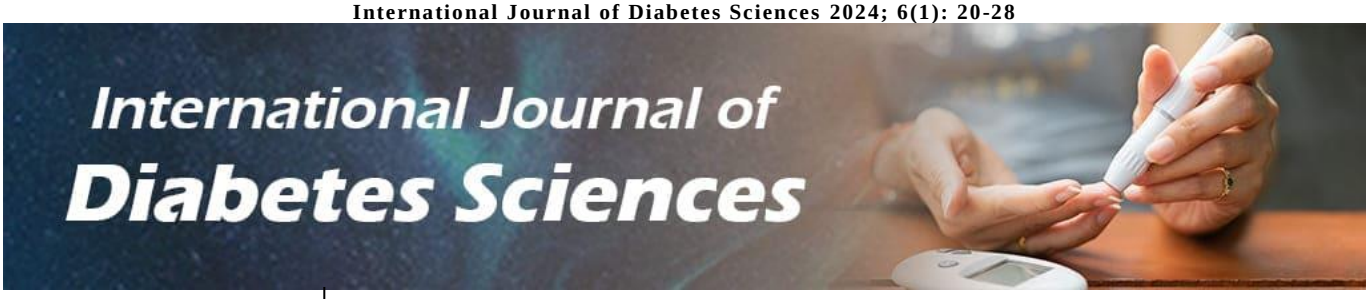

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The role of glycemic control variability in the onset of microalbuminuria among Type 1 Diabetic

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Abstract
Background: The primary objective of diabetes management is to achieve and sustain optimal glycemic control from the first phase of diabetes, with the aim of averting the initiation and advancement of diabetic micro vascular problems.
Aims of the study: Investigate biochemical changes associated with glycemic variability and their effect on kidney function.
Methodology: A cross-sectional study including 100 patients (52 males and 48 females) diagnosed with type 1 diabetes at Al-Fayhaa Specialized Diabetes Center in Basra, Iraq. Participants range in age from 6-17 years. Blood and urine samples were collected between November 2023 and March 2024 after obtaining verbal consent. The study excluded patients with kidney and liver diseases or immune diseases. 5 ml of blood was collected from each participant, placed in a gel tube and left to coagulate. Serum was isolated using a centrifuge and stored at -20 °C. HbA1c levels were measured using a Cobas c311 device, micro albumin levels using an Abbott device, and lipid and electrolytes levels using a Cobas c311 device.
Results: The study results showed a balanced distribution between genders (P=0.572). There were significant differences between age groups, with the age group <10 years accounting for 20% and >10 years 80% (p<0.0001). Regarding body mass index (BMI), 60% of individuals were below normal weight and 27% were in the normal range (P< 0.0001). The proportion of uncontrolled diabetes was 87% (HbA1c ≥7.5) versus 13% of controlled diabetes (p<0.0001). Urinary albumin levels were normal in 75% of patients and 25% had microalbuminuria (p<0.0001). There were no significant differences between genders in diabetes control (P=0.438). The study showed that diabetes control was higher in the age group less than 10 years compared to the older group (p<0.0001). There was no significant difference in diabetes control between the different BMI categories (P=0.871). HbA1c levels and albuminuria were higher in patients with uncontrolled diabetes (p<0.0001). There were no significant differences in the levels of other indicators such as cholesterol, sodium and potassium (p>0.05).
Conclusions: The study showed that uncontrolled diabetes is associated with increased HbA1c levels and albuminuria, which indicates worsening kidney function. Variation in diabetes control between age and BMI groups reflects the influence of age and weight factors on metabolism and response to treatment. Highlights the importance of careful medical follow-up for patients.

Key word: HbA1c, glycemic control variability, micro albuminuria, type 1 diabetes, kidney function and diabetes management

Introduction
The objective of diabetes treatment is to achieve and sustain optimal glycemic control from the first phase of diabetes, with the aim of preventing the development and advancement of diabetic micro vascular complications and arteriosclerotic illnesses [1]. In order to achieve this objective, it is vital to comprehend the level of glycemic control in patients. Hemoglobin A1c (HbA1c) has been widely utilized as a benchmark indicator of glycemic control. HbA1c is the predominant measure used to assess blood glucose management in clinical treatment and is acknowledged as the primary indicator for the progression of diabetic problems. Prior research has demonstrated that attaining optimal glycemic control is linked to a reduced occurrence and slower advancement of diabetic micro vascular problems, with HbA1c serving as an index of glycemic control [2]. Later, it was discovered that maintaining rigorous glycemic control by utilizing HbA1c as a measure did not result in the prevention of cardiovascular disease (CVD). Instead, it can lead to severe hypoglycemia, weight gain, and perhaps higher risk of cardiovascular death [3].

While HbA1c provides an average of blood glucose levels over the previous 1-3 months, it does not accurately reflect variations in glycemic levels, such as frequent episodes of high or low blood sugar [4]. Self-monitoring of blood glucose (SMBG) is utilized to assess daily glycemic control. However, it can only provide information on blood glucose levels at the specific time of measurement and is not adequate for evaluating hypoglycemia and hyperglycemia. Continuous glucose monitoring (CGM) offers a more comprehensive evaluation of daily glycemic control compared to self-monitoring of blood glucose (SMBG) since it continuously detects glucose levels in the fluid between the skin and tissue.

CGM technology has seen significant advancements, leading to its increased utilization in clinical practice [5]. Diabetic kidney disease (DKD) is the predominant etiology of end-stage kidney disease (ESKD). Individuals with DKD not only have a substantial risk of developing ESKD, but also experience a higher simultaneous increase in the risk of cardiovascular (CV) morbidity and mortality. Hence, it is crucial to optimize therapy in order to avoid the occurrence and advancement of DKD [6]. Diabetic ketoacidosis (DKD) only happens when there are high blood sugar levels (hyperglycemia), and the control of glucose is the primary factor that determines when nephropathy (kidney damage) begins. However, the question of whether optimizing glucose management might slow the progression of DKD is still a matter of debate. Nevertheless, there is accumulating data indicating that intensive glucose control may indeed slow down the loss of glomerular filtration rate (GFR) and potentially delay the progression to end-stage kidney disease (ESKD). Observational studies have provided evidence that maintaining adequate glucose management, particularly in people with type 1 diabetes (T1DM), is linked to enhanced kidney health, even in cases of severe diabetic kidney disease (DKD) [7, 8]. Diabetic nephropathy is a serious and late consequence of Type 1 diabetes mellitus (Type 1 DM) that is linked to considerable illness and death. Microalbuminuria is seen as a first indication of diabetic nephropathy. It occurs before chronic proteinuria and is a stage of diabetic nephropathy that can potentially be reversed [9]. Around 30-40% of individuals with Type 1 DM experience the development of microalbuminuria. Less than 50% of people with microalbuminuria will develop overt proteinuria during the next ten years, while a significant portion of patients will either see their microalbuminuria decrease or remain unchanged. Microalbuminuria in adulthood is linked to a higher likelihood of developing cardiovascular disease and experiencing premature death [10]. Microalbuminuria is present when there is a connection with inadequate control of blood sugar levels, high blood pressure, and a longer duration of diabetes. The frequency of microalbuminuria in children and adolescents with Type 1 DM ranges from 10 to 40% according to research. Nevertheless, only a small percentage, specifically 5-10%, of young individuals exhibit continuous increases in urine albumin excretion (UAE). The rapid decline and temporary occurrence of microalbuminuria in young individuals with Type 1 DM is believed to be caused by alterations in renal hemodynamic that occur throughout pubertal growth and development [11]. The current guidelines from the American Diabetes Association and the International Society for Pediatric and Adolescent Diabetes recommend that individuals with Type 1 DM undergo annual screening for microalbuminuria starting at the age of 10 and after having diabetes for at least five years [12]. For patients who are young and have consistently high levels of UAE (urinary albumin excretion) with no other known cause of renal disease, it is advised to undergo treatment with angiotensin-converting enzyme (ACE) inhibitors. It is essential to assess the factors that contribute to the occurrence of microalbuminuria in young persons with Type 1 DM in order to establish if these changes are caused by underlying kidney disease or functional alterations. Renal hemodynamic changes can be caused by uncontrolled diabetes and fluctuations in blood sugar levels, which are common during puberty, or they may arise during the period of pubertal growth and development [13, 14].

Methodology

cross-sectional study included (100) patients (52 males and 48 females) diagnosed with type 1 diabetes mellitus who attended Al-Fayhaa specialized diabetes, endocrine and metabolism center (FDEMC), Basra city, Iraq. All patients in this study were diagnosed by specialist physician. The age of the study population ranges between (6-17 years). The study carried out throughout the period November 2023 to March 2024. Verbal consent was obtained from all patients before blood was drawn. Urine collected randomly using a sterilized cup and processed to investigate microalbuminuria. Information about patients and the control group was taken according to the inclusion criteria included in the study. People with kidney and liver diseases or immune diseases were excluded. 5 ml was collected from each research participant, and the blood was placed in a gel tube and left for 15 minutes until coagulation. The blood serum was isolated using a centrifuge for 30 minutes at 3500. The serum was stored at -20 C until use. HBA1c levels were measured using Cobas c311, micro albumin levels were measured using Abbott device, and electrolytes levels were measured using Cobas c311 Measuring lipid levels using Cobas c311.

Statistical analysis

Statistical analysis is often used to analyze quantitative data and provides methods for data description and simple inference for continuous and categorical data. The procedure involves the collection of data, leading to a test of the relationship between two statistical data sets. In this study, all data are presented as mean ± standard deviation. The statistical analyses were performed using SPSS (version 26) and using dependent t-tests (two-tailed) and independent t-tests (two-tailed) for normally distributed variables, whereas the Mann-Whitney and Wilcoxon tests were used for those variables that were not normally distribute. $p<0.05$ was considered statistically significant.

Ethical approval

Before the samples were taken, all of the patients who were going to be part of this study were properly informed and gave their verbal permission. The Committee on Publication Ethics at the Al-Fayhaa specialized diabetes, endocrine and metabolism center (FDEMC), Basra, Iraq, gave its approval to the study.

Results

Demographic and Clinical Characteristics of the Study Population

The results of the study showed a balanced distribution between the sexes, with the percentage being 52% for males and 48% for females (P=0.572). Regarding age, there was a significant difference between age groups, with the < 10

years group accounting for 20% and the 10 years or older category 80% (p<0.0001). Regarding BMI, 60% of individuals were underweight (< 18.5) and 27% were within the normal range (18.5-23), while the proportions were lower in the other categories (p<0.0001). For diabetes, 87% of patients had uncontrolled diabetes (HbA1c ≥7.5) compared with only 13% of controlled patients (p<0.0001). Regarding urine albumin, 75% of patients had normal levels (<30 mg/dl) while 25% had microalbuminuria (30-300 mg/dl) (p<0.0001).

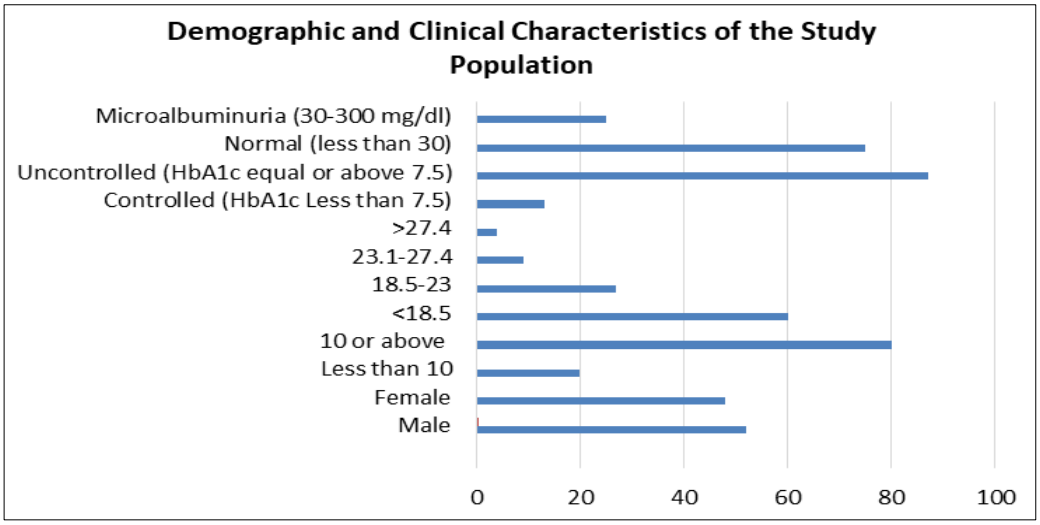

Fig 1: Demographic and Clinical Characteristics

Table 1: Gender Distribution, Age, BMI, Diabetes Control, and Albuminuria Levels

Characters	Categories	No. and Percentage	P-Value
Gender	Male	52(52%)	0.572
	Female	48(48%)	
Age	Less than 10	20(20%)	< 0.0001*
	10 or above	80(80%)	
BMI	<18.5	60(60%)	< 0.0001*
	18.5-23	27(27%)	
	23.1-27.4	9(9%)	
	>27.4	4(4%)	
Diabetic	Controlled (HbA1c Less than 7.5)	13(13%)	< 0.0001*
	Uncontrolled (HbA1c equal or above 7.5)	87(87%)	
Albuminuria	Normal (less than 30)	75(75%)	< 0.0001*
	Microalbuminuria (30-300 mg/dl)	25(25%)	

Gender Distribution and Diabetes Control Status

The results showed that the percentage of patients with controlled diabetes was 15.38% among males and 10.41% among females, while the percentage of uncontrolled patients was 82.69% among males and 89.58% among females. There was no significant difference between genders in diabetes control (P= 0.438).

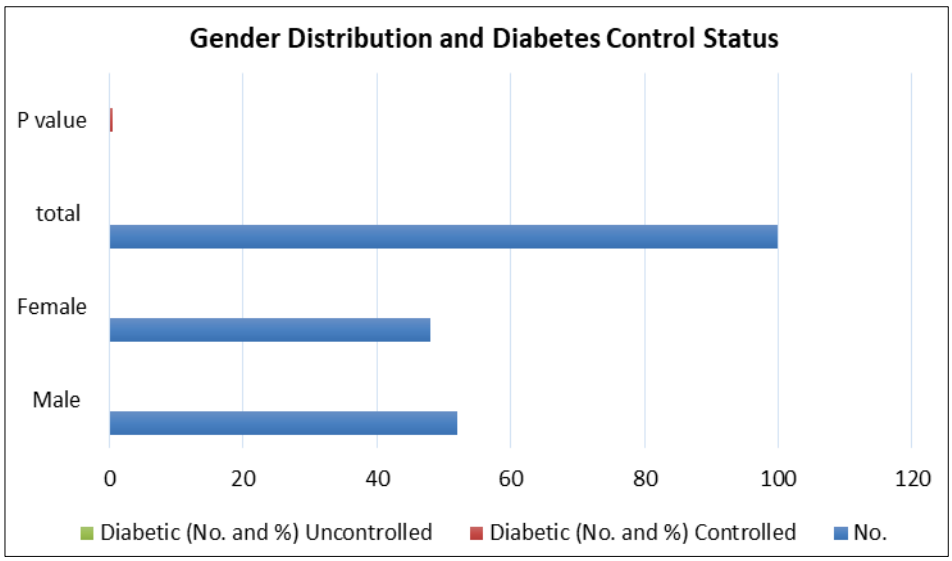

Fig 2: Comparison of diabetes control between genders

Table 2: Comparison of diabetes control between male and female participants

Gender	No.	Diabetic (No and %)	
		Controlled	Uncontrolled
Male	52	8(15.38)	43(82.69)
Female	48	5(10.41)	43(89.58)
total	100	13(13)	86(86)
P value		0.438	

Diabetes Control by Age Group

The results showed that the proportion of patients with controlled diabetes was higher among individuals younger than 10 years (55%) compared to individuals aged 10 years or older (2.5%). This shows the significant difference in diabetes control between the two age groups (p<0.0001).

Table 3: Comparison of diabetes control between younger and older age groups

Age	No.	Diabetic (No and %)	
		Controlled	
Less than 10	20	11(55)	Less than 10
10 or above	80	2(2.5)	10 or above
total		13(13)	total
P-Value		< 0.0001*	

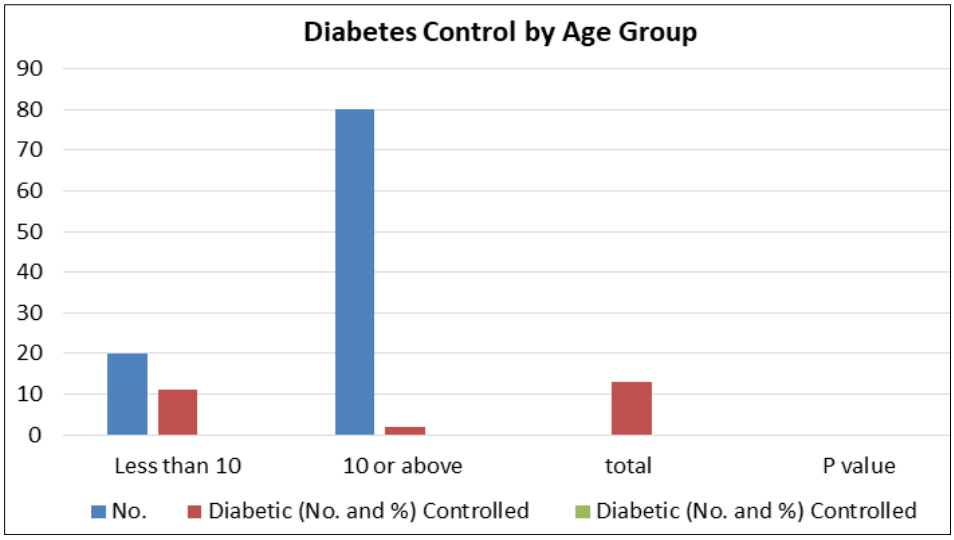

Fig 3: Comparison of diabetes control between age group

Diabetes Control by BMI Categories

The results showed that the proportion of patients with controlled diabetes was lower among individuals with a low BMI (<18.5) (11.66%) compared to those with a higher BMI (>27.4) (25%). However, there was no significant difference in diabetes control between the different BMI categories (P=0.871).

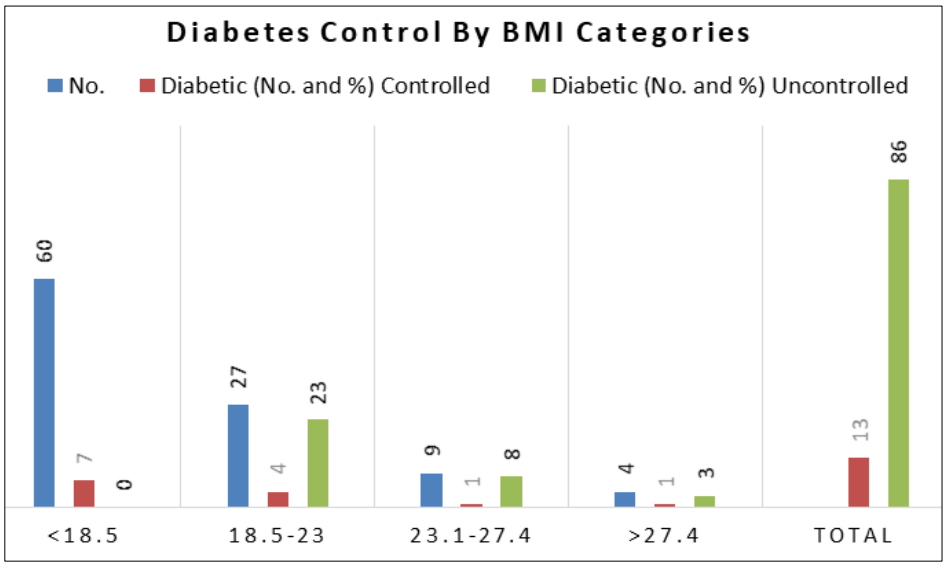

Fig 4: Analysis of diabetes control across BMI

Table 4: Analysis of diabetes control across different BMI ranges

BMI	No.	Diabetic (No and %)	
		Controlled	Uncontrolled
<18.5	60	7(11.66)	53(88.33)
18.5-23	27	4(14.81)	23(85.18)
23.1-27.4	9	1(11.11)	8(88.88)
>27.4	4	1(25)	3(75)
Total		13(13)	86(86)
P-Value		0.871	

Comparison of laboratory parameters between normal and microalbuminuria groups

The results showed that the average HbA1c level was significantly higher in the microalbuminuria group (12.26±0.51) compared to the normoalbuminuria group (10.21±0.28), (*P*=0.001). There were no significant differences in the levels of fasting glucose (FBS), triglycerides (TG), cholesterol (Chol), HDL, LDL, VLDL, selenium (Se.C), urea (B.Urea), and blood urea nitrogen (BUN), sodium (Na), potassium (K), or chloride (Cl) between the two groups (*P*>0.05).

Table 5: Statistical Analysis of HbA1c, FBS, and Other Biochemical Markers

Parameters	Groups		P-Value
	Normal	Microalbuminuria	
HbA1c	10.21±0.28	12.26±0.51	0.001*
FBS	257.17±13.8	299.24±24.8	0.135
TG	108.38±10.09	133.2±14.07	0.202
Chol	170.25±5.38	175.2±9.14	0.646
HDL	59.21±2.2	55.92±3.84	0.457
LDL	97.89±4.15	98.52±7.33	0.940
VLDL	20.89±2.01	27.8±4.36	0.112
Se.C	0.356±0.01	0.387±0.03	0.301
B.Urea	20.02±0.71	23.12±1.74	0.054
BUN	9.59±0.33	10.68±0.81	0.147
Na	136.6±0.37	135.6±0.62	0.189
K	4.37±0.04	4.26±0.05	0.256
Cl	99.16±0.34	98.78±0.72	0.603

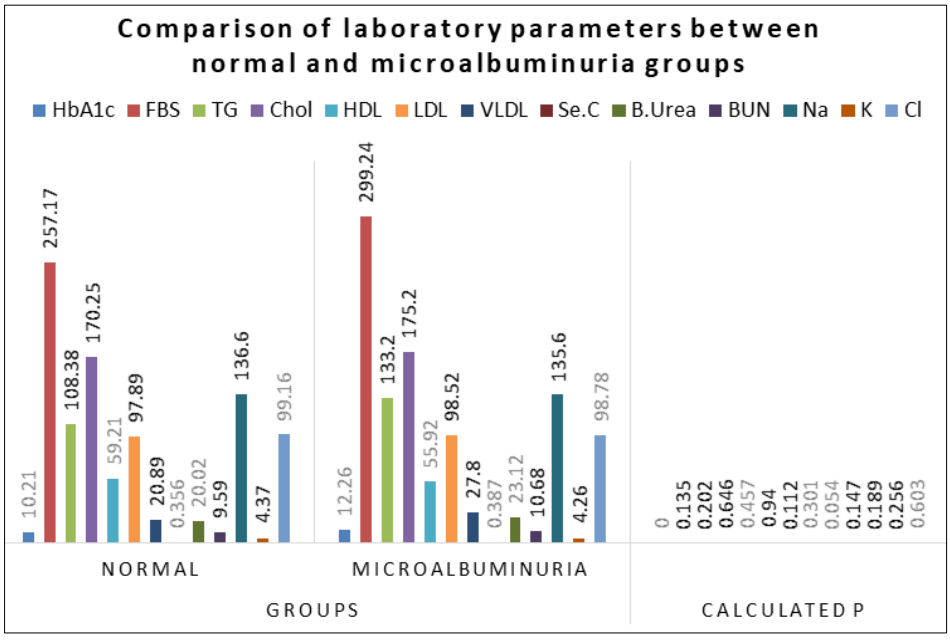

Fig 5: Comparison of laboratory parameters between study populations

Comparison of Laboratory Parameters in Controlled vs. Uncontrolled Diabetics

The results showed that the urine albumin level was significantly higher in uncontrolled diabetes patients (11.38±0.25) compared to controlled ones (7.02±0.1) (*p*<0.0001). Fasting glucose (FBS) levels were also significantly higher in uncontrolled diabetes patients (278.64±13.8) compared to controlled ones (205±13.1) (*p*<0.0001). HDL and chloride (Cl) levels were significantly higher in uncontrolled diabetes patients (59.71±2.12 and 98.77±0.30) than in controlled ones (50.86±3.68 and 100.7±1.14) (*P*=0.04 and *P*=0.028). There were no significant differences in the rest of the indicators such as TG, Chol, LDL, VLDL, Se.C, B.Urea, BUN, Na, and K (*P*> 0.05).

Table 6: Statistical differences in albuminuria, FBS, lipid profiles, and electrolytes

Parameters	Groups		P-Value
	Controlled diabetics	Uncontrolled diabetics	
Albuminuria	7.02±0.1	11.38±0.25	<0.0001*
FBS	205±13.1	278.64±13.8	<0.0001*
TG	128.5±318.3	112.12±9.33	0.488
Chol	162.13±7.83	173.14±5.25	0.398
HDL	50.86±3.68	59.71±2.12	0.04*
LDL	93.53±9.01	98.84±3.93	0.600
VLDL	25.73±3.69	22.07±2.11	0.489
Se.C	0.333±0.03	0.369±0.01	0.327
B.Urea	18.13±1.58	21.27±0.76	0.108
BUN	9.26±0.85	9.97±0.35	0.436
Na	137.8±1.1	136.11±0.31	0.06
K	4.44±0.09	4.32±0.04	0.282
Cl	100.7±1.14	98.77±0.30	0.028*

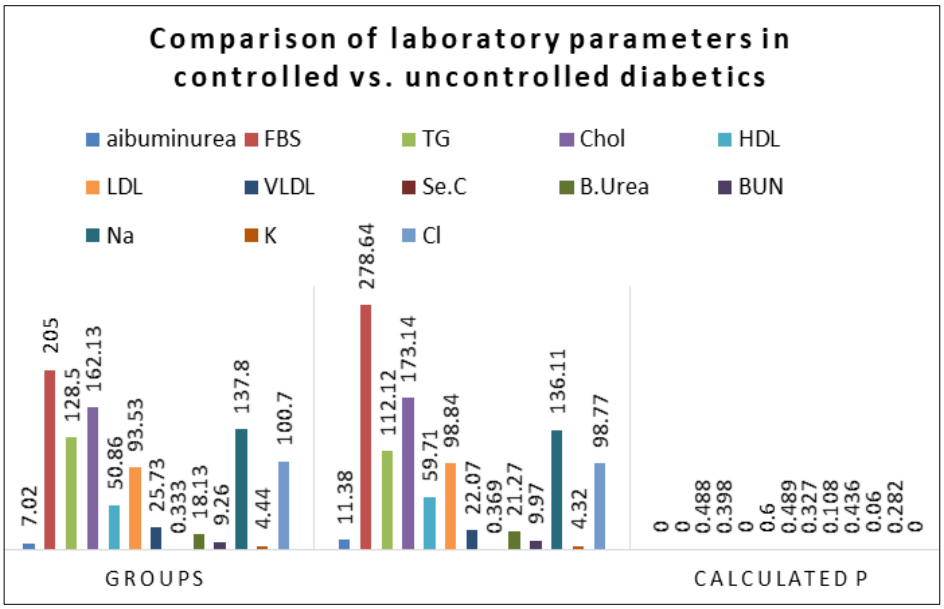

Fig 6: Comparison of laboratory parameters in controlled and uncontrolled diabetics group

Discussion

The results also indicated a substantial rise in the HbA1c levels between the control group and the group experiencing microalbuminuria. The results indicate that there is no statistically significant difference in the fasting blood sugar, TG, Chol, HDL, LDL, VLDL, Se.C, B.Urea, BUN, Na, K, and Cl levels between the two groups. The results are in line with [15-17]. Our research supported the idea that changes in HbA1C levels are strongly linked to the development of microalbuminuria, especially in people who already have it. We investigated the effect variations in HbA1C played in type 2 diabetics with normal or microalbuminuria after six years of tracking these individuals. Four main consequences were discovered by us. First, uric acid, CV-HbA1c, HbA1c-SD, and diabetes duration were greatest in the patients who had microalbuminuria for the first time after inclusion ($P<$ 0.001). The groups that later on developed microalbuminuria and the groups without it followed. Second, upon registration, those in the first group with microalbuminuria had a lower eGFR than those in the next two groups, both with and without microalbuminuria. With the highest mean, CV HbA1c, and cholesterol values was the third group. Those with high HbA1c-SD and microalbuminuria both had these. The individuals in the normal albuminuria with low HbA1c-SD group exhibited the lowest levels of cholesterol, CV HbA1c, and mean HbA1c. Additionally, greater fluctuations in HbA1C levels heighten the likelihood of developing macroalbuminuria in individuals who already exhibit microalbuminuria [17, 18]. Based on the findings of the United Kingdom Prospective Diabetes Study, the annual progression rate from diabetes diagnosis to microalbuminuria was 2.0%, whereas the annual progression rate from microalbuminuria to macroalbuminuria was 2.8%. Additionally, this study revealed that macroalbuminuria occurred in a relatively limited number of instances (Brownlee, 2001). In later cases with macroalbuminuria, however, the death rate was higher than the rate at which the nephropathy got worse. Also, our research showed that the patients who were in the first group to have macroalbuminuria after registration had diabetes for the longest time. This was followed by patients who had diabetes after the first group and then patients who did not have diabetes. There is a strong link between having more variable HbA1C and having more microalbuminuria that turns into macroalbuminuria. The higher pathology load could be caused by both the normal process of diabetes and the way it is treated. So, keeping blood sugar levels in a healthy range and avoiding changes in blood sugar levels through personalized treatment can stop more nerve damage [18]. More research needs to be done on the risk factors and the part those changes in HbA1C play in diabetics developing microalbuminuria and their kidneys losing their

ability to work properly. One large study looked at the link between changes in HbA1C levels and the chance that kidney disease caused by diabetes will get worse [19]. The amounts of albumin urea, fasting glucose, HDL, and CL were very different between the diabetics who had their condition under control and those who did not. The study's findings are in line with [20-22]. Researchers found that changes in HbA1c levels were linked to both type 1 and type 2 diabetes patients getting microalbuminuria and their kidney health getting worse. Five people with type 2 diabetes and four people with type 1 diabetes were in the study [22]. Follow-ups were done every 4.3 to 7.2 years on average. CV HbA1c showed it in one study and HBA1C-SD showed it in seven. Both were used in the same study looked at the link between changes in HbA1c and the rise in microalbuminuria [23, 24]. A further two studies examined the relationship between variations in HbA1c and the likelihood of nephritis becoming worse. Another investigation examined the relationship between HbA1c variations and chronic kidney disease (estimated glomerular filtration rate <60 mL/min per 1.73 m2) and heart disease (events of ischemic heart disease, heart failure, ischemic stroke, or peripheral vascular disease) [25]. The objective of our study was to examine the impact of variations in HbA1c levels on the occurrence of macroalbuminuria in individuals without any health issues and microalbuminuria in individuals diagnosed with type 2 diabetes. The disparities between these studies and our own may arise from variations in the duration of diabetes among the participants, the specific kidney complications they experienced (such as microalbuminuria, eGFR < 60, nephropathy, and macroalbuminuria), the specific types of HbA1c that were measured (such as CV HbA1c or HbA1c-SD), or the methodology employed in the statistical analysis [26]. Fluctuations in blood glucose levels may provide insights into the underlying causes of DKD, or alternatively, the observed associations could be purely coincidental. During a two-year period, a study examined the average magnitude of glucose fluctuations (MAGE) and the standard deviation of HbA1c levels. These were utilized to demonstrate the fluctuations in blood glucose levels throughout time, encompassing both immediate and prolonged periods [27]. Changes in blood sugar levels over short and long periods of time can make oxidative stress and chronic inflammation worse [28]. A retrospective analysis of the Diabetes Control and Complications study a study including individuals diagnosed with type 1 diabetes has also established a correlation between changes in HbA1c levels and the occurrence of micro vascular complications associated with diabetes. Long-term fluctuations in glycemia may contribute to the development of retinopathy and nephropathy in individuals with type 1 diabetes [29]. Our study additionally discovered that individuals with type 2 diabetes who currently have microalbuminuria have a greater likelihood of developing macroalbuminuria if their HbA1C variation increases after six years of follow-up. Our study did not investigate the impact of HbA1c fluctuations on the generation of oxidative stress and reactive oxygen species. Nevertheless, our findings indicate that elevated HbA1c standard deviation is associated with the occurrence of oxidative stress and chronic inflammation, hence accelerating the progression of macroalbuminuria. The path will become more evident following a subsequent investigation [30, 31]. Among the 471 individuals in this cohort with Type 1 DM, 13% exhibited isolated increases, 13% had high urinary albumin excretion (UAE), and 9.3% had chronic microalbuminuria. It has been suggested by some that the incidence of microalbuminuria and chronic microalbuminuria is approximately equal. According to the Oxford Regional Prospective Study, a range of 13-26% of young individuals with Type 1 diabetes experienced a progressive deterioration in their urinary albumin excretion (UAE), while 5% observed an improvement in their UAE over time [32]. Galego *et al*. (2006) say that between 6 and 18% of young people in Australia have high UAE levels [33]. 5.6% of the 426 young people in Sweden with Type 1 DM who were studied had microalbuminuria [34]. Teenage years are another thing that researchers have looked at as a possible risk factor for microalbuminuria. Based on what they found, having Type 1 DM before puberty might not be as important for microalbuminuria as having it after puberty. Donaghue *et al*. and Olsen *et al*. found that the amount of time a person had Type 1 DM before they turned 18 was not significantly linked to the development of micro-albuminuria. Hungary kept an eye on a small group of people for three years and found that puberty alone was a risk factor for getting microalbuminuria [35, 36]. These studies that claimed that the duration of diabetes before puberty had no bearing on the likelihood of having an elevated UAE might not have included enough patients or might have been biassed by changes in the kidneys' blood flow and function that can occur during puberty, which can raise UAE levels independent of the duration of diabetes. Within our sample of 8-12 year olds, this occurred [37]. Observational study of 1,706 teens with T1D found that changes in HbA1c were strongly linked to a higher risk of blindness, albuminuria, increased AER, and CAN. The study took into account known risk factors. This is the first time that CAN has been linked to blood sugar changes. We found the same things about blindness and early nephropathy as a recent review of the Diabetes Control and Complications Trial and a number of cohort studies that looked at people with T1DM [38, 39]. We demonstrate in a group of adolescents for whom there had been little clinical evidence previously that these issues are associated with HbA1c instability. Instead of the more sophisticated measurements employed in previous research, we additionally examined early elevation of AER, which forecasts future development of microalbuminuria. Our definition of retinopathy was a 1-level increase on the Early Treatment Diabetic Retinopathy Scale [40, 41]. These older clinical measures helped us show that the link with HbA1c variations is true for all kinds of kidney and eye disease. The link between glucose swings and a higher risk of problems could be caused by a number of things. There may be other things causing this link, such as how the surviving β-cells work and how insulin naturally comes out. If you change your blood sugar levels, it makes sense that cells will die (see reference 24 below). On the other hand, other health problems and things that make it hard to stick to treatment may have made this group's blood sugar levels change more and given them a higher risk of capillary problems [42]. More reactive stress is thought to be caused by changes in HbA1c. This is a major cause of diabetes problems [43, 44].

Conclusion

The study showed that uncontrolled diabetes is associated with increased HbA1c levels and albuminuria, which indicates worsening kidney function. The results indicate

that younger age groups (< 10 years) showed better diabetes control than older groups, which may reflect the influence of age factors on metabolism and response to treatment. As for body mass index, individuals who were within the normal range showed better diabetes control compared to those who were below normal weight. There were no significant gender differences in diabetes control, suggesting that gender is not a major influencing factor. This highlights the importance of careful medical follow-up and early intervention for patients to improve diabetes control and prevent complications.

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