Impact of Bolus/Basal Insulin Ratio on HbA1c and Lipid Profile in Adult Patients with Type 1 Diabetes Mellitus

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ABSTRACT

Objective: To evaluate the existence of any relationship between the bolus/basal (B/b) insulin ratio and HbA1c and lipid profile in patients with Type 1 Diabetes mellitus (T1DM) on a basal–bolus treatment regimen.

Study Design: Retrospective observational study.

Place and Duration of the Study: University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital, Ankara, Turkey, from January 2015 to March 2020.

Methodology: This retrospective-observational study included 181 adult patients with T1DM. They were divided into two groups with <1.5 and ≥1.5 B/b insulin ratios, and the parameters were compared.

Results: The subjects comprised 94 females and 87 males with a mean age of 30.1 ± 9.2 years. Microvascular complications and dyslipidaemia were found in 30.9% and 68.5% of the patients, respectively. B/b insulin ratio of ≥1.5 was observed in 65.1% of the patients. The HbA1c level was <58 mmol/mol in 11.6% of the patients. A positive correlation was found between the B/b insulin ratio and HbA1c level. Fasting Plasma Glucose (FPG) and HbA1c levels were higher in those with ≥1.5 B/b insulin ratio. The rate of patients who reached the optimal HbA1c level was 3.57-fold lower in those with ≥1.5 B/b ratio.

Conclusion: A higher B/b insulin ratio was associated with higher HbA1c levels in patients with T1DM treated with intensive insulin therapy. Prospective studies are needed to define a causal relationship between the B/b insulin ratio, glycaemic parameters, and lipid profile.

Key Words: *Bolus/basal insulin ratio, Type 1 Diabetes mellitus, HbA1c, Low-density lipoprotein, Lipid profile.*

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INTRODUCTION

Type 1 Diabetes mellitus (T1DM) is a chronic disease with absolute insulin deficiency due to beta-cell destruction in the pancreas. Patients with T1DM need multiple daily insulin injections to keep their blood glucose level within the normal range. Both first- and second-phase insulin secretions are impaired in patients with T1DM due to autoimmune beta-cell destruction.[1] Therefore, the standard treatment of patients with T1DM is basal and bolus insulin administration, which is similar to physiological insulin secretion.[2] With daily insulin therapy, regular blood glucose monitoring, and ongoing patient education, healthy life can be maintained, and several diabetes-related complications can be delayed or prevented.[2]

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The current guidelines suggest that the ratio between basal and bolus insulin requirements in patients with T1DM varies between 50/50 % and 40–60 %.[2,3] Several patients in the developing countries lack knowledge about accurate carbohydrate counting owing to the inadequate diabetes education.[4] Therefore, these patients receive fixed bolus insulin doses at each meal. The biggest challenge with the use of fixed-dose insulin is that the dose is not adjusted according to the amount of carbohydrate consumed in the meal; therefore, the bolus insulin dose may either be insufficient or excessive. This results in frequent hypo- or hyperglycaemic episodes and impairs the patient's quality of life. No study investigating the relationship between increased bolus/basal (B/b) insulin ratio and HbA1c, lipid profile, and success of treatment in adult patients with T1DM is available. Therefore, this study aimed to investigate the effect of insulin doses administered in patients with T1DM on metabolic control and examined the relationship of the B/b insulin ratio with lipid profile and glycaemic parameters.

METHODOLOGY

The study included 181 patients who were diagnosed with T1DM in the Endocrinology and Metabolism Department of

Diskapi Yildirin Beyazit Training and Research Hospital, between January 2015 and March 2020. The study was conducted as a retrospective observational study among outpatients with T1DM. The demographic data was obtained by scanning the patients' files. The HbA1c, fasting glucose (FG), fasting total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C) levels recorded in the last clinic visit were obtained from the medical records. Patients with other types of diabetes, pregnant or breastfeeding, those who use continuous subcutaneous insulin infusion (CSII), metformin and antihyperlipidaemic agents, those who adjust their insulin dose based on carbohydrate counting, those with additional endocrine diseases or drug use, such as corticosteroids that disrupt diabetes regulation, were excluded from the study. Dyslipidaemia in T1DM was defined by the American Association of Clinical Endocrinologists Medical Guidelines.[5] Patients with an HbA1c level of <58 mmol/mol (7.5%) with basal-bolus insulin therapy were considered to have reached the target HbA1c level. The total basal and bolus insulin doses used daily by each patient were calculated separately. The patients were divided into two groups with <1.5 and ≥1.5 B/b insulin ratios. Glycaemic parameters and lipid profiles were compared between the two groups.

The assays were performed in the authors' centre using a biochemical analyser. Biochemical parameters were measured by the Roche Cobas Integra 800 device (Roche Diagnostic Ltd). HbA1c was measured using the high-performance liquid chromatography method. The lipid profile was determined using enzymatic colorimetric assays by spectrophotometry.

Statistical analyses were performed using SPSS software (version 23.0, SPSS, IBM Corporation, NY, USA). Categorical data, such as gender, insulin type, and B/b insulin ratio, were summarised with frequencies and percentages (%). Variables were preliminarily tested for normal distribution with the Kolmogorov–Smirnov test. All continuous variables with normal distribution were expressed as mean ± standard deviation (SD), and nonnormally distributed variables were expressed as median (range) values. The independent samples t-test was used to compare continuous variables with normal distributions. The Mann–Whitney U test was used for nonnormally distributed variables. The differences between categorical variables were analysed by Chi-square analysis, and the correlation between numerical variables was analysed by Pearson's correlation analysis. Binary logistic regression analysis was performed to evaluate the relationships between independent variables. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 181 patients with T1DM were enrolled in the study. The patients comprised 94 (51.9%) females and 87 (48%) males with a mean age of 30.1±9.2 years. The demographic and biochemical data of the whole study group are presented in Table I.

Table I: Demographic and laboratory data of the patients with T1DM.

	Total population (n = 181)
Age (year)	30.1 ± 9.2
Gender (F/M)	94(51.93%)/87(48.06%)
BMI (kg/m^2)	22.5 ± 2.5
Diabetes duration (year)	7 (1–39)
FPG (mg/dL)	256 ± 119.6
HbA1c (mmol/mol)	97.8 ± 40.8
Creatinine (mg/dL)	0.79 (0.4–4.07)
Albumin/creatinine (µg/mg)	10.7 (1.9–3142)
Total cholesterol (mg/dL)	179.5 ± 48.1
Triglyceride (mg/dL)	105 (38–705)
LDL cholesterol (mg/dL)	120.1 ± 38.5
HDL cholesterol (mg/dL)	49.2 ± 13.6
Non-HDL cholesterol (mg/dL)	119.7 (43–331)

F: Female, M: Male, BMI: Body mass index, FPG: Fasting plasma glucose, LDL: Low-density lipoprotein, HDL: High-density lipoprotein.

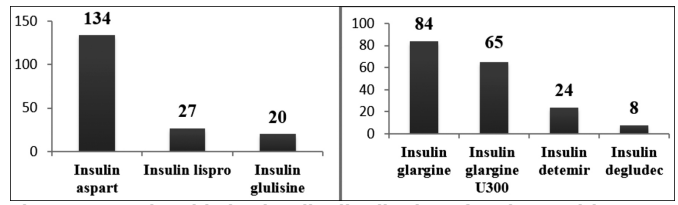

Figure 1: Basal and bolus insulin distribution of patients with Type 1 Diabetes mellitus.

The HbA1c level was <58 mmol/mol (7.5%) in only 11.6% (n=21) of the patients. The mean daily insulin dose was 55.9±25.1 units. The mean daily basal insulin dose was 20.8±9.8 units, and the daily bolus insulin dose was 35.1±17.6 units. Basal and prandial insulin types used by the patients are shown in Figure 1.

Microvascular complications were found in 56 (30.9%) patients. Neuropathy, nephropathy, and retinopathy were found in 39 (21.5%), 26 (14.4%), and 24 (13.3%) patients, respectively. More than one microvascular complication was found in 22 (12.1%) patients. The rate of dyslipidaemia in the patients with T1DM was 68.5% (124/181). High LDL-C was the most frequent type of dyslipidaemia. Of the patients with T1DM, 67.9% (123/181), 43% (78/181), and 28.7% (52/181) had high LDL-C, non-HDL-C, and TG levels, respectively. Abnormality in all lipid profile parameters was found in 18.7% of the patients. LDL-C (122 [10–241] mg/dL, 92.5 [55–201] mg/dL; p=0.01) and TG (111 [39–705] mg/dL, 63 [38–149] mg/dL; p=0.001) levels were found to be lower among patients with optimal HbA1c levels.

A positive correlation (r=0.287, p<0.001) was found between the B/b insulin ratio and HbA1c level. The clinical and biochemical data of patients with ≥1.5 and <1.5 B/b insulin ratios are reported in Table II. No difference between the two groups in terms of age, gender, BMI, and duration of diabetes was noted. Fasting plasma glucose (FPG) and HbA1c levels were higher in those with ≥1.5 B/b insulin ratio. The rate of patients who reached the target HbA1c level was higher in patients with <1.5 B/b ratio (20.6%, 7.6%; p=0.01). As a result of the binary logistic regression analysis, the number of patients who reached the target HbA1c level was 3.57-fold higher in those with <1.5 B/b insulin ratio (odds ratio=3.57, 95% confidence interval: 1.3–9.1; p=0.008).

Table II: Analysis of variables according to the B/b insulin ratio.

	B/b insulin ratio <1.5 (n = 63)	B/b insulin ratio ≥1.5 (n = 118)	p-value
Age (year)	30.7 ± 10.1	29 ± 8.4	0.26 *
Gender (F/M)	28(44.4%)/35(55.6%)	66(55.9%)/52(44.1%)	0.14**
BMI (kg/m^2)	23 ± 2.7	21.6 ± 2.6	0.13*
Diabetes duration (year)	8 (1–39)	7.5 (1–30)	0.67***
FPG (mg/dL)	231.1 ± 106.4	275.6 ± 130.8	0.02*
HbA1c (mmol/mol)	89.6 ± 30.5	104.4 ± 46.9	0.02*
Creatinine (mg/dL)	0.76 (0.44–7.69)	0.80 (0.4–4.07)	0.34***
Albumin/creatinine (µg/mg)	8.8 (1.9–16.7)	12.1 (2–31.42)	0.38***
Total cholesterol (mg/dL)	188.8 ± 44.5	174.2 ± 51.3	0.13*
Triglyceride (mg/dL)	101 (40–705)	106 (38–686)	0.65***
LDL cholesterol (mg/dL)	127.8 ± 36.6	116.7 ± 39.7	0.11*
HDL cholesterol (mg/dL)	50.2 ± 13	48.6 ± 14.2	0.56*
Non-HDL cholesterol (mg/dL)	124.5 (90–290)	113 (43–331)	0.06***
The rate of patients who reached the target HbA1c	13 (20.6%)	9 (7.6%)	0.01**
Neuropathy	14 (22.2%)	27 (22.9%)	0.92**
Nephropathy	12 (19%)	18 (15.2%)	0.51**
Retinopathy	8 (12.7%)	16 (13.6%)	0.87**

B/b: Bolus/bazal, F: Female, M: Male, BMI: Body mass index, FPG: Fasting plasma glucose, LDL: Low-density lipoprotein, HDL: High-density lipoprotein.
**The independent samples t-test was used, **Chi-square analysis was used, ***The Mann–Whitney U test was used.*

Lipid profiles were similar between the two groups. No relationship was found between microvascular complications and the B/b insulin ratio (p=0.57). When the microvascular complications were evaluated separately, no relationship was found between the three complications and the B/b insulin ratio (neuropathy, p=0.92; nephropathy, p=0.51; retinopathy, p=0.87).

DISCUSSION

Several observational studies have reported that the vast majority of patients with T1DM fail to reach the HbA1c target despite the proper treatment and follow-up.[4,6,7] In the present study, only 11.6% of the patients had HbA1c at the targeted level, which is <58 mmol/mol. In patients with T1DM, factors, such as good diabetes management, self-care, and nutrition, are critical for disease prognosis and have been shown to minimise the risk of complications. A recent meta-analysis has demonstrated the relationship between poor diabetes management, being far from the HbA1c target level, and low socioeconomic status.[4] The studies examining large patient groups have conclusively shown that the patients who count carbohydrates have better metabolic control and lower HbA1c levels.[8,9] Furthermore, it has been known that CSII provides better glycaemic control than basal–bolus insulin therapy in patients with T1DM.[10] However, the CSII technology is costly and inaccessible, especially in most developing countries. Although CSII is recommended instead of basal–bolus insulin therapy in adult patients with T1DM owing to providing better glycaemic control, the basal–bolus insulin regimen is still the most commonly used insulin therapy in treating T1DM due to the cost and accessibility problems of CSII, especially in developing countries.[10] Since patients who use CSII and know carbohydrate counting were not included in this study, the number of patients who reached the target HbA1c level was low.

The American Diabetes Association guideline recommends that 50% of the basal 50% of the daily insulin requirement be administered as a bolus in patients with T1DM.[4] The Society of Endocrinology and Metabolism of Turkey guideline recommends that a minimum of 40% of the daily insulin requirement be administered as basal insulin.[3] Despite these recommendations, the rates cannot be fully applicable in a real-life setting owing to patient-related factors. Particularly, patients who do not know how to count carbohydrates administer a daily fixed-dose of basal and bolus insulin and adjust the bolus dose according to the postprandial glucose level. Few real-life studies have evaluated the relationship between the B/b insulin ratio and glycaemic parameters among patients with T1DM.[6,11] In the current study, the basal insulin dose was found to be >40% of the daily insulin dose in only 34.8% of the patients. Moreover, in this study, the HbA1c level was lower in patients with <1.5 B/b ratio, and the number of patients who reached the target HbA1c level was higher. According to the results of this study, it was determined that the increase in the B/b insulin ratio was associated with the high HbA1c level. Additionally, the results showed that achieving the HbA1c target level was more difficult in patients who needed more bolus insulin. It can be hypothesised that the reason for the high HbA1c level in patients with a high B/b insulin ratio is that the fixed bolus dose administered is not compatible with the amount of carbohydrate consumed. Particularly, the fixed bolus insulin dose administered at each meal may either be insufficient or excessive according to the amount of food consumed, and this may cause glycaemic variability that causes blood glucose fluctuations in patients with diabetes. In the literature, several studies support this hypothesis and report that HbA1c levels are higher in patients with Type 1 Diabetes mellitus with glycaemic variability.[12,13] Carbohydrate counting may be more appropriate than fixed bolus dose titration in patients with postprandial hyperglycaemia. Therefore, the significance of education and the effect on glycaemic parameters should be thoroughly explained to patients who do not know carbohydrate counting, and patients should be motivated in this regard.

Recently, some studies have reported that glycaemic variability is involved in the pathogenesis of diabetic complications and is a possible independent risk factor for these complications.[14] However, the effect of glycaemic variability on microvascular complications is still under debate due to the inconclusive evidence.[15] In this study, the authors believed that glycaemic variability may be higher in patients who used more bolus insulin doses than those who used basal insulin, and a higher rate of microvascular complications was expected in these patients. Conversely, no relationship was found between the B/b insulin ratio and microvascular complications in the present study. The result is believed to be due to the young age of patients with diabetes and the small number of patients with microvascular complications.

Dyslipidaemia is a well-known risk factor for atherosclerotic cardiovascular diseases.[16] Patients with T1DM have a 2–4 fold greater risk of developing atherosclerosis than individuals with no diabetes.[17] The prevalence of dyslipidaemia in patients with T1DM ranges from 14% to 72%.[17-19] Regarding the atherogenic profile, the most commonly reported findings of patients with dyslipidaemia in T1DM include elevated LDL-C, non-HDL-C, and TG values, which are consistent with the results of the present study.[17] Here, the most common type of dyslipidaemia was the increased LDL level. The recent studies have reported that glycaemic control is associated with dyslipidaemia.[20,21] Consistent with the results of this study, it has been reported that higher LDL-C and TG levels are more common in patients with poor glycaemic profiles in the literature.[20,21] In this study, dyslipidaemia was detected in the majority of the patients, which was believed to be because the glycaemic target levels were not achieved in most of the patients.

This study has some limitations. First, this is a retrospective single-centre study. Second, the daily physical activities and carbohydrate consumption of the patients are not exactly known. Finally, VLDLs, apolipoproteins, and lipoprotein (a) levels could not be evaluated in this study. The effect of the B/b insulin ratio on the lipid profile of patients with T1DM can be more clearly demonstrated by studies that include the abovementioned lipid levels and are specifically conducted for this purpose.

CONCLUSION

Bolus insulin comprised >60% of the total daily insulin dose in the vast majority of patients with T1DM treated with fixed basal–bolus insulin dose, and only 11.6% of the patients had optimal HbA1c levels. A positive correlation was observed between the B/b insulin ratio and HbA1c level, and the number of patients reaching the target HbA1c level was lower in those with a B/b insulin ratio of ≥1.5. Further prospective studies, including patients who know carbohydrate counting, are necessary to define a causal relationship between the B/b insulin ratio, lipid profile, and glycaemic parameters.

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ETHICAL APPROVAL:
The study was approved by the Ethics Committee of Diskapi Yildirim Beyazit Training and Research Hospital.

PATIENTS' CONSENT:
Informed consent was obtained from all participants included in the study.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
MC, IOU, DS: Participated in data collection.
MC, MES: Contributed to interpretation of results and data analyses.
MC, IOU, MES: Contributed to the discussion.
MC: Wrote and edited the manuscript.
MC, MO, EC: Contributed to the study design and reviewed the manuscript.
All authors have approved the final version of the manuscript to be published.

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