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ASSOCIATION OF REACTIVE HYPOGLYCEMIA WITH BODY MASS INDEX, HOMEOSTATIC MODEL ASSESSMENT OF INSULIN RESISTANCE AND COMORBIDITY

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Abstract

Objectives: Untreated hypoglycemia at profoundly low levels restrains the delivery of energy to vital organs and causes a series of extreme adverse events, ultimately resulting in coma and death. The purpose of the study was to determine the relationship between body mass index (BMI), homeostatic model assessment of insulin resistance (HOMA-IR), and co-morbidities in patients experiencing hypoglycemia during an oral glucose tolerance test (OGTT).

Materials and Methods: We retrospectively analyzed the medical records of all patients presented to the diet outpatient clinic between 2015 and 2020 for OGTT. After an overnight fast of 10-12 hours, the patient's fasting insulin (HOMA-IR) and fasting glucose were recorded. A 330cc solution of glucose (containing 75 grams of dextrose anhydride) drink was used for the OGTT. Following this, blood glucose was measured at 30, 60, 120, 180, and 240 minutes. The obtained data were analyzed using descriptive and inferential statistics.

Results: A total of 614 patients were analyzed. A positive correlation was found between BMI and HOMA-IR ($p \leq 0.001$), BMI and blood glucose ($p \leq 0.001$). Although hypoglycemia rates were higher in overweight and obese patients, the difference was not significant ($p = 0.316$). The presence of co-morbidity did not affect the incidence of hypoglycemia ($p = 0.413$).

Conclusion: We observed that increased BMI was associated with having HOMA-IR and high glucose levels at 0-30-60-120 minutes in OGTT. Although hypoglycemia during the OGTT was not associated with BMI in this study, large-scale studies are needed to reveal this relationship.

Keywords: Glucose tolerance test, reactive hypoglycemia, insulin resistance.

Introduction

Glucose, the main source of energy for the body, plays an integral role in maintaining the dynamic balance of the body. According to the American Diabetes Association, a fasting plasma glucose value between 70 to 99 mg/dL (3.9 mmol/L-5.5 mmol/L) is considered normal.[1] Any variation in these values results in either hypoglycemia or hyperglycemia, each with its own significant consequences. During the initial phases of hypoglycemia (<70-54 mg/dL), a series of autonomic nervous symptoms are observed, including tachycardia, tremor, sweating, nausea, and hunger. With the further reduction of blood glucose (<54 mg/dL), there is a loss of energy supply to vital organs resulting in confusion, dizziness, lethargy, seizures, coma, and sudden death.[1-3] Reactive or biochemical hypoglycemia is a postprandial hypoglycemic state that mostly occurs after 2-5 hours of food intake.[4,5] Possible mechanisms include insulin resistance in combination with inappropriately high insulin levels, impaired insulin clearance, and insulin hypersensitivity.[6,7]

Although reactive hypoglycemia does not attract attention, if left untreated, it may result in emotional disturbances, irritability, risk of trauma due to falls or road traffic accidents, and sudden death.[2,8] Despite the increased prevalence of reactive hypoglycemia during oral glucose tolerance test (OGTT) among the general population (0.53-50%), there are limited studies available that focus on the factors associated with these hypoglycemic episodes.[4,9-11] Hence, the present study was carried out to determine the association between body mass index (BMI), homeostatic model assessment of insulin resistance (HOMA-IR) and the presence of co-morbidity in people with hypoglycemic episodes during OGTT.

Materials and Methods

A retrospective study was carried out to analyze the medical records of patients who visited the Diet outpatient clinic for OGTT between 2015 and 2020. The study was approved by the institutional ethical committee. All patients with symptoms of hypoglycemia regardless of weight, patients who experienced rapid weight gain (at least 1.50 kg per month for three months within the past year) with mild or no symptoms of hypoglycemia and those patients with a pre-diagnosis of hypoglycemia were included in the study. Children ≤14 years of age, pregnant women, patients with gradual weight gain (in more than a year), patients with diabetes, those using an antidiabetic medication, or patients unable to continue the test due to their hypoglycemic symptoms such as nausea, vomiting, and low blood pressure within the first hour of OGTT were excluded from the study. Informed consent was obtained prior to the test. The patient's age, sex, height, and weight were recorded before the test. Height and weight for BMI were measured using a stadiometer (model 240, Seca, Germany) and a digital scale (WB-300 Plus, Tanita, Japan).

Patients were instructed not to consume food after 22.00 hours on the previous night and fast for at least 10 hours prior to the test. Water intake of only one glass was permitted, if necessary. A single antecubital intravenous catheter was inserted for blood sampling. At the 0th minute, blood was drawn to check fasting glucose and insulin. An apple-flavored glucose drink (Glucosol)® containing 91 kcal in 100 cc solution was used for the OGTT. The patients were asked to drink measuring 330 ccs containing 82.50 grams of dextrose monohydrate, equivalent to a total of 75 grams of dextrose anhydride. Following this, blood samples were drawn at 30 min, 60 min, 120 min, 180 min, and 240 min to check blood glucose levels. Glucose was measured by the hexokinase enzymatic method using a gel tube with the Beckmann Coulter AU480 instrument. Insulin was measured with the Chemiluminescence method with the Beckmann Coulter Access2 instrument using a gel tube.

Definition of variables

The blood glucose level of < 70 mg/dL (3.9 mmol/L) and ≥ 54 mg/dL (3.0 mmol/L) was considered as the cut-off value for hypoglycemia.[1] BMI was calculated as weight divided by height squared (kg/m^2), and patients were categorized as underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥30 kg/m^2).[12] HOMA-IR was calculated by multiplying fasting glucose with fasting insülin divided by 405. Regardless of gender, a value ≥ 2.5 was considered significant, suggesting insulin resistance.[13] The association of the following co-morbidities with hypoglycemia was studied: hypothyroidism, unspecified (E03.9), anxiety disorder, unspecified (F41.9), headache (R51), essential (primary) hypertension (I10), asthma (J45), excessive, frequent and irregular menstruation (N92), dizziness and giddiness (R42) (based on the ICD-10 Version-2019).[14]

Statistical analysis

The obtained data were entered in Microsoft Excel and analyzed using SPSS version 23. The descriptive statistics were expressed in terms of number and percentage. The continuous variables were compared using a one-way analysis of variance (ANOVA) test followed by Tukey's Post Hoc Analysis, while the frequency of dichotomous variables was performed by Chi-Square analysis or Fischer Exact Test (as appropriate). Pearson's correlation coefficient was used to analyze the relation between two continuous variables. A two-sided $p \leq 0.05$ was considered significant.

Results

The present study analyzed 614 patients, 545 (88.76%) females and 69 (11.24%) males. The mean age of patients was 37.90 ± 10.83 years, and the mean BMI was 29.30 ± 5.40 kg/m^2. Among the 614 patients, 125

(20.36%) had normal BMI, 249 (40.55%) were overweight, and 240 (39.09%) were obese. The average fasting glucose was 93.40± 9.90 mg/dL. Fasting insulin was measured only in 365 patients; the mean fasting insulin was 9.70 ± 5.70 µIU /mL. Similarly, the average score of HOMA-IR among 365 patients was 2.3 ± 1.5. HOMA-IR of ≥ 2.5 was observed in 134 (36.71%) patients.

A positive correlation was found between BMI and HOMA-IR (p≤0.001) (Table 1). Additionally, the HOMA-IR in the normal weight and overweight patients was significantly different from the obese patients (Table 2). Similarly, a positive correlation was found between the BMI and glucose levels of patients. The higher the blood glucose, the BMI was found to be significantly higher (p≤0.001). Table 3 shows the difference in the BMI levels of patients at each blood sugar estimation phase. It was found that the blood glucose was significantly higher among obese patients at fasting (p=0.002), 30 minutes (p≤0.001), 60 minutes (p≤0.001), and 120 minutes (p≤0.001) as compared to other groups. However, at 180 minutes (p=0.181) and at 240 minutes (p=0.448), there was a decrease in blood glucose levels among obese patients.

During OGTT, blood glucose was examined a total of 3684 times, that is six times in 614 patients each. Among these patients, hypoglycemia was detected in 344 patients (56.02%) 421 times (11.42%). A higher incidence of hypoglycemia (90.94%) was observed between 180 and 240 minutes during OGTT. Of these, 78.82% of hypoglycemia occurred in patients with a BMI of ≥25. Blood glucose levels between 54 and 70 mg/dL, suggesting 1st-degree hypoglycemia, were observed in 294 (85.43%) patients at 371 (88.11%) times. 2nd-degree hypoglycemia was characterized by a blood glucose value of <54 mg/dL observed in 50 (14.64%) patients at 50 (11.91%) times. Hyperglycemia (≥200 mg/dL) and hypoglycemia (<70 mg/dL) occurred in the same case in 33 (5.37%) patients. Most of the patients (270, 44.0%) had a single episode of hypoglycemia, followed by two episodes in 71 (11.58%) patients, and three episodes were observed in 3 (0.49%) patients (Fig. 1). Multiple episodes were common in patients in the overweight and obese category as compared to normal weight; however, the difference was not statistically significant (p= 0.316). We observed a significant difference in the mean BMI levels regarding different recurrence rates of hypoglycemia (p=0.011) (Table 4).

In our study, a total of 181 (29.47%) patients had associated co-morbidities. Among them, hypoglycemia was observed in 106 (58.56%) patients (Fig. 2). The most common co-morbidity in patients with hypoglycemia was hypothyroidism (25.62%), followed by irregular menstruation (24.45%), anxiety disorder (18.46%), hypertension (12.77%), headache (10.93%), dizziness (3.93%), and asthma (3.86%). Among 270 patients with no hypoglycemia, co-morbidity was present in 76 (28.15%) patients. Irregular menstruation (27.34%) was the most common finding, followed by hypothyroidism (20.95%), anxiety disorder (19.13%), hypertension (15.21%), headache (9.86%), dizziness (5.02%) and asthma (3.16%). Co-morbidity was slightly higher in patients with hypoglycemia than in patients without hypoglycemia (30.84% versus 28.11%). We did not observe a significant association between the presence of co-morbidity with hypoglycemia (p=0.413) and also

with the frequency of hypoglycemic episodes (p= 0.568). Table 5 summarizes the presence or absence of hypoglycemia with the presence of co-morbidity and its association with BMI levels. Higher BMI was found in individuals who exhibited both hypoglycemia and co-morbidity; however, this difference was not statistically significant (p= 0.188).

Table 1. Association of BMI and HOMA- IR.

Group	n	Mean HOMA-IR	Std. Deviation	F	p
Normal Weight	50	1.79	0.90	13.434	≤0.001*
Overweight	159	2.03	1.19		
Obese	156	2.74	1.77		

(BMI: Body Mass Index; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance)
*ANOVA test, the p-value is significant at <0.05

Table 2. Tukey's Post Hoc Analysis for checking the association of BMI and HOMA- IR.

(I) BMI	(J) BMI	Mean Difference (I-J)	Std. Error	p
Normal Weight	Overweight	-0.24	0.23	0.561
	Obese	-0.95*	0.23	≤0.001*
Overweight	Normal Weight	0.24	0.23	0.561
	Obese	-0.72*	0.16	≤0.001*
Obese	Normal Weight	0.95*	0.23	≤0.001*
	Overweight	0.72*	0.16	≤0.001*

(BMI: Body Mass Index; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance)
*Tukey's Post Hoc Analysis. The mean difference is significant at the 0.05 level.

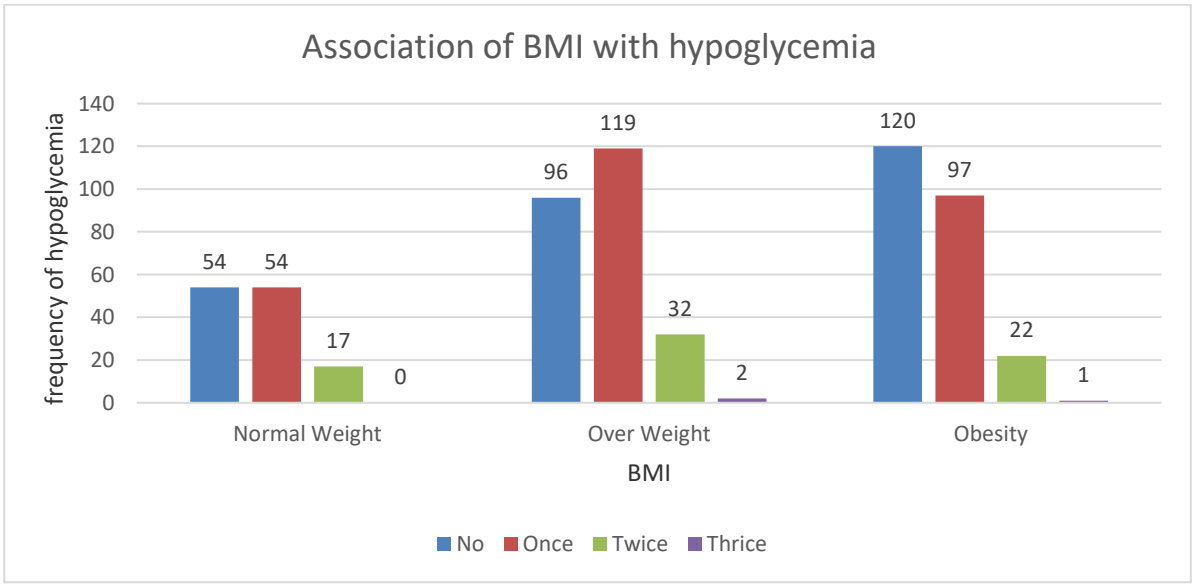

Figure 1. Bar diagram showing the frequency of hypoglycemic episodes with different grades of Body Mass Index (BMI).

Table 3. Association between BMI and Blood glucose levels at different intervals.

BMI *Blood glucose		n	Mean- Blood glucose	Std. Deviation	F	p
0 Minutes					6.238	0.002*
	Normal Weight	125	91.50	8.94		
	Overweight	249	92.76	9.54		
	Obese	240	95.05	10.60		
30 Minutes					14.872	≤0.001*
	Normal Weight	125	138.70	27.18		
	Overweight	249	146.35	28.49		
	Obese	240	154.96	27.54		
60 Minutes					24.404	≤0.001*
	Normal Weight	125	124.94	36.80		
	Overweight	249	136.29	38.98		
	Obese	240	153.43	40.46		
120 Minutes					15.780	≤0.001*
	Normal Weight	125	100.86	24.34		
	Overweight	249	108.18	29.00		
	Obese	240	118.06	31.34		
180 Minutes					1.716	0.181
	Normal Weight	125	77.34	21.07		
	Overweight	249	76.43	20.64		
	Obese	240	79.66	17.70		
240 Minutes					0.805	0.448
	Normal Weight	125	75.72	11.24		
	Overweight	249	75.95	9.98		
	Obese	240	76.96	10.53		

(BMI: Body Mass Index)
*ANOVA test, the p-value is significant at <0.05

Table 4. Correlation of Mean BMI with the frequency of hypoglycemia.

Hypoglycaemia	**n**	**Mean**	**Std. Deviation**	**F**	**p**
No	270	30.12	5.77	3.771	0.011*
Once	270	28.82	5.38		
Twice	71	28.19	4.30		
Thrice	3	28.47	1.75		

(BMI: Body Mass Index)
*ANOVA test, the p-value is significant at <0.05

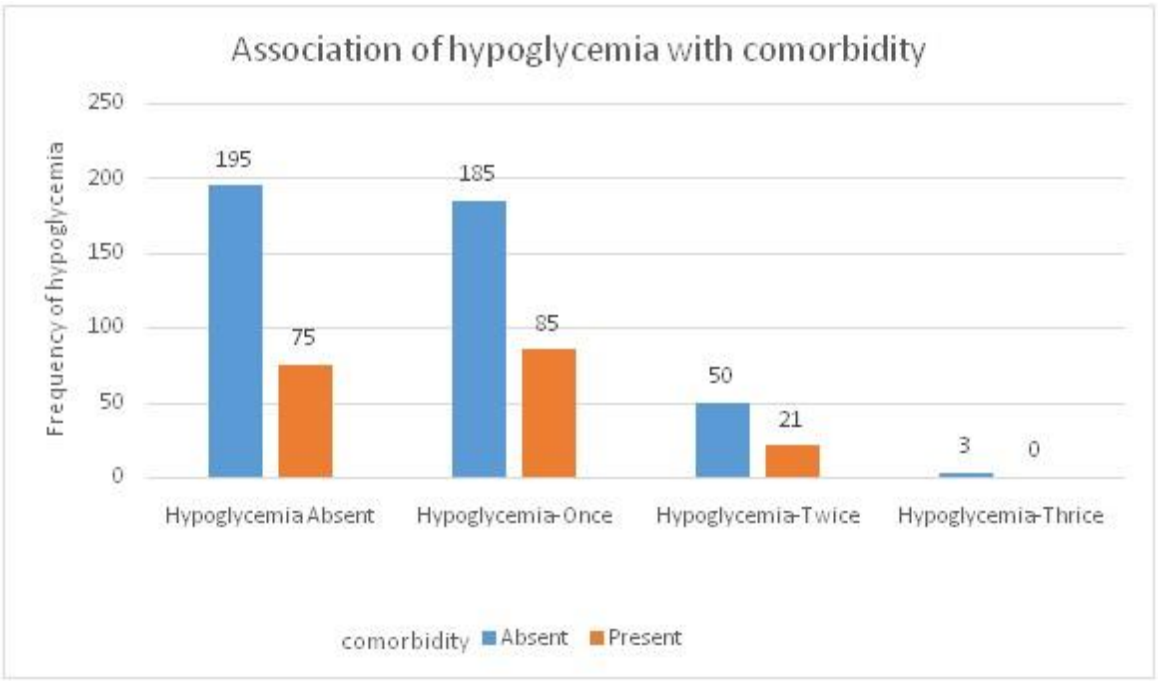

Figure 2. Bar diagram showing the frequency of hypoglycemic episodes in patients with co-morbidities.

Discussion

A drop in blood glucose levels below the normal limits after a few hours of food intake is known as reactive or biochemical hypoglycemia. Based on varying causes, it can either be idiopathic, alimentary, or diabetic. Regular insulin secretion with increased insulin sensitivity and the decreased response of glucagon are characteristics of reactive hypoglycemia.[4] Also, the presence of insulin resistance leads to basal-fasting hyperinsulinemia with subsequent insensitivity of beta-cell secretion. The resultant decrease or failure of first-phase insulin response results in exaggerated compensatory second-phase insulin secretion with resultant delayed hypoglycemia.[9] Although hypoglycemia is relatively rare finding as compared to hyperglycemia during OGTTs, it must not be ignored. Untreated hypoglycemia, especially the 2nd degree, characterized by profoundly low levels of blood glucose, is associated with increased morbidity and mortality.[8] In view of this, the present study was carried out to evaluate the association of hypoglycemia during OGTT with BMI, HOMA-IR, and the presence of co-morbidity.

The presence of clinical symptoms and low blood glucose during laboratory investigation and the reversal of symptoms with glucose ingestion confirms the diagnosis of hypoglycemia. However, the symptoms of hypoglycemia are unspecific, and there is a lack of a standardized questionnaire.[15,16] With a blood glucose cut-

off value of <70 mg/dL, the incidence of hypoglycemia in our study was 56.02%. Among these, 85.43% had 1st-degree hypoglycemia (between 54-70 mg/dL), and 14.64% had 2nd-degree hypoglycemia (<54 mg/dL). Incidence was much higher as compared to the previous studies in which the rates were between 0.53% and 5,0% at <54 mg/dL, between 12.3% and 46.6% at 70 mg/dL.[4,5,8,10,17] The difference in the incidence could be because of the variable cut-off values used in the definition of hypoglycemia. However, the incidence of hypoglycemia was higher in our study compared to the studies using <70 mg/dL as the cut-off value as well. This could be because our study cohort consisted of patients with a pre-diagnosis of hypoglycemia who either described symptoms of hypoglycemia themselves or OGTT was requested by the clinician with the pre-diagnosis of hypoglycemia because they gained weight in a short time.

In our study, increased BMI (>25 kg/m^2) was observed in 79.64% of patients. The mean age of the patients with hypoglycemia in our study was less (37.9 ± 10.8 years) as compared to the age reported by Cai et al. (42.5 ± 13.1 years), while the mean BMI was much higher (29.3±5, 42 vs. 2.8 ± 3.2 kg/m^2).[9] Previous studies have suggested that in Type 2 Diabetes Mellitus with an increased BMI, the severity of hypoglycemia decreases.[18] Elliott et al. and Alghamdi et al. suggested that low body weight is a strong predictor of hypoglycemia. It is believed that a lower BMI may partially reflect a state of malnutrition, which invariably increases the risk of hypoglycemia.[17-19] On the contrary, Lv et al. suggested a positive correlation between BMI and hypoglycemia.[2] In our study, the incidence of hypoglycemia was higher with increased BMI; however, the difference was statistically insignificant. Also, the frequency of hypoglycemic episodes was independent of BMI. Despite higher secretion of insulin, there was a gradual reduction in blood glucose in obese patients suggesting insulin resistance resulting in secondary hyperinsulinemia and lower blood glucose levels.[2]

According to Altuntas et al., hypoglycemia due to alimentary causes has an early onset (<120 minutes), while idiopathic hypoglycemia and diabetic hypoglycemia have late onset, commonly observed at 180th minutes and 240th-300th minutes, respectively.[4] We observed a higher incidence of hypoglycemia (90.94%) between the 180th and 240th minutes during OGTT. A positive correlation between BMI and blood glucose was observed in our study. Although higher blood glucose was observed in obese patients during the initial phases of OGTT, there was a decrease in blood glucose at 240th minutes. Our results are in accordance with Lv et al., who reported no significant difference in the fasting glucose levels between different BMI groups; however, they observed a sharp decline of glucose levels in the obesity group as compared to the normal and overweight groups.[2]

Basal hepatic glucose production reflecting hepatic insulin sensitivity is closely related to fasting blood glucose. Fasting glucose levels were higher in polycystic ovary syndrome cases with increased BMI, which explains the higher blood glucose observed in our study group. The decrease in insulin sensitivity in the form of late hypoglycemia occurring at 4 hours postprandial explains the hypoglycemia observed at 240th minutes.[4]

Insulin resistance, a risk factor for hypoglycemia and subsequent diabetes, affects 25% of the general population. Previous case reports have suggested that reactive hypoglycemia associated with insulin resistance and impaired glucose tolerance subsequently normalized after appropriate treatment.[20,21] This suggests that reactive hypoglycemia might be an indicator of early beta-cell dysfunction. Hyperinsulinemic-euglycemic clamp (HEC) is the gold standard for measuring insulin resistance; however, it is neither feasible nor cost-effective.[22] HOMA-IR used in our study is easy to calculate and effectively reflects insulin resistance. Higher levels of HOMA-IR were observed in patients with hypoglycemia, suggesting higher insulin resistance.[9] We observed insulin resistance in 36.7% of patients.

Similar to the findings by Awede et al. and Lv et al., a direct correlation between BMI and HOMA-IR was observed in our study.[2,23] To maintain blood glucose homeostasis, insulin secretion is higher in patients with a higher degree of insulin resistance, suggesting a direct correlation between insulin demand and weight gain. Moreover, these patients have decreased insulin sensitivity, which delays the secretion of insulin. A combination of increased insulin resistance and decreased insulin sensitivity results in delayed hypoglycemia.[24,25] On the contrary, Parekh et al. have suggested a mechanism of increased insulin sensitivity rather than insulin resistance resulting in hypoglycemia during 2-hour OGTT suggesting a lower diabetic risk; however, further studies were warranted in this regard.[10]

Excess fat mass and visceral adiposity are potential risk factors for diabetes and cardiovascular diseases, amongst others.[13] Previous studies have suggested an association between hypoglycemia in diabetic patients in the presence of comorbid conditions such as a history of cardiovascular diseases, stroke, renal disease, polycystic ovary syndrome, and cystic fibrosis.[4,10,13,19,26] In our study, the most common co-morbidity in patients with hypoglycemia was hypothyroidism (25.62%), followed by irregular menstruation (24.45%), anxiety disorder (18.46%), hypertension (12.77%), headache (10.93%), dizziness (3.93%) and asthma (3.86%). However, we did not observe a significant association between the presence of co-morbidity with hypoglycemia and the frequency of hypoglycemic episodes. Similar to the results by Yun et al., we did not observe a strong relationship between hypoglycemia in higher BMI patients with co-morbidities.[18]

The study has certain limitations. A smaller sample size and selection bias of the study cohort limits the generalizability of the study results. Further, data on fasting insulin was available only in a subset of the population, which might have affected the correlation between BMI and HOMA-IR. Hypoglycemia was considered only based on the OGTT values without taking clinical symptoms into account. We would like to emphasize the necessity of larger epidemiological studies to assess the risk factors associated with hypoglycemia in the general population.

In conclusion, we observed that increased BMI was associated with having HOMA-IR and high glucose levels at 0-30-60-120 minutes in OGTT. The occurrence of biochemical/reactive hypoglycemia during OGTT may be an indicator of early β-cell dysfunction and insulin resistance, suggesting the presence of underlying disease. Since biochemical hypoglycemia is linked to higher BMI due to poor diet and lifestyle habits, it is essential to identify these people in the initial phases through OGTT and intervene at the earliest to reduce the subsequent disease burden. Although hypoglycemia during the OGTT was not associated with BMI in this study, large-scale studies are needed to reveal this relationship.

Ethical Considerations: The study was approved by the local ethics committee (Reference No. 17.12.2020-40).

Conflict of Interest: The authors declare no conflict of interest.

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