Contrary to expectations, patients using basal-bolus insulin analogs showed better glycemic control and quality of life compared to those using premixed human insulin. Factors such as the type of insulin utilized, sociodemographic characteristics, and social class contribute to the differences in patients' perspectives between the two groups. The findings highlight the importance of considering patients' perspectives and preferences when selecting insulin regimens to optimize their quality of life.

Authorship

Each author listed in the manuscript has approved the submission of this version of the manuscript and takes full responsibility for it.

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Conflict of interest:

Authors declare that they do not have any conflicts of interest to declare.

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Ethics statement:

Before enrolling participants, the research study secured approval from the Institutional Review Board (IRB) committee of Zagazig University Hospital, granted under reference number #6864/11-4-2021.

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