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Hypovitaminosis D and Poor Nutritional Status are Independent Risk Factors of Insulin Resistance in Patients on Maintenance Hemodialysis

Dr. Md Abdul Hakim[1*], Prof. Dr. Md. Nazrul Islam[2], Dr. Md. Safayet Hossain Pramanik[3], Dr. Md. Saeed Hossain[4], Dr. Md. Tamim Aziz[5], Dr. Md. Shoriful Islam[6]

Abstract

Background: Insulin resistance is one of the essential components of metabolic syndrome, is recognized in patients on maintenance hemodialysis, and is directly associated with increased cardiovascular mortality. Vitamin D deficiency is a risk factor for glucose intolerance, and 1,25 dihydroxy cholecalciferol regulates insulin secretion. Malnutrition is also a risk factor for insulin resistance and is associated with increased morbidity and mortality.

Aims: To assess hypovitaminosis D, poor nutritional status, and independent risk factors of insulin resistance in patients on maintenance hemodialysis.

Methods: This cross-sectional study was conducted in the Department of Nephrology, Dhaka Medical College, Dhaka, from May 2021 to October 2022. This study included one hundred twenty patients on maintenance hemodialysis according to inclusion and exclusion criteria. Statistical analyses of the results were obtained using window-based computer software devised with statistical packages for social sciences (SPSS-26).

Results: It was observed that almost one-third (32.6%) of subjects belonging to age 41-50 years were insulin resistant, and 14(41.2%) were non-insulin resistant. The mean age was 50.36±12.03 years and 48.24±10.17 years in insulin and non-insulin resistance, respectively. More than half (53.5%) of subjects were male in insulin resistance, and 20(58.8%) in non-insulin resistance. According to the TST Z-score, 29(33.7%) and 2(5.9%) were malnourished in insulin-resistant presence and absence. According to the MAC Z-score malnourished was found 46(53.5%) insulin resistant were present, and 3(8.8%) were absent. According to the MAMC, Z-score malnourished was found in 37(43.0%) insulin-resistant patients and 3(8.8%) insulin-resistant patients. The difference between the two groups was statistically significant ($p<0.05$). Study subjects according to malnutrition score based on SGA, it was observed that more than two-thirds (67.4%) of subjects were mild to moderately malnourished in insulin resistant and 4(11.8%) in non-insulin resistant. The difference was statistically ($p<0.05$) significant between the two groups. About 78(90.7%) subjects had found Vitamin D deficiency (<20) levels in insulin resistant and 9 (26.47%) in non-insulin resistant subjects. Vitamin D deficiency had a 12.4 times risk of developing insulin resistance (OR=12.34; 95% CI=4.2-38.1). Eighteen (20.9%) of subjects had lower (<35g/l) serum albumin in insulin resistance and 2(5.9%) in non-insulin resistance. Low albumin had a 4.24 times risk of developing insulin resistance (OR=4.2;95% CI=0.9-28.2). The difference was statistically ($p<0.05$) significant between the two groups. Based on subjective global assessment, a significant positive

A iliation:

[1]Junior Consultant (Medicine), Upazila Health complex, Bagmara, Rajshahi, Bangladesh

[2]Professor & Head, Department of Nephrology, Dhaka Medical College, Dhaka, Bangladesh

[3]Medical Officer (IMO), Rajshahi Medical College Hospital, Rajshahi, Bangladesh

[4]Junior Consultant (Medicine), Upazila Health Complex, Sirajdikhan, Munshiganj, Bangladesh

[5]Assistant Registrar (Medicine), Shaeed M Monsur Ali Medical College hospital, Sirajgonj, Bangladesh

[6]Senior Consultant, Department of Medicine, 250 Beded General Hospital, Jashore, Bangladesh

***Corresponding author:**
Md. Abdul Hakim, Department of Nephrology, Dhaka Medical College, Dhaka, Bangladesh.

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and malnutrition scores. There is a negative significant correlation between insulin resistance and vitamin D.

Conclusion: Most of the patients on maintenance hemodialysis are Vitamin D deficient. Low Vitamin D levels and muscle mass will likely cause more insulin resistance in patients on maintenance hemodialysis.

Keywords: Chronic Kidney Disease; Dialysis; Insulin Resistance; Malnutrition; Nutritional Parameters; Vitamin D.

Introduction

Chronic kidney disease is a significant risk factor for cardiovascular disease, which is the leading cause of mortality in these patients. Cardiac mortality in dialysis patients is more than 10-fold more significant than that of the general population [1]. The excess cardiovascular mortality in patients with CKD is not fully explained by traditional risk factors such as hypertension, hypercholesterolemia, and smoking [2]. Chronic kidney disease is associated with insulin resistance, which plays a vital role in the pathogenesis of cardiovascular diseases [3]. The hyperinsulinemic-euglycemic clamp is the gold standard for IR determination because it directly measures whole-body sensitivity to insulin. Another is an oral glucose tolerance test, which primarily measures glucose tolerance, reflecting IR and beta-cell function. However, due to the complexity of these methodologies, more practical methods, such as homeostatic model assessment (HOMA) and the quantitative insulin sensitivity check index, are widely used in clinical studies [4]. Vitamin D deficiency has long been considered a glucose intolerance risk factor [5]. An inverse correlation between serum concentration of vitamin D and insulin resistance was found in NHANES III (National et al. Survey) participants [6]. Vitamin D has two bioequivalent forms, D2 (ergocalciferol) and D3 (cholecalciferol). Vitamin D3 is synthesized mainly from 7 dehydrocholesterol in keratinocytes of skin stimulated by UVB of sunlight. At the liver, cholecalciferol is hydroxylated to 25-hydroxycholecalciferol by the enzyme vitamin D-25-hydroxylase then finally to the primary active metabolite 1,25-dihydroxycholecalciferol in the kidney via further hydroxylation. In the intestine, 1,25-dihydroxycholecalciferol promotes calcium and phosphorus absorption, bone reabsorption, and the renal conservation of phosphorus. Vitamin D has a direct and indirect effect on insulin resistance. It stimulates pancreatic beta-cell receptors, increases insulin secretion and several insulin receptors, and increases the sensitivity of insulin receptors, thereby decreasing insulin resistance [7]. In chronic kidney disease, vitamin D status has been related to IR; however, minimal information is available on dialysis patients and factors affecting IR [8]. Insulin resistance can be physiologic (e.g., in pregnancy) or pathologic, as in chronic kidney disease, and it is linked to protein energy wasting and malnutrition in dialysis patients [9]. Again, protein-energy malnutrition is common in maintenance hemodialysis patients. Nutritional status is frequently ignored in many dialysis centers, even though simple nutritional assessment methods could favor patient management [10]. Muscle mass and body fat have significant associations with IR in dialysis patients [11]. Siew et al. have highlighted that IR is an essential determinant of protein breakdown in CKD. In CKD patients requiring dialysis, skeletal muscle is the primary tissue responsible for IR. IR increases with skeletal muscle mass; however, in sarcopenic patients, other factors such as metabolic acidosis, inflammation, and oxidative stress might be the main contributors to IR [8]. Protein-energy malnutrition causes insulin resistance, a state of metabolic derangement characterized by loss of somatic and visceral protein stores not entirely accounted for by inadequate nutrient intake. Insulin resistance has been associated with accelerated protein catabolism in the general population. Among end-stage renal disease (ESRD) patients, enhanced muscle protein breakdown has been observed in patients with Type II diabetes compared to ESRD patients without diabetes. In the absence of diabetes mellitus (DM) or severe obesity, insulin resistance is detectable in dialysis patients. It is strongly associated with increased muscle protein breakdown by activating a common proteolytic pathway [12]. Periodical monitoring of the nutritional status of dialysis patients is crucial for preventing, diagnosing, and treating protein energy malnutrition. Subjective global assessment (SGA) is a valuable and reproducible instrument for assessing the nutritional status of dialysis patients. Because of its strength, the National Kidney Foundation Kidney Disease/ Dialysis Outcome and Quality Initiative (NKF/KDOQI) recommends assessing the nutritional status of patients undergoing MHD using SGA at least once every six months [13]. Therefore, this study aims to assess hypovitaminosis D and poor nutritional status as independent risk factors of insulin resistance in patients on maintenance hemodialysis.

Methodology & Materials

This cross-sectional study was conducted in the Nephrology Department of Dhaka Medical College. Patients were selected by purposive sampling according to inclusion and exclusion criteria. One hundred twenty patients were enrolled in this study 18 months from [start] to [end]. After informing each participant about the study's aim, objectives, and procedure, informed written consent was obtained. Meticulous history was taken, and a physical examination was performed to include and exclude each patient. The study obtained ethical approval from the Research Review Committee (RRC) of the Department of Nephrology DMC.

Inclusion criteria:

- Patients on maintenance hemodialysis.

Exclusion criteria:

- Age <18 years.
- Patients on vitamin D supplementation.
- Patients with Chronic liver disease and polycystic ovarian syndrome
- Obesity (>30 kg/m2)
- Hyperthyroid, Hypothyroid, and Malignancy.
- Pregnant women.
- Patients are receiving any medications that may alter vitamin D levels (anticonvulsant, OCP, glucocorticoid).

Operational definitions:

ESRD patients are on regular hemodialysis for 8-12 hours/ week for at least three months [14]. Insulin resistance is when the hormone cannot bind to its receptors and signals the expected physiological responses, e.g., insufficient or defective insulin sensitivity [15]. Body mass index or BMI is a statistical index using a person's weight and height to estimate body fat in males and females of any age. It is calculated by taking a person's weight, in kilograms, divided by their height, in meters square. BMI defines a person as underweight, average weight, overweight, or obese instead of traditional height vs. weight charts. However, individual variations do exist. WHO recommends that ≥ 30.0 is obese, 25-29.9 is overweight, 18.5-24.9 is normal, and <18.5 is underweight [16].

Malnutrition:

Based on malnutrition score [17]-

- Patients were nourished with a score range of 7 to 10
- Mild to moderately malnourished with a score range of 11 to 20
- Moderate to severely malnourished with a score range of 21 to 35

Vitamin D status:

The 25 (OH) vitamin D reference values are per the Endocrine Society's guidelines [18].

Endocrine Society's classification of vitamin D status:

References value of 25 (OH) vitamin D	Ranges in serum (ng/ml)
Vitamin D sufficiency	≥30
Vitamin D insufficiency	20-29.99
Vitamin D deficiency	<20

Patient data on baseline characteristics (age, gender, BMI) associated with risk factors of CKD and hemodynamics, along with all other relevant socio-demographic particulars, were recorded in a predesigned data collection sheet. Then, the patients were assessed with investigations. Patients were instructed to attend the dialysis center on the scheduled day of dialysis with overnight (at least 8 hours) fasting state, and blood was taken from the peripheral vein before the start of dialysis for biochemical testing. Patient venous blood (5ml) was collected by sterile disposable syringe with aseptic precaution and immediately transferred to two dry clean test tubes. To estimate fasting blood glucose, 2cc blood was collected in a tube mixed with anticoagulant sodium chloride, and the rest of the blood was collected in another tube to analyze fasting insulin. After collection, samples were sent to the laboratory within thirty minutes and were measured by a fully automated biochemistry analyzer (Atellica, Siemens Germany, Capillar 3 Octa). Then, patients with insulin resistance will be diagnosed with the HOMA-IR index.

For the measurement of 25-hydroxy vitamin D, a 3ml blood venous blood sample was drawn. Then, it was collected in a tube, and after labeling it with the patient's name, ID number, and collection date, it was sent within 30 minutes for analysis. The serum was separated by centrifuge and was put on an analyzer (Atellica, Siemens Germany). Serum albumin was measured by an analyzer (Atellica, Siemens Germany, Beckman Coulter-DxC 700 AU). All laboratory investigations were carried out in the biochemistry laboratory of Bangabandhu Sheikh Mujib Medical University (BSMMU).

BMI and anthropometry were measured after dry weight was achieved. For BMI, height and post-dialysis weight were taken. Then, BMI was calculated using the weight formula (in kilograms)/height (in meters)2. Anthropometry in patients on maintenance haemodialysis was assessed 10- 20 minutes after the termination of the dialysis session. According to the National Health and Nutrition Examination Survey, anthropometry of mid-arm circumference (MAC), mid-arm muscle circumference (MAMC), and triceps skin fold thickness (TST) was measured on the non-fistula arm. The midpoint was marked between the upper edge of the acromion process's posterior border and the olecranon process's tip. This was the site for measuring mid-arm circumference (MAC) and triceps skin fold thickness (TST). Mid-arm circumference was measured using a flexible, non-stretchable measuring tape. All skin folds were measured with the skinfold caliper. Nutritional status was assessed using a malnutrition score based on subjective global assessment. Detailed patient-related medical history was obtained regarding the end dialysis dry weight (overall change in the past six months), dietary intake, gastrointestinal symptoms, functional capacity, and co-morbidities. Physical examination was done to observe subcutaneous fat loss and

signs of muscle wasting. The scoring sheet consists of two parts and seven elements. During each patient's evaluation, a questionnaire regarding the first five components or the patient's related medical history was obtained to facilitate the optimal evaluation.

Data Collection and Analysis:

Data was collected in a pre-tested questionnaire by taking history, conducting a clinical examination, determining laboratory findings, and determining patient outcomes. The researcher himself collected the data. Following data collection, the collected data was assessed for completeness, accuracy, and consistency before analysis was commenced. Data analysis was done using SPSS version 22 (IBM). Exploratory data analysis was conducted to describe the study population, where categorical variables were summarized using frequency tables. In contrast, continuous variables were summarized using measures of central tendency and dispersion such as mean, median, percentiles, and standard deviation. Qualitative or categorical variables were described as frequencies and proportions. The correlation was determined by Spearman's correlation coefficient (r). A level of P< 0.05 was considered statistically significant.

Results

The study included 120 subjects, 86 being insulin resistant and 34 not insulin resistant. Table 1 shows that almost one-third (32.6%) of subjects were 41-50 years in insulin resistant and 14(41.2%) non-insulin resistant. More than half (53.5%) of subjects were male in insulin resistance, and 20(58.8%) in non-insulin resistance. For the TST, 29 subjects (33.7%) in the insulin-resistant group had increased TST measurements compared to only two subjects (5.9%) in the non-insulin-resistant with significant differences. In the insulin-resistant group, 46 participants (53.5%) had increased MAC readings; in the non-insulin-resistant group, only three subjects (8.8%) had similar readings. The insulin-resistant group had 37 participants (43%) with more excellent MAMC readings than the non-insulin-resistant group, which included three subjects (8.8%). The two groups had a statistically significant difference (Table 2). According to the results, patients classified as well-nourished (SGA score 7 to 10) demonstrated a notably lower prevalence of insulin resistance compared to those categorized as mildly to moderately malnourished (SGA score 11 to 20). Specifically, 88.2% of well-nourished patients were found to be insulin resistant, in contrast to only 11.8% among the mildly to moderately malnourished group (Table 3). It is observed that 78 (90.7%) subjects had found Vitamin D deficiency (<20) levels in insulin resistant and 9 (26.47%) in non-insulin resistant subjects. Vitamin D deficiency had 12.4 times the risk of developing insulin resistance (OR=12.34; 95% CI=4.2-38.1). Serum albumin levels were lower (<35 g/l) in 18 (20.9%) of insulin-resistant patients and 5.9% in non-insulin-resistant subjects. Low albumin increased the likelihood of developing insulin resistance by 4.24 times (OR=4.2; 95% CI=0.9-28.2). The difference was statistically (p<0.05) significant between the two groups (Table 4). There was significant positive correlation between HOMA-IR with BMI (r=0.673;p=0.001), between HOMA-IR with TST (r=0.456;p=0.001), between HOMA-IR with MAC (r=0.589;p=0.001), between HOMA-IR with MAMC (r=0.393; p=0.001), between HOMA-IR with malnutrition score based on SGA (r=0.498; p=0.001) (Figure 1-5). A significant negative correlation was found between HOMA-IR and vitamin D levels (r = -0.532; p = 0.001) (Figure 6).

Table 1: Distribution of the study subjects according to demographic profile (N=120)

Demographic profile	Insulin resistant			
	Present (n=86)		Absent (n=34)	
Age (years)	n	%	n	%
<30	2	2.3	1	2.9
31-40	22	25.6	6	17.6
41-50	28	32.6	14	41.2
51-60	27	30.2	9	26.5
>60	8	9.3	4	11.8
Sex				
Male	46	53.5	20	58.8
Female	40	46.5	14	41.2

Table 2: Malnutrition status in the study population according to anthropometric measurement (N=120)

Anthropometric measurement	Insulin resistant				P value
	Present (n=86)		Absent (n=34)		
	n	%	n	%	
TST (mm)	29	33.7	2	5.9	0.001s
MAC (cm)	46	53.5	3	8.8	0.001s
MAMC (cm)	37	43	3	8.8	0.001s

Table 3: Distribution of the study subjects according to malnutrition score based on SGA (N=120)

Malnutrition score	Insulin resistant				P value
	Present (n=86)		Absent (n=34)		
	n	%	n	%	
Well (7 to 10)	28	32.6	30	88.2	0.001s
Mild to moderately (11 to 20)	58	67.4	4	11.8	
Severe (21 to 35)	0	0	0	0	

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Table 4: Distribution of the study subjects according to laboratory variable (N=120)

Laboratory variable	Insulin resistant				OR (95%CI)	P value
	Present (n=86)		Absent(n=34)			
25(OH)D (ng/ml)	n	%	n	%		
Vitamin D deficiency (<20)	78	90.7	9	26.47	12.4(4.2-38.1)	0.001s
Vitamin D insufficiency (20-29.99)	8	9.3	25	73.53		
Serum Albumin (g/l)						
Low (<35g/l)	18	20.9	2	5.9	4.2(0.9-28.2)	0.001s
Normal (35-50g/l)	68	79.1	32	94.1		

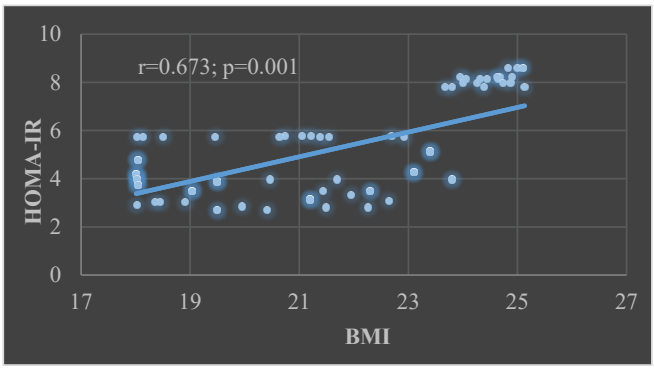

Figure 1: Scatter diagram showing correlation of HOMA-IR with BMI among study subjects

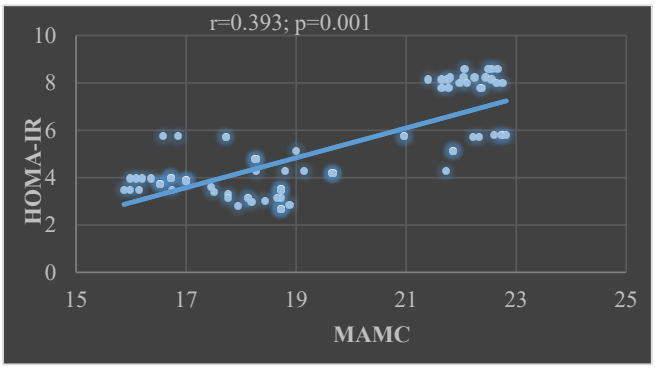

Figure 4: Scatter diagram showing the correlation of HOMA-IR with mid-arm muscle circumference (MAMC) among study subjects

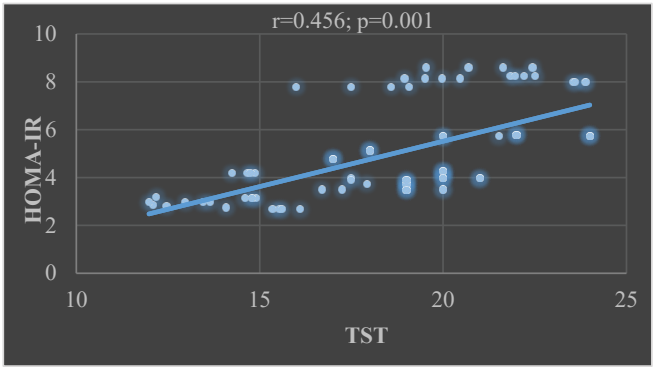

Figure 2: Scatter diagram showing correlation of HOMA-IR with triceps skin fold thickness (TST) among study subjects

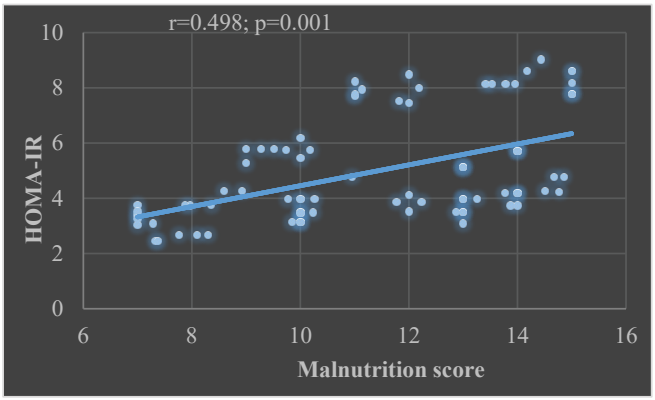

Figure 5: Scatter diagram showing correlation of HOMA-IR with malnutrition score based on subjective global assessment among study subjects

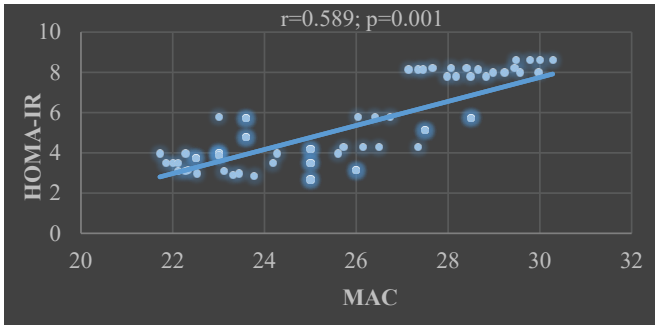

Figure 3: Scatter diagram showing correlation of HOMA-IR with mid arm circumference (MAC) among study subjects

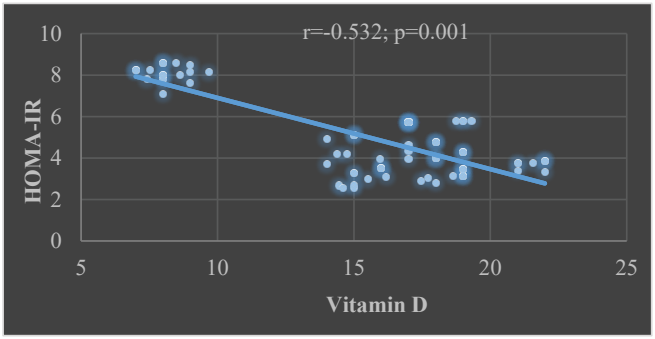

Figure 6: Scatter diagram showing the correlation of HOMA-IR with vitamin D among study subjects

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Discussion

This cross-sectional study was carried out to measure fasting serum insulin, fasting blood glucose, and insulin resistance by HOMA-IR and to measure serum vitamin D levels. This study also determines the nutritional status by measuring different anthropometric indices and subjective global assessment in patients on MHD and determining the correlation between IR with vitamin D level and nutritional status. In this present study, It was observed that almost one-third (32.6%) of subjects aged 41-50 years were insulin resistant, and 14(41.2%) were non-insulin resistant. The mean age was 50.36 ± 12.03 years and 48.24 ± 10.17 years in insulin-resistant and non-insulin, respectively. Similarly, Zhang et al. study observed that the mean age was 50.38 ± 13.47 years in the insulin-resistant group and 48.01 ± 9.17 years in the non-insulin-resistant group, consistent with the current study [19]. In another study, Han et al. found that the mean age was 52.7 ± 13.5 years and 48.3 ± 13.5 years in insulin-resistant and non-insulin-resistant subjects, respectively, supporting the present study [20]. A more minor mean age was observed by Ehrampoush et al., where they found that the mean age of the participants was 39.8 ± 10.8 years [21]. The above authors' higher and lesser mean age may be due to geographical variations, racial and ethnic differences, and genetic causes that may significantly influence their study subjects. In our study, it was observed that in the insulin-resistant group, 53.5% of the subjects were male, 45.5% were female, and in the non-insulin-resistant group, 58.8% of subjects were male, 41.2% were female, which closely resembled Jhorawat et al. and Nazzal et al. studies [8,22]. Similar observations regarding the male predominant were also observed by Zhang et al., Ehrampoush et al., and Fan et al., 2019 [19,21,22]. Our observation shows that over two-thirds (67.4%) of subjects were mild to moderately malnourished in insulin resistance, and 4(11.8%) were non-insulin resistant. The difference was statistically ($p<0.05$) significant between the two groups, which is comparable with the study of Jhorawat et al. [8]. The possible reason might be that those who underwent hemodialysis for a prolonged period had poor nutritional status, and patients living alone were more malnourished than patients living with their families. Our study observed that 78 (90.7%) subjects had found Vitamin D deficiency (<20) levels in insulin resistant and 9(26.47%) in non-insulin-resistant subjects. Vitamin D deficiency had a 12.4 times risk of developing insulin resistance (OR=12.34; 95% CI=4.2-38.1). A similar result was found in studies by Jhorawat et al. and Nazzal et al. [8,22]. Vitamin D deficiency is common in MHD patients due to decreased vitamin D binding protein, proteinuria, reduced dietary intake, advanced age, and malabsorption. Ehrampoush et al. study revealed that the average serum Vitamin D was 22.3 ± 8.9 ng/ml, which is higher than the present study because of race/ethnicity, physical activity, body mass index (BMI), and sunlight exposure [21]. Eighteen (20.9%) of subjects had lower (<35g/l) serum albumin in insulin resistance and 2(5.9%) in non-insulin resistance. Low albumin had a 4.24 times risk of developing insulin resistance (OR=4.2; 95% CI=0.9-28.2). The difference was statistically ($p<0.05$) significant between the two groups, which was consistent with the Nazzal et al. study, where they found the mean serum albumin was 37.3±4.0 g/l because of lack of meal and food content, lack of dietary intake, proteinuria, etc. [22]. Our findings showed a positive significant correlation ($r=0.673$; $p=0.001$) between HOMA-IR and BMI, TST, MAC, and MAMC. A similar correlation was found in the study of Jhorawat et al., Han et al., and Tucker [8,20,24]. This means that muscle mass has significant associations with insulin resistance. Insulin resistance increases with skeletal muscle mass. In this current study, it was observed that there was a positive correlation ($r=0.094$; $p=0.345$) between HOMA-IR and malnutrition scores based on SGA. Our result is consistent with the findings of another study [8]. A possible reason might be that those who underwent hemodialysis for a prolonged period had poor nutritional status, and patients living alone were more malnourished than patients living with their families. The subjective nature restricts its reliability because the SGA criterion solely depends on subjective impression. Our study concluded a negative significant correlation ($r=-0.532$; $p=0.001$) between HOMA-IR and vitamin D. Similar correlation was observed by many researchers [19-22]. Possible causes were reduced dietary intake, advanced age, malabsorption, and lack of sunlight exposure. So, most of the patients on maintenance hemodialysis were Vitamin D deficient. Low Vitamin D levels and muscle mass were likely more insulin resistant in patients on maintenance hemodialysis.

Limitations of the study

The study population was exclusively drawn from a single hospital in Dhaka city, potentially limiting the generalizability of the findings to the entire country. Additionally, the study was conducted over a brief timeframe, which could impact the breadth of conclusions drawn. Furthermore, the small sample size represents another constraint of the study. Consequently, future research should consider expanding to larger sample sizes for more comprehensive insights.

Conclusion and Recommendations

The majority of the patients on maintenance hemodialysis are maltreated and vitamin D deficient. A significant positive correlation exists between insulin resistance with different anthropometric indices and malnutrition scores based on subjective global assessment. There is a negative significant correlation between insulin resistance and vitamin D.

Conflict of interest: None declared.

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Ethical Approval

The study was approved by the Institutional Ethics Committee.

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