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Association of High HbA1c with Interdialytic Weight Gain in Diabetic Patients on Maintenance Hemodialysis

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Abstract

Background: Chronic kidney disease (CKD) is a progressive loss of kidney function over months or years. The majority of CKD patients ultimately reach ESRD and need RRT. Hemodialysis is one of the treatment options for end-stage renal disease (ESRD). Excessive fluid gain between hemodialysis sessions is one crucial factor associated with hypertension and shortened survival for patients. In addition, excessive weight gain between hemodialysis predisposes to an increase in the risk of intradialytic hypotension or morbidity due to corresponding increased ultrafiltration rates when the duration of dialysis sessions cannot be extended. Many studies have shown that increased IDWG is associated with increased glycosylated hemoglobin. The glycosylated hemoglobin (HbA1c) test has been the most widely accepted, reliable biomarker for evaluating long-term glycemic control in patients with diabetes mellitus. Diabetic patients on MHD have increased thirst, and a recent multi-center study showed that they were more likely to have more significant interdialytic weight gain than nondiabetic patients. Aim of the study: To determine the association between interdialytic weight gain and glycosylated hemoglobin in diabetic patients on maintenance hemodialysis.

Methods: This hospital-based prospective analytical study was conducted at the Department of Nephrology, Dhaka Medical College. A total of 109 diabetic patients with MHD were included in this study according to selection criteria. HbA1c was determined for each patient. IDWG was calculated from two weights measured between two dialysis sessions. A pretested questionnaire was used for the interview. Informed written consent was obtained. Seventeen patients were dropped out, so, finally, data were analyzed for 92 patients. ANOVA, Student's t-test, and Chi-squared test were carried out. Following the completion of data collection, data were analyzed using SPSS version 26.

Result: The mean age of the patients was 45.86±14.10 years, ranging from 23-78 years. Males (65.2%) were predominant than females (34.8%). Male to female ratio was 1.88:1. HbA1c level was significantly elevated as age increased (p=0.037). Sixty-one (66.3%) patients had interdialytic weight gain. Mean weight gain was 2.88±1.04 kg, ranging from 0.6 kg to 4.67 kg. Among the study subjects, 15.2%, 30.4%, and 54.3% had HbA1c ≤6%, 6.1-7.9%, and ≥8%, respectively. A significant (p=0.023) association was observed. HbA1c was elevated as the increment of IDWG. There was a significant positive correlation between HbA1c and IDWG (r=0.365; p<0.001). Interdialytic weight gain decreased as per increment of the duration of dialysis. There was a significant negative correlation between interdialytic weight gain and the duration of dialysis (r= -0.382; p<0.001).

Conclusion: The results of this study demonstrated that interdialytic weight gain (IDWG) is positively correlated with high HbA1c and inversely related to the duration of dialysis.

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Introduction

Chronic kidney disease (CKD) is an essential challenge for health systems around the world, consuming a considerable proportion of healthcare finances. It is even more significant for developing countries, which now face the double burden of infectious diseases and growing problems of non-communicable diseases such as obesity, diabetes, and hypertension. Morbidities and mortalities emanating from CKD in these countries are immense and related to limited access to treatment options [1]. Renal replacement therapy (RRT) is the mainstay of care for end-stage renal disease (ESRD) patients. Dialysis as an option of RRT prolongs survival, reduces morbidities, and improves quality of life. However, despite many technical advances, morbidities and mortalities of patients on dialysis remain unacceptably high, and their quality of life is often poor [2]. Chronic hemodialysis (HD) patients often suffer from volume overload and interdialytic weight gain (IDWG). In patients with chronic volume overload before every dialysis time, the mortality risk is two times that of non-diabetic patients [3]. Additionally, high-risk mortality is only seen with severe IDWG. However, studies showed that they have even less ID with increasing natality. Other studies show the amount of IDWG that was associated with increased mortality was >5% body weight [4], >6% body weight [5], and ≥4% body weight [6]. IDWG is used as a parameter for fluid intake while considering the daily urine output. A higher IDWG is associated with higher pre-dialysis blood pressure, more significant intradialytic reductions in blood pressure due to higher ultrafiltration rates, and increased mortality [4]. Achieving normal hydration status is one of the significant targets of hemodialysis (HD) therapy, and the attainment of the so-called 'dry weight' is an integral part of the routine dialysis practice [7]. Interdialytic weight gain (IDWG), corresponding to ultrafiltration losses during dialysis, is mainly influenced by oral fluid intake minus residual urine output (when present) and insensible fluid losses. Oral fluid intake is primarily driven by thirst due to sodium intake from food and, to a lesser degree, from dialysate sodium (DNa) concentration or intradialytic, intravenous saline administration. Other contributors to thirst may include high blood glucose levels in diabetic patients, potassium depletion, angiotensin II, and psychological factors [8]. On the other hand, Diabetes mellitus (DM) is the leading cause of chronic kidney disease (CKD) worldwide, accounting for approximately 45% of end-stage renal disease (ESRD), and measuring glycated hemoglobin (HbA1c) has been suggested as a means of assessing glycemic control in patients with diabetes. Current guidelines recommend a target HbA1c of approximately 7% to prevent or delay microvascular complications, including diabetic kidney disease [9]. Several randomized controlled trials of patients with type 2 DM and preserved kidney function have demonstrated that tight glycemic control targeting a HbA1c level of <6%–6.5% reduced the development and progression of albuminuria [10]. Another study showed that, in dialysis-dependent people with DM, patients with higher HbA1c levels, particularly those without anemia, exhibit poorer survival rates than the patients in the HbA1c range of 5%–6% [6]. It is shown that diabetic patients have IDWG 20% more than non-diabetic patients [11]. In diabetic patients, the percentage of increasing IDWG and higher HbA1c is associated with the severity of xerostomia. Insulin deficiency at HbA1c ≥9% may synergistically affect xerostomia [12]. Minimal data on the relationship between HbA1c and IDWG worldwide is available. With this background in mind, this study may help increase clinical knowledge and enable clinicians to manage their patients better.

Methodology & Materials

This prospective analytical 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 nine adult diabetic patients who had been established on twice-weekly hemodialysis for more than three months were included in this study. Following the information about the study's aim, objectives, and procedures, informed written consent was obtained from each participant. Baseline demographic information of the patients was recorded initially.

Inclusion criteria:

Patients with DM on maintenance hemodialysis.

Exclusion criteria:

Individuals with known congestive cardiac failure, cirrhosis of the liver, hypothyroidism, hemoglobinopathies, severe anemia, acidosis, hypoxia, and age <18 years were not considered for enrollment in the study.

HbA1c was measured for each patient at the beginning of the study. A total of 109 patients were selected. Then, 109 patients were categorized into three groups according to HbA1c level: Group A (≤6%), Group B (6.1 to 7.9%), and Group C (≥8%). Then, interdialytic weight gain was measured in each patient using a mechanical round dial weighing scale M306800 manufactured by ADE Germany. Interdialytic weight gain was calculated by measuring pre-HD weight minus post-HD weight from the previous session. The IDWG of each patient was measured every week, and then the mean IDWG of each patient was measured during the first three months. Patients with interdialytic weight gain of >4% were considered to have significant interdialytic weight gain.

A total of 17 patients were lost from the study at the end of 3 months due to 3 patients dying, and 14 patients were lost

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to follow-up. For measurement of HbA1c, 5 ml blood was drawn from a peripheral vein with all aseptic precautions. Then, it was collected in a test tube, and after labeling it with the patient's name, ID number, and date of collection, it was sent for analysis. Samples were stored at 2 to 8° C temperature. HbA1c was measured using the Dimension EXL-200/ ERBA XL-200/Maglumi 2000 Analyzer made in Germany.

After an initial hemolysis step, samples underwent reverse-phase partition chromatography, and hemoglobin fractions were detected by dual-wavelength spectrophotometry. HbA1c was calculated as the HbA1c fraction as a percentage of total HbA and then corrected using calibration factors to produce a % HbA1c standardized to the method used in the Diabetes Control of Complications Trial [13]. After that, the mean IDWG of all Group A, B, and C patients were measured. Among the 92 patients, 22 had undergone dialysis <6 months, 33 had undergone 6 to 9 months, and 37 had undergone dialysis > nine months. Their IDWG was measured according to the duration of dialysis to observe the relationship between the IDWG and the duration of hemodialysis. At least a relationship between mean IDWG and HbA1c was observed among the three groups.

Operational definitions:

Maintenance Hemodialysis (MHD):

ESRD patients are on regular dialysis for 8 hours/week for at least three months.

Glycosylated Hemoglobin (HbA1C):

The slow, non-enzymatic covalent attachment of glucose to hemoglobin (glycation) is known as Glycosylated hemoglobin [14]. Well-controlled DM, HbA1C≤6 %, Not Well controlled DM, HbA1C 6.1 to 7.9% and Uncontrolled DM, HbA1C ≥8% [15].

IDWG:

It is the weight gain between two hemodialysis sessions. Interdialytic weight gain is calculated by measuring pre-HD weight minus post-HD weight from the previous session. HD patients should gain no more than 2% of their body weight in fluid between sessions (1.4 kg in a 70 kg adult). Gains of >4% (2.8 kg in a 70 kg adult) are described as sizeable interdialytic weight gain.

Duration of Dialysis:

It is the time frame from the onset of dialysis to a few months to years after dialysis [20].

Data collection statistical analysis:

A semi-structured questionnaire has been developed in Bengali. The questionnaire has been developed using the selected variables according to the specific objectives. Collected data were compiled and edited first. The data were then processed with the help of software named Statistical Package for Social Sciences (SPSS, version-26, Chicago, IL) for Windows. The statistical analysis for different variables was performed using the Chi-Square, Unpaired Student's t-test, ANOVA, and Bonferroni tests. Spearman correlation was also done. A 'p' value <0.05 was considered statistically significant.

Results

A total of 92 subjects were included in the study. The age of the participants ranged from 23 to 78 years, with a mean age of 45.86±14.10 years, where the age of the majority was 21 to 40 years (45.7%). Males (65.2%) were predominant than females (34.8%). Male to female ratio was 1.88:1 (Table 1). The distribution of HbA1c levels among the study subjects revealed that 14 patients (15.2%) had HbA1c levels of ≤6%, 28 patients (30.4%) had levels between 6.1% and 7.9%, and the majority, 50 patients (54.3%), had levels of ≥8%. The HbA1c levels ranged from 4.50% to 10.80%, with a mean of 7.60±1.42% (Table 2). Table 3 Sixty-one patients (66.3%) and thirty-one patients (33.7%) had interdialytic weight gain >4% and ≤4%, respectively. Mean weight gain was 2.88±1.04 kg, ranging from 0.6 kg to 4.67 kg. Statistical analysis revealed a significant association ($p < 0.001$) between higher HbA1c levels (≥ 8%) and greater IDWG (> 4%) (Table 4). Additionally, there was a notable relation ($p = 0.023$) between higher HbA1c levels (≥ 8%) and greater IDWG (> 4%). Although the association for patients with IDWG ≤ 4% did not reach statistical significance ($p = 0.081$), a clear trend of increasing IDWG with higher HbA1c levels was noticed (Table 5). Table 6 indicates that patients on dialysis for less than six months (n = 22, 23.9%) had an average IDWG of 3.30 ± 0.89, those on dialysis for 6 to 9 months (n = 33, 35.9%) had an average IDWG of 3.08±1.03, and those on dialysis for more than nine months (n = 37, 40.2%) had a lower average IDWG of 2.44±1.01. The Bonferroni test revealed statistically significant differences in IDWG between the groups: $p = 0.005$ for <6 months vs.> nine months, $p = 0.027$ for 6-9 months vs.> nine months, and $p = 0.003$ for the overall comparison among the three groups. The scattered diagram shows that there was a significant positive correlation between HbA1c and IDWG ($r=0.365$; $p<0.001$) (Figure 1). Furthermore, a significant negative correlation of interdialytic weight gain with a duration of dialysis ($r = -0.382$; $p <0.001$) was observed (Figure 2).

Table 1: Distribution of the study subjects according to age and gender (N=92).

Age (years)	Frequency (n)	Percentage (%)
21-40	42	45.7
41-60	33	35.9
>60	17	18.5
Mean ± SD	45.86 ± 14.10	
Min-max	23-78	
Gender		
Male	60	65.2
Female	32	34.8

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Table 2: HbA1c status of the study subjects (N=92).

HbA1c (%)	Frequency (n)	Percentage (%)
≤6	14	15.2
6.1-7.9	28	30.4
≥8	50	54.3
Mean±SD	7.60±1.42	
Min-max	4.50-10.80	

Table 3: Interdialytic weight gain (IDWG) of the study subjects (N=92).

Interdialytic weight gain (IDWG)	Frequency (n)	Percentage (%)
≤4%	31	33.7
>4%	61	66.3
Mean±SD	2.88±1.04	
Min – max	0.60-4.67	

Table 4: Distribution of subjects with HbA1c between different groups of IDWG in study subjects (N=92).

HbA1c (%)	IDWG				p-value
	≤4% (N=31)		>4% (N=61)		
	n (%)	(Mean ± SD)	n (%)	(Mean ± SD)	
≤6	8 (25.8)	5.37 ± 0.46	6 (9.8)	5.71 ± 0.21	0.123
6.1-7.9	11 (35.5)	6.63 ± 0.51	17 (27.9)	6.58 ± 0.39	0.756
≥8	12 (38.7)	6.77 ± 0.64	38 (62.3)	8.73 ± 0.71	<0.001
Total	31	6.36 ± 0.80	61	7.84 ± 1.32	

Table 5: Association of Interdialytic weight gain (IDWG) with HbA1c (N=92).

IDWG	HbA1c (%)						p-value
	≤6 (n=14)		6.1-7.9 (n=28)		≥8 (n=50)		
≤4% (n=31)	8	1.22±0.38	11	1.50±0.55	12	1.83±0.56	0.081
>4% (n=61)	6	2.10±0.07	17	2.62±0.07	38	4.22±0.13	0.023

Table 6: Association of Interdialytic weight gain (IDWG) with duration of dialysis (N=92).

Duration of dialysis of different groups (months)	Interdialytic weight gain	
	n (%)	Mean ± SD
<6 (a)	22 (23.9)	3.30 ± 0.89
6-9 (b)	33 (35.9)	3.08 ± 1.03
>9 (c)	37 (40.2)	2.44 ± 1.01
Bonferroni test		
Duration of dialysis	p-value	
a vs b	1	
a vs c	0.005	
b vs c	0.027	
a vs b vs c	0.003	

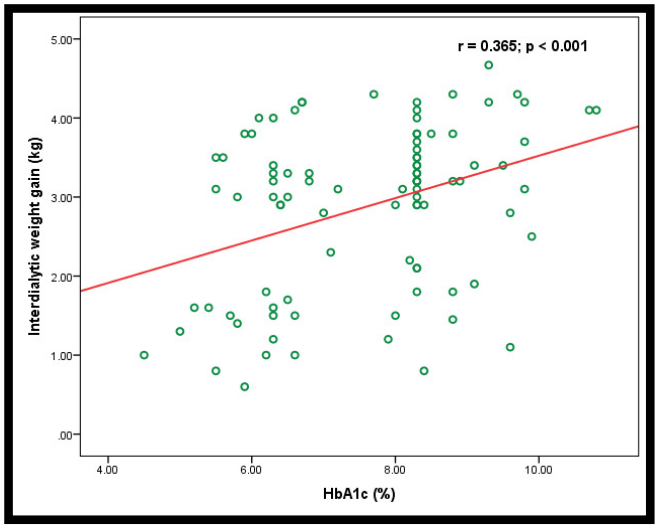

Figure 1: Scattered diagram showing correlation of HbA1c with Interdialytic weight gain (IDWG).

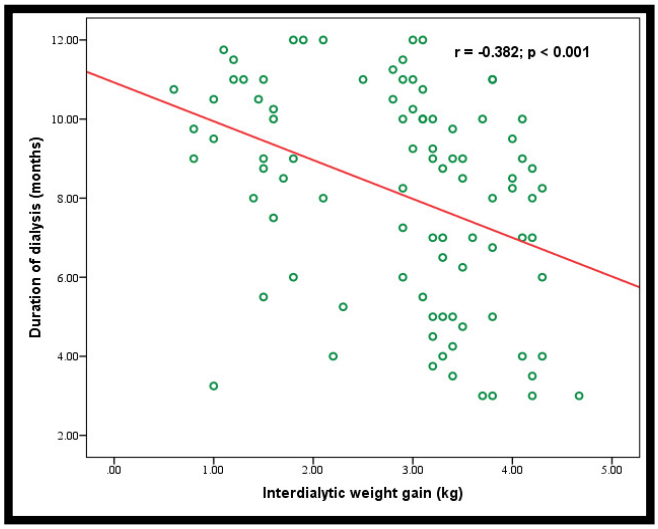

Figure 2: Scattered diagram showing correlation of interdialytic weight gain with duration of dialysis.

Discussion

This study observed the association between interdialytic weight gain and glycosylated hemoglobin in maintenance hemodialysis patients. This prospective analytical study consisted of 109 patients with diabetes mellitus on maintenance hemodialysis. In this present study, the mean age of the patients was 45.86±14.10 years, ranging from 23-78 years. Similar studies found a mean age of 63.23±10.85 in their observation [16]. Males (65.2%) were predominant than females (34.8%). Male to female ratio was 1.88:1. These findings were supported by Lopez-Gomez et al., where 70 males and 64 females were present and did not show any significant association between age and HbA1c (p<0.072) [17]. On the other hand, Zahed et al. showed that females

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were more predominant than males, and their findings were statistically insignificant (p< 0.066) [18]. IDWG was elevated with the HbA1c increment in this study. Mean IDWG was 2.10±0.07, 2.62±0.07, and 4.22±0.13 in HbA1c ≤6.0%, 6.1-7.9%, and ≥8.0% groups respectively, which were statistically significant (p= <0.023). This may be due to poor diabetic control, increasing plasma osmolality as well as polyuria. As a result, changes happen in the hypothalamic osmoregulatory center, which leads to increased thirst and salt intake. Zahed et al. did not find any association between HbA1c and IDWG because the main limitation of their study was the low proportion of patients with HbA1C >6% [18]. Moreover, other risk factors such as intradialytic hypotension, intravenous fluid administration, or high salt intake were more important in their patients. Sixty-one patients (66.3%) had interdialytic weight gain >4%. Thirty-one patients (33.7%) had interdialytic weight gain ≤4%. The mean weight gain was 2.88±1.04 kg, ranging from 0.6 kg to 4.67 kg (Table 3). This increased IDWG was due to uncontrolled diabetes mellitus, which ultimately increased thirst and salt intake. Many studies supported these findings. One study showed that IDWG >4.8%, which was also due to uncontrolled diabetes mellitus [4]. Another study that was partially supported by our study where found IDWG >5.7% due to uncontrolled diabetes mellitus, skipping and shortening dialysis sessions, and hyperphosphatemia [5]. Furthermore, Kalantar-Zadeh et al. showed that IDWG ≥4% but found that younger patients, male and diabetic patients, and those with higher protein intake and better nutritional status were greater fluid retainers [6]. In addition, they found in their study that increased sympathetic nervous system, renin-angiotensin-aldosterone system, and antidiuretic hormone release can lead to a vicious circle that leads to increased IDWG. Moreover, they observed that administration of albumin or neurohormonal antagonists such as vasopressin receptors antagonists, aldosterone antagonists, or nesiritide helped to reduce IDWG [6]. Among the study subjects, fourteen patients (15.2%) had ≤6% HbA1c (Group A), twenty-eight patients (30.4%) had 6.1-7.9% HbA1c (Group B), and fifty patients (54.3%) had ≥8% HbA1C (Group C). Mean HbA1C was 7.60±1.42, ranging from 4.50 to 10.80. A significant association of IDWG with HbA1C was found. There was a significant positive correlation between HbA1c and IDWG (p= <0.023). This study showed that diabetic patients with poor diabetic control and high HbA1c values had increased thirst and, therefore, were prone to greater interdialytic weight gain. Zahed et al. did not show similar results [18]. They found HbA1C was <6% in 158(68%) patients (group A), 6-7% in 40(17%) patients (group B), and >7% in 33(14%) patients (group C). They found no significant association of IDWG with HbA1C because they showed that factors such as nutritional state and dialysis-dependent factors can increase IDWG, such as excessive fluid and salt intake [18]. Pre-dialysis hyponatremia had been linked to overhydration and increased IDWG. They also showed that higher dialysate sodium improved hemodynamic tolerance to ultrafiltration; however, it might increase inter-dialytic weight gain. Moreover, according to their statement, hypokalemia, angiotensin II, psychologic factors, and xerostomia were risk factors for increasing IDWG [18]. In this current study, we expressed IDWG in percentage where 61 patients having IDWG >4% and their mean±SD (4.22±0.13) was significant (p=<0.023) than 31 patients having IDWG ≤4% and their mean±SD (1.83±0.56) was not significant (p=<0.081). We found a significant association of IDWG with HbA1C (p= <0.023). Diabetic patients on maintenance hemodialysis who did not control their diabetes mellitus faced difficulties in controlling their IDWG as well. The more their diabetes was uncontrolled, the more they were polyuric as well as thirsty. So, they developed a vicious cycle of increased thirst and consequently increased water and salt intake. Some studies found an association between the effects of different medications of diabetic patients on IDWG, but our study did not support that. Ifudu et al. also found a significant association of IDWG with HbA1C (<0.01). They found mean IDWG (4.2%±0.19%) than the weight gained by controls (3.23%±0.2%; P <0.0001). They also showed in their study that Insulin-treated diabetic patients gained the most weight between dialysis sessions (5.3%±0.37%), while diabetic patients on oral hypoglycemic agents gained more weight (4.4%±0.19%) than those diabetic patients controlled by diet alone (3.3%±0.23%; P <0.001) [16]. In addition, the insulin-treated diabetic patients had the highest HbAlc (11.1%±1.7%), compared with 5.9% ± 0.38% for those on oral hypoglycemic agents and 5.7%±0.25% for the diabetic patients on diet control (P <0.0002). Those diabetic patients with poor glycemic control (n=5; defined by HbAlc >8.5%) gained more weight (5.6%±0.4%) than did other diabetic patients with good control (n=18; defined by an HbAlc <8.5%; weight gain=3.9%±0.2%) (P <0.01). On the other hand, Zahed et al. demonstrated that the mean IDWG was 2.44 kg in group A, 2.25 kg in group B, and 2.71 kg in group C, which showed no significant association between IDWG and HbA1C. They identified several confounding factors like hypokalemia, angiotensin II, psychologic factors, and xerostomia rather than uncontrolled diabetes mellitus alone [18]. There was a significant positive correlation between HbA1c and IDWG (r=0.365; p<0.001) (Figure 1). It showed that with the increment of HbA1c, IDWG was increased because plasma osmolality was raised due to uncontrolled diabetes mellitus, which stimulated the hypothalamus's osmoregulatory center and ultimately increased thirst and salt intake. This was supported by one study where they showed a positive correlation (r=0.5, slope=0.17, P <0.02) between IDWG and glycemic control as measured by the HbAlc [19]. Interdialytic weight gain decreased as per increment of duration of dialysis,

which was statistically significant (p=0.003). In our study, 22(23.9%) patients got hemodialysis less than six months (group a), 33(35.9%) patients got hemodialysis around nine months (group b), and 37(40.2%) patients got hemodialysis more than nine months (group c). In terms of duration of hemodialysis, group a vs. b was statistically insignificant (p= 1.00), but group b vs. c (p=0.027), group a vs. c was statistically significant (p=0.005) as well as group a vs. b was statistically significant (p=0.003) This was because the patient had a positive attitude towards fluid and diet compliance. Several studies supported these findings. Wahyuni et al. also found similar results in their study [20]. They showed that almost all respondents who underwent hemodialysis <12 months had an intolerable IDWG, namely 23 of 24 respondents (95.8%), and almost all respondents who underwent hemodialysis for 12-24 months had an intolerable IDWG, namely 7 of 9 respondents (77.8%) and all respondents who underwent hemodialysis >24 months had a tolerable IDWG, namely 9 out of 9 respondents (100%). Moreover, the longer the patient underwent hemodialysis therapy, the more knowledge they gained and the more positive attitude they had towards fluid and diet compliance [20]. So, the longer he or she undergoes hemodialysis, the more familiar the patient is with fluid and diet settings. This caused IDWG to be at a tolerable level. Figure 2 showed a significant negative correlation of interdialytic weight gain with duration of dialysis (r= -0.382; p<0.001). A similar finding was observed in the study of Wahyuni et al., where a strong negative correlation between the length of hemodialysis and interdialytic weight gain was revealed [20]. They showed that the longer the patient underwent hemodialysis therapy, the more knowledge they gained and the more positive attitude they had towards fluid and diet compliance. Each patient took a different amount of time to improve his or her knowledge and attitude.

Limitations of the study: This study's limitations include its single-center design, which may restrict the generalizability of the findings to broader populations. Additionally, the small sample size limits the ability to thoroughly evaluate all factors associated with interdialytic weight gain (IDWG) and HbA1C levels. The study's scope was also constrained by economic limitations, potentially impacting the comprehensiveness of data collection and analysis. Consequently, the results should be interpreted with caution, and further multi-center studies with larger sample sizes and better funding are necessary to validate these findings and provide a more robust understanding of the variables involved.

Conclusion and Recommendations

In this study, interdialytic weight gain (IDWG) was significantly higher in diabetic patients with high HbA1c who were on maintenance hemodialysis. Moreover, it showed a significant association of IDWG with the duration of dialysis. Interdialytic weight gain decreased as per increment of the duration of dialysis..

Conflict of Interest: None declared.

Ethical Approval

The study was approved by the Institutional Ethics Committee.

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