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REVIEW ARTICLE

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Double Diabetes: Insulin Resistance and Metabolic Syndrome in Sudanese Patients with Type 1 Diabetes Mellitus

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ABSTRACT

Background: Double diabetes is a combination of characteristics of type 1 diabetes (T1DM) with metabolic syndrome and insulin resistance. The presence of insulin resistance and the metabolic syndrome are risk markers for macrovascular disease and several studies have found an increased incidence of chronic complications in T1DM patients with double diabetes.

Objective: The aim of this study was to determine the frequency of metabolic syndrome and insulin resistance (double diabetes) among T1DM at Gabir Abualiz Hospital, Khartoum State March to November 2020.

Method: This was an analytical cross-sectional study conducted at Gaber Abu-Aliz Hospital during the period from August to November 2020, in which 60 T1DM patients were enrolled. Insulin resistance was assessed by estimated glucose disposal rate (eGDR), a low rate correlates with increased insulin resistance. Metabolic syndrome was diagnosed according to the American Heart Association/National Heart, Lung, and Blood Institute criteria.

Results: Among 60 patients, the majority were females (81.7%). Metabolic syndrome was found in 27% of patients and abdominal obesity (male WC> 40; female WC> 35 inches) was the component of the metabolic syndrome in 42% of patients. The mean eGDR was 7.88 (2.6-11.6), and 25% had low eGDR levels (most insulin resistance < 4.5). The metabolic syndrome was significantly common among patients with eGDR below 3rd tertile (< 7.8) (P value= 0.000). Moreover, the presence of metabolic syndrome and insulin resistance was significantly associated with obesity, positive family history of T2DM, Lantus use, HbA1c above 9%, retinopathy and nephropathy.

Conclusions: The features of double diabetes (metabolic syndrome and insulin resistance) are common among Sudanese T1DM patients. Both metabolic syndrome and insulin resistance were significantly correlated with poor glycemic control, obesity, positive T2DM family history and microangiopathic complications..

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KEYWORDS

Type 1 diabetes mellitus, Double diabetes, Metabolic syndrome, Insulin resistance.

Abbrevations

AHA/NHLBI: American Heart Association/National Heart, Lung, and Blood Institute, DM: Diabetes mellitus, eGDR: Estimated glucose disposal rate, IDF: International Diabetes Federation, SPSS: Statistical Package for Social Sciences, T1DM: Type 1 diabetes.

Introduction

Diabetes mellitus (DM) is considered as one of the most common diseases worldwide affecting the life of millions of people. Type 1 diabetes results from autoimmune destruction of the insulin-producing beta cells of the pancreas, while type 2 diabetes is due to a combination of insulin resistance and reduction in insulin secretion. Precise identification and diagnosis of these two types of diabetes have been becoming increasingly difficult, this resulted in adding a new category, namely double or hybrid diabetes that reveals symptoms of both type 1 and type 2 through the accelerator hypothesis [1].

In 1991, the term 'double diabetes' was first introduced when patients with type 1 DM and who had a family history of type 2 DM were observed to have an increased risk of obesity and hardly achieved satisfactory glycemic control even with higher doses of insulin. Double diabetes can be defined as a combination of characteristics of type 1 diabetes with metabolic syndrome and insulin resistance [2]. The metabolic syndrome constitutes a cluster of connected cardiovascular risk factors, centered around central obesity, insulin resistance, dyslipidemia, and

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hypertension. Moreover, the metabolic syndrome increases the risk of cardiovascular disease in both nondiabetic and type 2 diabetic patients. There are several definitions for metabolic syndrome, the most recent being the agreement from the International Diabetes Federation (IDF) [3].

The American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) proposed criteria to diagnose metabolic syndrome including; central obesity (male waist of more than 40 and female waist of more than 35 inches), high triglyceride (more than 150 mg/dl) or on lipid lowering agent, low HDL cholesterol (less than 40 in male and 50 in females) or on a HDL improving drug, blood pressure more than 130/85 mmHg or on treatment and high fasting glucose (more than 100 mg/dL) or on glucose lowering agent. Three of the above are required for diagnosis [4].

Apart from using labor-intensive and invasive euglycemic-hyperinsulinemic clamp techniques, determining insulin resistance in type 1 diabetes is challenging as simpler tools like the homeostasis model are not suitable for these patients [5,6]. In clinical settings, insulin resistance among type 1 diabetic patients is usually recognized by their increasing needs for insulin. However, in recent years a validated tool for estimated glucose disposal rate (eGDR) has been established. Based on clinical factors, this tool calculates a score, which reveals a close relationship to insulin resistance when formally measured by the clamp method. By using this technique, the Pittsburgh Epidemiology of Diabetes Complications Study has found that high insulin resistance (means low eGDR) to be significantly associated with a higher risk of coronary artery disease, peripheral vascular disease, and nephropathy [3].

Objectives

This study aimed to determine the frequency of metabolic syndrome and insulin resistance (double diabetes) among T1DM patients and to identify the factors associated with metabolic syndrome and insulin resistance among T1DM patients. Moreover, to assess the complications of double diabetes among T1DM patients.

Methods

Study Design

This is an analytical cross-sectional study conducted at a hospital setting.

Study Setting and Period

The study was conducted from March to August 2020 at Gaber Abu-Aliz Hospital, Khartoum State, Sudan, a large diabetic center.

Study Population

The study population included adult patients (>18 years) with type 1 diabetes mellitus attending Gaber Abu-Aliz Hospital.

Inclusion and Exclusion Criteria

Inclusion criteria:

- Adult patients (>18 years)
- Patients with type 1 diabetes mellitus
- Males and females

Exclusion Criteria:

- Critical ill patients
- Refusal to participate in the study

Sampling Technique

The total coverage method was used during the study period, and 60 patients were enrolled.

Data Collection Tools and Methods

Data collection was carried out by the principal researcher. Data were collected through a structured questionnaire consisting of: demographic, clinical characteristics, laboratory results, medical history, complications, glycemic control and diet control.
Insulin resistance was assessed by estimated glucose disposal rate (eGDR) as follows

$$\text{eGDR} = 24.31 - 12.22\,(\text{WHR}) - 3.29\,(\text{hypertension status}) - 0.57\,(\text{HbA}_{1c})$$

Where HTN is the presence of hypertension (0 = no, 1 = yes) and WC is waist circumference.

Metabolic syndrome was diagnosed according to American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) criteria including:

- A waist circumference of 32” to 40” based on gender and race
- Elevated triglycerides greater than or equal to 150 mg/dL
- Reduced HDL less than 40 mg/ dL in men, less than 50 mg/ dL in women
- Elevated blood pressure greater than or equal to 130 mmHg systolic and/or greater than or equal to 85 mmHg diastolic
- Elevated fasting glucose greater than or equal to 100 mg/ dL
- Metabolic syndrome is identified by the **presence of three or more**

Data Analysis

Data were analyzed by using the Statistical Package for Social Sciences (SPSS V. 21.0). The analyzed data were presented in tables and figures designed by Microsoft Excel 2007. The chi-Square test was used as a significance test and the P. value less than 0.05.was considered as significant.

Results

In total this study enrolled 60 type 1 diabetes mellitus patients, 49 (81.7%) were females and 11 (18.3%) were males, their mean age was 21.5±2.6 years. Most of them were students (n=32; 53.3%) and singles (n=56; 93.3%). Furthermore, the mean BMI of the participants was 23.9±3.9 kg/m2, and the majority of them (n=34, 56.7%) had normal BMI levels (Table 1).

Regarding the duration of DM, 32 (54%) of the patients had DM duration ranging from 5-10 years, while 5 (8%) of them had DM for more than 15 years. Moreover, the mean of HbA1c was 9.3±1.6% and most of the subjects (n= 41, 68.3%) had HbA1c ranged from 6-9%. The vast majority of the patients (n=55, 92%) were taking mixed insulin and 5 (8%) of them were taking Lantus insulin, all the patients received insulin doses ranging from 0.6-1 IU/Kg. Positive family history of T2DM was found in 32 (53.3%) patients (Table 2). Regarding the blood pressure, the mean of systolic blood pressure was 119±15 mmHg and the

mean diastolic blood pressure was 80±9 mmHg. In addition, 6 (10%) patients used Antihypertensive agents (Table 2).

Table 1: The demographic data of patients with type 1 diabetes mellitus (N=60).

	N	%
Age (Years); mean ± SD	**21.5±2.6**	
Gender		
Female	49	81.7
Male	11	18.3
Occupation		
Student	32	53.3
Housewife	3	5.0
Worker	2	3.3
Unknown	23	38.3
Marital status		
Single	56	93.3
Married	4	6.7
WC	**N**	
Abdominal obesity >40 M / >35 F inches	27	42%
Normal	33	58%
BMI		
Underweight	3	5%
Normal	34	56.7%
Overweight	16	26.6%
Obese	7	11.7%

Table 2: The Disease Characteristics of patients with type 1 diabetes mellitus (n =60).

	N	%
Duration of T1DM years		
• 5-10	32	53.3%
• 11-15	23	38.3%
• >15	5	8.4%
DM control (HbA1c)		
< 7%	5	8.3%
7% - 9%	31	51.7%
> 9%	24	40%
Family history of T2Dm		
• Yes	32	53.4%
• No	28	46.6%
Treatment (type of Insulin)		
Mixed insulin	55	92%
Lantus insulin	5	8%
Complication		
• Retinopathy	19	31.7%
• Nephropathy	14	23.3%
• DSF	1	1.7%
• Non	31	51%
Blood pressure; (Mean BP 119/80)		
• > 130/85	13	21.7%
• On medication	6	10%
Lipid profile		
• Cholesterol		
• High TGL	11	18.3%
• Low HDL	7	11.7%
• On lipid lowering agents	2	3.3%

In this study, the mean of cholesterol was 168±42 mg/dl, triglyceride was 151±54 mg/dl, HDL-cholesterol was 49±14 mg/dl and LDL-cholesterol was 99±53 mg/dl. Two (2.3%) patients used Lipid lowering agents (Table 2). Concerning the complications, 19 (31.7%) patients had retinopathy, 14 (23.3%) had nephropathy and one (1.7%) patient had diabetic septic foot (DSF) (Table 2). With respect to metabolic syndrome indicators, 27 (42%) patients had abdominal obesity (male WC> 40 cm; female WC> 35 cm), 13 (21.7%) had blood pressure >130 /85 or on treatment, 11 (18.3%) patients had high triglyceride above 150 mg/dl or on lowering agent, and 7 (11.7%) patients had low HDL (male < 40 mg/dl; female < 50 mg/dl) (Table 1, 2).

According to AHA NHLBI criteria, metabolic syndrome was found in 16 (27%) patients (Figure 1). Estimated glucose disposal rate (eGDR) was used to assess insulin resistance among our study patients, in which 15 (25%) patients had eGDR levels below 25th tertile (highest insulin resistance< 4.5), 15 (25%) had eGDR levels from 25th to 75th tertile (moderate insulin resistance= 4.5-7.8) and 30 (50%) patients had eGDR levels above 75th tertile (lowest insulin resistance > 7.9) (Figure 2).

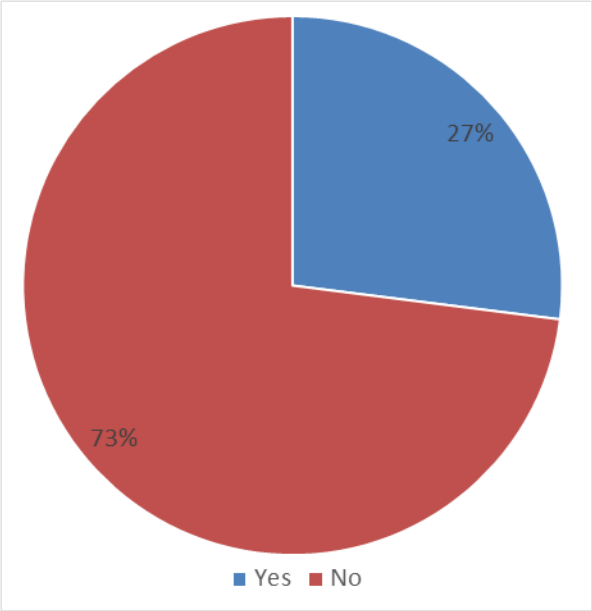

Figure 1: The presence of metabolic syndrome among patients with type 1 diabetes mellitus (N=60).

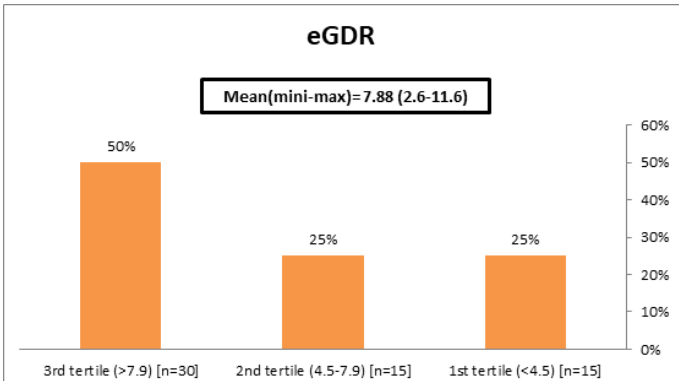

Figure 2: The levels of estimated glucose disposal rate (eGDR) and insulin resistance among type 1 diabetes mellitus (T1DM) patients (N=60).

The association between metabolic syndrome and diabetic characteristics showed that the metabolic syndrome development among our subjects was significantly associated with HbA1c levels above 9% (P value= 0.013) and Lantus insulin was used more than mixed insulin (P value= 0.011). However, the duration of DM was not significantly affected by metabolic syndrome (P. value= 0.170) (Table 3). Table 3 revealed a significant association between metabolic syndrome and eGDR below 3rd tertile (< 7.8) (P. value= 0.000).

Table 3: The association between metabolic syndrome and insulin resistance.

	Metabolic syndrome		P. value
	Yes	No	
eGDR			
• 1st tertile (<4.5)	9	6	<0.001
	60.0%	40.0%	
• 2nd tertile (4.5-7.9)	6	9	
	40.0%	60.0%	
• 3rd tertile (>7.9)	1	29	
	3.3%	96.7%	

Table 4 showed that metabolic syndrome was significantly common among obese patients (57.1%) compared to other patients (P. value= 0.025).

Table 4: The association between metabolic syndrome and BMI.

	Metabolic syndrome		P. value
	Yes	No	
BMI			
• Underweight	1	2	0.025
	33.3%	66.7%	
• Normal	7	27	
	20.6%	79.4%	
• Overweight	4	12	
	25.0%	75.0%	
• Obese	4	3	
	57.1%	42.9%	

Metabolic syndrome was significantly more frequent among patients with a positive family history of T2DM when compared to other patients (43.8% vs 7.1%; P. value= 0.007). Metabolic syndrome was significantly common among patients with retinopathy (63.2% vs 17.1%; P. value= 0.001) and nephropathy (47.4% vs 12.2%; P. value= 0.004), whereas patients without metabolic syndrome were less likely to developed complications (P. value= 0.000) (Table 5).

The association between insulin resistance and diabetic characteristics showed that the larger number of the lowest eGDR tertile (most insulin resistance<4.5) were found among patients with HbA1c above 9% (P. value= 0.02) and Lantus insulin users (P. value= 0.028). Although, the duration of DM was not significantly correlated with insulin resistance (P. value= 0.125) (Table 6).

Table 6 showed that a family history of type 2 diabetes was significantly associated with lower eGDR tertile (<4.5) (P value= 0.000). Furthermore, this study revealed that the lowest eGDR tertile (most insulin resistance<4.5) was significantly associated with retinopathy (P. value= 0.000) and nephropathy (P. value= 0.000), whilst patients with the highest eGDR tertile (most insulin sensitive> 7.9) were less likely to developed complications (P. value= 0.000).

Table 6: The association between insulin resistance and diabetic characteristics.

	Metabolic syndrome		P. value
	Yes	No	
Diabetes duration (Yrs)			
• 5-10	7	25	0.170
	21.9%	78.1%	
• 11-15	7	16	
	30.4%	69.6%	
• >15	2	3	
	40.0%	60.0%	
HbA1c (%)			
• 6-9	0	5	0.013
	0.0%	100.0%	
• 10-12	6	25	
	19.4%	80.6%	
• >12	10	14	
	41.7%	58.3%	
Types of insulin			
• Mixed	12	43	0.011
	21.8%	78.2%	
• Lantus	4	1	
	80.0%	20.0%	
Family history of T2Dm			
• Yes	14	18	0.007
	43.8%	56.2%	
• No	2	26	
	7.1%	92.9%	
Complication			
• Retinopathy	12	7	0.001
	63.2	17.1	
• Nephropathy	9	5	0.004
	47.4	12.2	
• Dsf	0	1	0.683
	0%	2.4%	
• No complication	2	29	<0.001
	10.5%	70.7	

Table 7 demonstrated that obese patients were more likely to have the lowest eGDR tertile (most insulin resistance<4.5) (P. value= 0.021).

Table 7: The association between insulin resistance and BMI.

	eGDR			P. value
	1st tertile (<4.5)	2nd tertile (4.5-7.9)	3rd tertile (>7.9)	
BMI				
• Underweight	1	0	2	0.021
	33.3%	0.0%	66.7%	
• Normal	6	8	20	
	17.6%	23.5%	58.8%	
• Overweight	5	3	8	
	31.3%	18.8%	50.0%	
• Obese	3	4	0	
	42.9%	57.1%	0.0%	

Discussion

This study aimed to determine the frequency of metabolic syndrome and insulin resistance (double diabetes) among 60 Sudanese Type 1 diabetic patients in Gaber Abu-Aliz Hospital, and to identify the factors associated with metabolic syndrome and insulin resistance in Type 1 DM patients.

Using the AHA/NHLBI criteria, this study found that the frequency of metabolic syndrome in patients with type 1 DM was 27% (n= 16). This finding was comparable with the results reported by Merger et al. in a large epidemiological study which revealed that a total of 25.5% of patients suffering from type 1 DM presented with metabolic syndrome [7]. Similar data have been reported by the Diabetes Control and Complications Trial [2], Juan J et al. [8] and Angela S et al. [9]. Those reported prevalence of 27.7%, 31% and 30.1%, respectively, using the same criteria. Studies of Americans with type 1 DM found that rates of metabolic syndrome ranging from 8%-31%, depending on the diagnostic criteria used [10]. On the other hand, a higher rate of metabolic syndrome was reported by the Finn-Diane study in which the prevalence of the metabolic syndrome was 38% [11]. This difference could be due to socio-demographic characteristics of the study participants.

Out of all the components of the metabolic syndrome (apart from hyperglycemia, which was present in all the subjects), the most frequent component was abdominal obesity (male WC> 40 inches; female WC> 35 inches) which was reported in 27 (42%) patients. These observations were consistent with the study of Juan J et al. who also revealed that abdominal obesity and hypoalphalipoproteinemia were the commonest components of the metabolic syndrome [8].

The current study found a significant association between the metabolic syndrome and the high HbA1c levels (above 9%) (P value = 0.013) and Lantus insulin more than the mixed insulin (P value = 0.011). Similarly, ERIC S et al. reported in the Diabetes Control and Complications Trial that HbA1c is higher in metabolic syndrome patients when compared to other patients (9.2 ± 1.6% vs 8.8 ± 1.5%) [2]. Similarly, Juan J et al. noticed that uncontrolled HbA1c has a significant and strong association with the presence of metabolic syndrome [8]. Moreover, the Finn-Diane study reported that the prevalence of metabolic syndrome was 31% in patients with good glycemic control, 36% in patients with intermediate glycemic control, and 51% in patients with poor glycemic control (P < 0.001) [11]. Metabolic syndrome was significantly common among obese patients (57.1%) compared to others (P value= 0.025). This finding was in accordance with the study which conducted by Juan J et al. who found a significant association between obesity and metabolic syndrome [8]. Obesity is linked with insulin resistance and poor metabolic control along with many other problems [12]. Among our study group, metabolic syndrome was significantly frequent among patients with a positive family history of T2DM more than others (43.8% vs 7.1%; P. value= 0.007). This finding was consistent with another study conducted by Teupe B et al. [13]. Remarkably, metabolic syndrome was common among patients with retinopathy (63.2% vs 17.1%; P. value= 0.001) and nephropathy (47.4% vs 12.2%; P. value= 0.004). These results were strongly in agreement with Merger SR et al. who stated that double diabetes demonstrated an increased risk for nephropathy and retinopathy [7]. Correspondingly, Juan J et al. reported that patients with type 1 DM and the metabolic syndrome had a significantly higher prevalence of microangiopathic complications (retinopathy, neuropathy and nephropathy) compared to type 1 Diabetic patients without the metabolic syndrome [8]. Additionally, in the Finn-Diane study patients with metabolic syndrome had a 3.75-fold odds ratio for diabetic nephropathy (95% CI 2.89–4.85) [11]. The risk of diabetic nephropathy increases with increasing number of metabolic syndrome components per patient [14].

The present study showed that metabolic syndrome was significantly common among patients with eGDR below 3rd tertile (< 7.8) (P value= 0.000). This finding was consistent with ERIC S et al. who found low eGDR was significantly correlated with the metabolic syndrome (7.4 ± 1.7 vs 8.3 ± 1.3) [2]. Similarly, Mihaela L et al. observed that patients with metabolic syndrome have lower eGDR than patients without metabolic syndrome (5.82±2.22 vs. 7.18±2.25), the difference being statistically highly significant (p=0.0001) [15]. Similar results were found by Chillaro'n J et al., in which eGDR level less than 8.77 was found to be strongly associated with the metabolic syndrome [16].

Our study demonstrated that the highest proportions of insulin resistance were found among patients with HbA1c above 9% (P. value= 0.02) and Lantus insulin users (P. value= 0.03). These findings were consistent with other previous studies such as Eric J et al. [17], Chillaro'n J et al. [16] and Katherine V et al. [18] those reported HbA1c was inversely associated with eGDR. HbA1c has a significant association with insulin resistance, as several studies indicating a strong association between HbA1c levels and insulin sensitivity in individuals with normal glucose tolerance [19-21].

This study revealed that obesity (BMI>29.9 kg/m2) was significantly associated with insulin resistance (P value = 0.021). This result was comparable to the studies of Eric J et al. [17] and Katherine V [18]. Although, Enrique P et al. failed to find a significant correlation between eGDR and BMI among young (<18 years) type 1 diabetic patients [22], and this might be related to the study population.

The present study showed that a positive family history of type 2 diabetes was significantly associated with insulin resistance (P value= 0.000). Consistently, Eric J et al. [17], Katherine V et al. [18] and Silva A. Arslanian et al. [23] reported that a family history of type 2 diabetes was more frequent among patients with lower eGDR tertile (i.e. insulin resistance). Interestingly, the current study illustrated that lowest eGDR tertile (most insulin resistance<4.5) was significantly associated with retinopathy (P. value < 0.001) and nephropathy (P. value < 0.001), whilst patients with highest eGDR tertile (most insulin sensitive > 7.9) were less likely to develop complications (P. value= 0.000), which is indicating that insulin resistance among T1DM patients was significantly associated with development of complications among those patients. Similarly, Eric S et al. in the Diabetes Control and Complications Trial reported that the low eGDR at baseline strongly predicted the development of retinopathy, nephropathy, and cardiovascular disease (hazard ratios 0.75,

0.88, and 0.70, respectively, per mg · kg^{-1} · min^{-1} change; P < 0.001, P = 0.005, and P = 0.002, respectively) [2]. Furthermore, a study conducted by Mihaela L et al. showed that the chronic complications of T1DM patients were significantly associated with the lowest eGDR tertile [15]. Chillaro'n J et al. found all patients with diabetic complications had eGDR values below 8.16. In addition, eGDR level was significantly lower in patients with diabetic retinopathy (5.97 ± 1.2), diabetic neuropathy (5.06 ± 0.4), and diabetic nephropathy (5.79 ± 1.5) compared to others (9.38 ± 2.0, P 0.001; 9.26 ± 2.0, P 0.001; and 9.19 ± 2.2, P 0.001) [16]. Regarding the limitations of this study, due to the limited time and resources, the sample size was limited and the study was conducted in a single study area.

Conclusion

The present study concluded that the double diabetes features (metabolic syndrome and insulin resistance) were common among Sudanese Type 1 DM patients. Both metabolic syndrome and insulin resistance were significantly correlated with poor glycemic control (HbA1c> 9%), obesity (BMI> 29.9 kg/m^2), and microangiopathic complications (retinopathy and nephropathy). The eGDR can be considered as an accurate indicator of insulin resistance in type 1 DM patients. It is a simple tool and it can be easily calculated. Based on that, we recommended using it as a routine insulin resistance indicator among type 1 DM patients. Additionally, reducing risk factors such as: poor glycemic control and high BMI can effectively prevent the development of double diabetes. Special consideration should be directed toward type 1 DM patients with a positive family history of type 2 DM to reduce the incidence of double diabetes.

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Ethical Consideration

Ethical approval was obtained from the Sudan Medical Specialization Board (SMSB) and the hospital authority. Written consents were attained from patients. Data were used anonymously by using identity numbers instead of names in order to protect the patient's identity and kept securely and in separate files.

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