Assessment of Neuropeptides B & W, Leptin and Adiponectin in Children and Adolescents with Type 1 Diabetes Mellitus

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ABSTRACT

Background: Given the serious health consequences including impaired metabolic control among type 1 diabetes mellitus (T1DM), neuropeptide B (NPB), neuropeptide W (NPW), leptin and adiponectin collectively could serve as biomarkers of T1DM progression. **Objectives:** Comparison of serum levels of NPB, NPW, leptin and adiponectin among children and adolescents with T1DM treated either by multiple daily doses of insulin (MDI) or continuous subcutaneous insulin infusion (CSII), and healthy age and sex matched controls. **Patients and methods:** This comparative cross-sectional study included 60 children and adolescents with type 1 diabetes mellitus divided equally into 2 groups according to the type of insulin regimen (MDI or CSII). The cases were recruited from attendees of the Pediatrics and Adolescents Diabetes Unit (PADU), Children's Hospital, Ain Shams University, Cairo, Egypt. Cases were compared to 30 healthy age and sex-matched controls. Demographic and anthropometric data, medical history, estimated glucose disposal ratio and glycated hemoglobin were collected. Measurements of NPB, NPW, leptin and adiponectin were performed using enzyme-linked immunosorbent assay (ELISA). **Results:** There was a significant difference between the diabetic groups and the control group regarding NPB, NPW, leptin and adiponectin, where NPB, NPW and leptin levels were significantly decreased among MDI and CSII groups compared to the control group ($p=0.001$), while adiponectin was significantly increased among the MDI and CSII groups compared to the control group ($p=0.001$). However, there was no statistically significant difference between the MDI and CSII groups ($p>0.05$). **Conclusion:** The lower levels of NPB, NPW and leptin among both MDI and CSII groups could be attributed to decreased body fat, and lower BMI which is a reflection of their metabolic control. Similarly, elevation in adiponectin among both MDI and CSII groups compared to the control group might be a result of hyperglycemia and impaired glycosylation process. Further studies on larger scale are warranted to confirm our data.

Keywords: Adiponectin, Continuous Insulin infusion, leptin, Multiple daily doses of insulin, NBP, NBW.

INTRODUCTION

Type 1 DM is one of the most common chronic metabolic diseases in childhood and adolescence with an increasing prevalence **(Tuomilehto et al., 2020)**. Type 1 DM can reduce both quality of life and life expectancy. High-quality T1DM care, especially during childhood and adolescence, is crucial for achieving optimal metabolic control throughout life **(Buchmann et al., 2023).** With regards to insulin administration, the standard treatment in most settings of clinical practice worldwide is administering multiple daily injections (MDI) of insulin analogs that have different pharmacokinetic properties **(Danne et al., 2018).** However, a continuous subcutaneous insulin infusion (CSII) or insulin pump trying to mimic the function of the pancreas may be more physiological **(Blair et al., 2018; Rys et al., 2018).** Neuropeptide B (NPB) and neuropeptide W (NPW) are suspected to play a role in etiopathogenesis and/or outcome of T1DM. Both neuropeptides demonstrate expression in pancreatic β cells while NPW exerts a potent suppressive effect on blood leptin concentrations thus showing its direct involvement in regulation of energy homeostasis **(Takenoya et al., 2015; Wojciechowicz et al., 2021)**. At the adipose tissue level, certain adipokines, such as leptin and adiponectin, have been shown to play a role in the regulation of carbohydrate metabolism and via those mechanisms potentially contribute to the outcomes of T1DM **(Kim et al., 2019).** Leptin has also a significant effect on the stimulation of proinflammatory cytokines in T1DM **(Soedling et al., 2015).** Studies indicate that adiponectin influences insulin sensitivity in T1DM hypothesizing that deregulation of the circulatory level of both leptin and adiponectin could cause insulin resistance in patients with T1DM **(Pereira et al., 2012).** Therefore, NPB, NPW, leptin and adiponectin, could serve as biomarkers of T1DM progression.

PATIENTS AND METHODS

Ethical consideration: This study was approved by Ain Shams University Research Ethics Committee (REC).

An informed consent was taken from all enrolled patients and/or care givers before starting the study and an informed assent was taken from all patients older than 7 years.

Data from medical records were collected and used for private and confidential research purposes.

The patients and parents have the right to withdraw at any time.

There was no conflict of interest regarding the study or publication.

There is no financial support or sponsorship.

Sample size : by using PASS 11 program for sample size calculation, setting power at 80 % alpha error at 5% and after reviewing previous study results **(Grzelak et al.,2019)** showed that the means of leptin level in serum among patients with type 1 diabetes mellitus versus healthy controls were (2.10 ± 2.98 and 6.09 ± 5.53 respectively); based on that, a sample size of at least 21 pediatric patients with type 1 diabetes mellitus treated by MDI and 21 pediatric patients treated by CSII and 21 healthy controls would be sufficient to achieve study objective.

Inclusion criteria: 3 to 18 years old patients of both sexes, who were previously diagnosed with T1DM according to ISPAD (2022) for at least 1 year **(Greeley et al., 2022).**

Exclusion criteria: Medical conditions that could affect growth were excluded as:
Familial short stature, hypothyroidism, celiac disease and having HbA1c greater than 11.1%

Study procedure: This comparative cross-sectional study included 60 T1DM cases recruited from Pediatrics and Adolescents Diabetes Unit (PADU), Children's Hospital, Ain Shams University during the period from January 2023 to June 2023
The study included:.
Group A (patient group): 60 T1DM patients attending PADU. The patient group were divided equally into two subgroups (30 patients in each group) according to the mode of insulin administration (MDI or CSII)
Group B (control group): 30 pediatric healthy controls who are age and sex-matching attending the general outpatient clinic for general check-up.

All patients were subjected to:
1-**Medical history** including : duration of diabetes, insulin therapy and diabetic complications.
11-**Clinical examination** including :anthropometric measurements (height, weight, waist hip ratio (WHR), waist/height ratio, and body mass index [BMI]) and blood pressure.
111-**Laboratory investigations** including : Glycated haemoglobin (HbA1c) measurement was carried out using Tina-quant ® HbA1c kit supplied by Roche ® Diagnostics on the Roche/Hitachi Cobas ® c501 System based on turbidimetric inhibition immunoassay (TINIA). The quantitative double-antibody sandwich enzyme-linked immunoassay (ELISA) was used to assay NPB, NPW, leptin and adiponectin levels.
Estimated glucose disposal ratio (eGDR) was calculated with the waist/ hip ratio, history of systemic arterial hypertension and HbA1c level, that are inversely related to IR according to the following equation:
eGDR= 24.4 – (12.97 × W/H) – (3.39 × AH) – (0.60 × A1c) **(Williams et al., 2000).**

Statistical analysis:

The analysis was performed using IBM SPSS Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. Qualitative data were described as number and percent then compared using Chi-Square test, while quantitative data were described using median and inter quartile range. For non-parametric data, Mann-Whitney U test was used to compare 2 independent groups and Kruskal Wallis test was used to compare > 2 independent groups, while mean and standard deviation was used for parametric data, where Student t-test was used to compare 2 independent groups and One Way ANOVA test was used to compare >2 independent groups. The diagnostic performance of a test was evaluated using Receiver Operating Characteristic (ROC) curve analysis and significance of the obtained results was judged at the (0.05) level. The Spearman's rank-order correlation was used to determine the strength and direction of a linear relationship between one non-normally distributed continuous variable and one normally distributed continuous variable.

RESULTS

Our results will be demonstrated in the following tables and figures:

Table (1): Baseline characteristics of the studied participants

Anthropometric data and BP		MDI group (N=30)		CSII group (N=30)		Control group (N=30)		Test of sig.	P
		N	%	N	%	N	%		
Sex	Male	13	43.3	14	46.7	12	40	χ^2=0.27	0.87
	Female	17	56.7	16	53.3	18	60		
Age (year)	Mean±SD	11 ± 3.4		11.7 ± 3.4		10.9 ± 3.3		F= 0.51	0.61
	Min-Max	3.5-17		3.5-17		3-17			
Duration of diabetes (year)	Mean±SD	5.38 ± 3.29		6.68 ± 3.57		-		t= -1.47	0.15
	Min-Max	0.5-13		1-13.5		-			
Weight (kg)	Mean±SD	34.9 ± 13.1		36.2 ±13.4		38.9 ± 11.5		F= 0.81	0.45
	Min-Max	13-63		12-62		14-61			
Weight percentile (%)	Median (IQR)	30.3 (6.2-53.8)		30.2 (6.8-53.0)		37.6 (9.3-60.7)		KW=11.6 P=0.003*	P_1=0.98 P_2=0.003* P_3=0.004*
	Min-Max	0.1-79.7		0.1-90.4		0.1-98.7			
Height (cm)	Mean±SD	138.4 ± 17.2		143.4 ± 17.6		140.5 ± 14.8		F= 0.69	0.51
	Min-Max	92-165		86-172		98-155			
Height percentile (%)	Median (IQR)	20.4 (3.5-63.6)		25.8 (12.1-49.2)		40.2 (16.9-59.8)		KW=2.13	0.35
	Min-Max	0.1-96.7		0.2-98.9		0.3-95.8			
BMI (kg/m^2)	Mean±SD	17.5 ± 3.3		17 ± 3.4		19.3 ± 3.7		F=3.61 P=0.03*	P_1=0.57 P_2=0.01* P_3=0.05*
	Min-Max	13.7-25.9		10.5-23.9		13.2-28.9			
BMI percentile (%)	Median (IQR)	34.4 (20.5-66.1)		25.6 (6-67)		76 (27.2-92.8)		KW=11.0 P=0.004*	P_1=0.32 P_2=0.002* P_3=0.015*
	Min-Max	3.4-94.7		0.1-98.2		1-99.9			
WHR	Mean±SD	0.85 ± 0.4		0.86 ± 0.03		0.82 ± 0.04		F= 16.22 P=0.001*	P_1=0.37 P_2=0.001* P_3=0.001*
	Min-Max	0.78-0.94		0.82-0.91		0.75-0.9			
	Median (IQR)	120 (110-130)		120 (120-130)		110 (103.75-120)		KW=25.4 P=0.001*	P_1=0.63 P_2=0.001*

SBP (mmHg)	Min-Max	100-130	100-130	100-120		P_3=0.001*
DBP (mmHg)	Median (IQR)	80 (73.3-80)	80 (77.5-80)	70 (70-76.25)	KW=23.5 P=0.001*	P_1=0.44 P_2=0.001* P_3=0.001*
	Min-Max	70-90	70-90	60-80		

Table (1) shows no statistically significant difference among MDI, CSII and the control groups regarding age and sex. There was no significant difference between the MDI and CSII groups regarding diabetes duration. However, it shows highly significant increase among diabetic groups including both MDI and CSII groups and the control group regarding WHR, SBP and DBP, while weight percentile, BMI and BMI percentile were significantly decreased among the MDI and CSII patients compared to the control group.

Table (2): Disease history and clinical characteristics of the studied participants

Clinical characteristics		**MDI group (N=30)**		**CSII group (N=30)**		**Control group (N=30)**		**Test of sig.**	**P**
		N	**%**	**N**	**%**	**N**	**%**		
Nephropathy		4	13.3	5	16.7	-	-	χ^2=0.13	0.72
Retinopathy		5	16.7	7	23.3	-	-	χ^2=0.42	0.52
Neuropathy		2	6.7	6	20	-	-	χ^2=2.31	0.13
DKA frequency during last year	Median (IQR)	2 (1-3)		3 (2-3)		-		U=230.5	0.001*
	Min –Max	1-5		1-5		-			
TDD (U/kg/day)	Median (IQR)	1.33 (1.2-1.6)		1.32 (1.1-1.4)		-		U=312.5	0.04*
	Min-Max	1.16-2		0.87-1.59		-			
HbA1c (%)	Median (IQR)	7.5 (7.1-9.1)		8.7 (7.8-10.7)		5.6 (5.4-5.8)		KW=60.6 P=0.001*	P_1=0.006* P_2=0.001* P_3=0.001*
	Min-Max	5.5-11.1		6.8-12.5		5.1-6.1			
eGDR (mg/kg/min)	Median (IQR)	8.7 (8.1-9.1)		8.2 (7.1-8.5)		10.4 (10.2-10.8)		KW=59.2 P=0.001*	P_1=0.003* P_2=0.001* P_3=0.001*
	Min –Max	5.6-10.6		3.6-9.4		9.4-11.2			

Table (2) shows that the frequency of DKA (during the last year) was significantly higher among CSII group compared to MDI group, while TDD of insulin was significantly lower among CSII group compared to MDI group. It also shows that HbA1c was significantly higher among the CSII and MDI groups compared to the control group and it was significantly higher among the CSII group compared to MDI group. While eGDR was significantly lower among MDI and CSII groups compared to the control group and it was significantly lower among CSII patients compared to MDI group denoting higher insulin resistance among CSII group.

Table (3): Serum levels of biomarkers in the studied participants

Biochemical markers		MDI group (N=30)	CSII group (N=30)	Control group (N=30)	Test of sig.	P
NPB (ng/ml)	Median (IQR)	1.4 (1.2-1.6)	1.5 (1.5-1.9)	4.4 (4.1-4.1-5.7)	KW=218.1 P=0.001*	P_1=0.06 P_2=0.001* P_3=0.001*
	Min-Max	0.64-2.4	0.59-6.9	3.4-7.9		
NPW (ng/ml)	Median (IQR)	0.69 (0.58-83)	0.78 (0.53-0.94)	4.2 (3.03-7.5)	KW=77.1 P=0.001*	P_1=0.57 P_2=0.001* P_3=0.001*
	Min-Max	0.43-1.01	0.13-5.8	2.2-20.2		
Leptin (ng/ml)	Median (IQR)	0.23 (0.17-0.29)	0.25 (0.18-0.32)	1.5 (1.2-2.6)	KW=134.4 P=0.001*	P_1=0.39 P_2=0.001* P_3=0.001*
	Min-Max	0.09-0.39	0.07-2.3	0.86-4.8		
Adiponectin (mg/L)	Median (IQR)	18.9 (13.2-21.7)	13.8 (11.5-20.6)	2.7 (2.3-7.6)	KW=133.7 P=0.001*	P_1=0.09 P_2=0.001* P_3=0.001*
	Min-Max	8.2-28.4	9.2-29.3	1.9-14.6		

Table (3) shows that NPB, NPW and leptin levels were significantly reduced among the MDI and CSII groups compared to the control group (p=0.001), while adiponectin was significantly elevated among the MDI and CSII groups compared to the control group (p=0.001).

Table (4): Validity of laboratory data

Lab parameter	AUC	p	Sensitivity (%)	Specificity (%)	95% CI	Cutoff
NPB	0.98	0.001*	100	96.7	0.94-1	2.97
NPW	0.99	0.001*	100	96.7	0.96-1	1.95
Leptin	0.99	0.001*	100	98.3	0.97-1	0.76
Adiponectin	0.95	0.001*	100	80	0.91-1	8.06

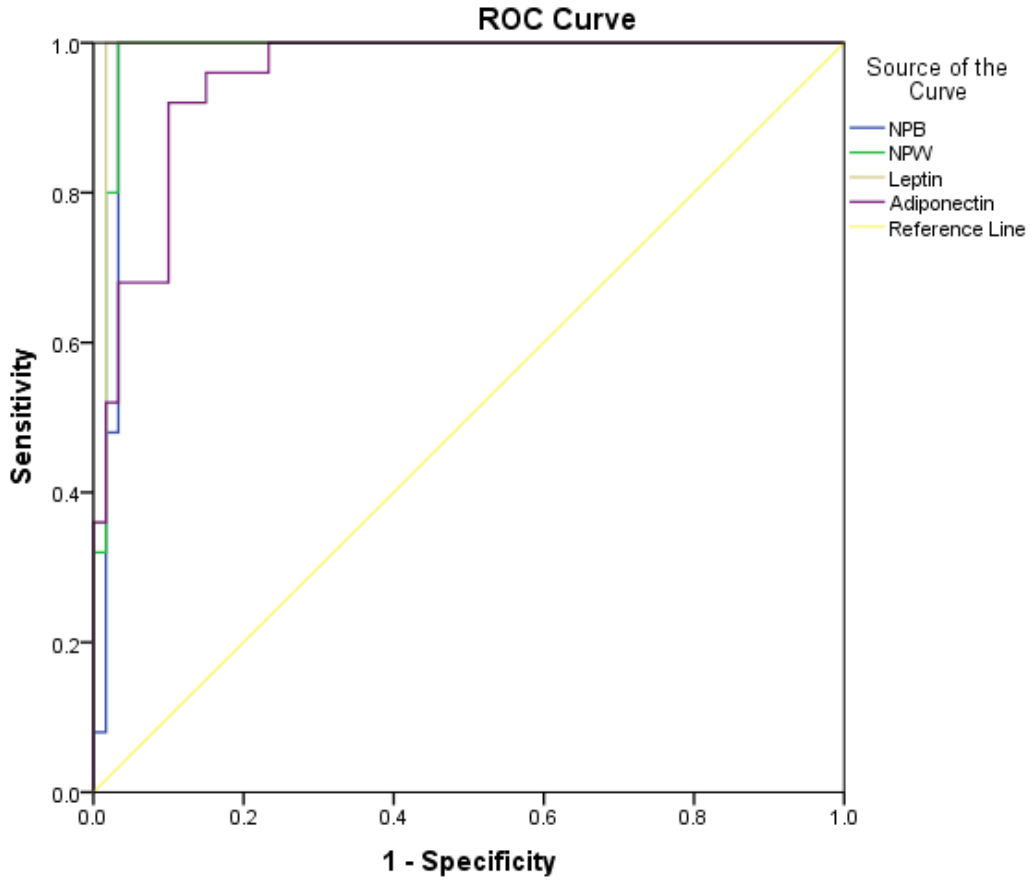

Figure (1): ROC curve of NPB, NPW, leptin and adiponectin

Table (4) and figure (1) show that that the area under ROC curve for NPB, NPW, leptin and adiponectin in differentiating diabetic cases was 0.98, 0.99, 0.99 and 0.95, respectively, with the best detected cut off point is 2.97 ng/ml, 1.95 ng/ml, 0.76 ng/ml and 8.06 mg/L, respectively.

DISCUSSION

This study demonstrated lower weight and BMI percentiles among diabetic groups compared to the healthy control group (p=0.001), which might be attributed to weight loss or poor control, while WHR was significantly higher among the diabetic participants compared to controls (p=0.001). Comparing the two diabetic groups regarding WHR, BMI, weight and BMI percentiles, there was no statistically significant difference between the two groups (p=0.37, 0.57, 0.45 and 0.32, respectively).

This was in line with a study conducted by **Hussein et al. (2023)** in Iraq including 84 diabetic children and 84 controls. They found that the anthropometric measures, including weight for age and BMI were significantly lower in diabetic patients compared to the controls suggesting that diabetes has a negative impact on nutritional status and body built (p<0.001).

As regards blood pressure, our results demonstrated that SBP and DBP were significantly higher among the diabetic subgroups compared to controls, (p=0.001 and 0.001), respectively.

Similar to our results, a prospective cross-sectional study performed by **Bulum et al. (2022)** included 84 stable T1DM adolescents in Croatia and found that they had significantly higher SBP compared to the control group, (p=0.035). This might be explained by the impaired baroreceptor reflex in diabetic children or the higher rate of abnormal blood pressure in puberty stage. This finding emphasizes the influence of hormonal changes in diabetic cases.

As regards glycemic control, our results showed that the MDI group had better glycemic control compared to the CSII group, as evident by HbA1c and frequency of DKA (in the last year) which were both elevated among the CSII group compared to MDI group (p=0.001). This could be due to delayed technical consultation among new Insulin pump patients, and the need for more regular follow up to solve any rising technical issues. Also, our pump patients had slightly longer duration of diabetes and had higher insulin resistance as evident by the lower levels of eGDR which makes them more difficult to control. We have evaluated the insulin resistance in terms of eGDR levels that was significantly lower among the 2 diabetic subgroups, compared to healthy controls (p=0.001), and it was significantly lower among CSII group compared to MDI group (eGDR levels were 8.2 mg/kg/min vs 8.7 mg/kg/min, respectively p=0.003).

This was in concordance with a metanalysis conducted by **Pala et al. (2019)** that included 40 trials and enrolled 1110 and 1142 patients in CSII and MDI groups, respectively. There was a significant increased risk of DKA in CSII compared to conventional insulin therapy, mainly due to malfunction of insulin pump, catheter occlusion or infusion set problems. However, they also showed that CSII produces a small improvement in HbA1c with no difference in hypoglycemia compared to MDI group and that this improvement is smaller when MDI is correctly performed using a basal-bolus regimen.

On the other hand, a metanalysis of 23 studies was conducted by **Calderon Martinez et al. (2024)** that included 3,512 participants to assess the relationship between CSII and MDI and glycemic control in children and

adolescents with T1DM. While a majority of the studies (61%) indicated improved glycemic control with CSII, the remaining (39%) found no significant clinical benefit compared to MDI. The observed heterogeneity in the analyses might be attributed to variations in study designs, patient populations, or other factors such as technology improvement of CSII devices.

This present study revealed no significant difference as regards microvascular complications including retinopathy, nephropathy and neuropathy between the MDI and CSII groups (p=0.75).

Similarly, **Almazrouei et al. (2022)** studied 134 Emirati diabetics, almost half of the patients (49.3%) were using CSII therapy while the other half were using MDI. They reported no significant difference regarding microvascular complications (retinopathy, nephropathy, neuropathy) between the MDI and CSII groups**,** (p=0.549).

In this study, TDD was significantly higher among MDI patients compared to CSII patients (p=0.04).

This was in line with a retrospective cohort study conducted by **Hu et al. (2021)** that included children and adolescents with T1DM (n=208) divided equally as CSII group and MDI. Children using MDI therapy used lower TDD of insulin compared to those treated with CSII at the beginning of therapy, after 4 years of treatment and in all the time periods, the dose of CSII group at the same time point was significantly lower than MDI group (p<0.05).

In the present study, there was no statistically significant difference between MDI and CSII groups as regards serum levels of NPB, NPW, leptin and adiponectin. However, NPB, NPW and leptin levels were significantly lower among the diabetic groups compared to the control group (p=0.001).

Similarly, **Grzelak et al. (2019)** conducted a cross-sectional study in Poland that included 58 patients with T1DM and 25 healthy controls to evaluate NPB, NPW, leptin and adiponectin levels in diabetic patients. The concentrations of NPB, NPW and leptin in the T1DM group were significantly lower ($p < 0.013$, < 0.008, <0.0004, respectively).

In explanation, in case of T1DM, there is a depletion of body fat stores as proved by the lower weight in diabetic group. This rapid progressive loss of body fat stores is accompanied by a pronounced decrease in plasma leptin levels **(Manglani et al., 2024).**

As for adiponectin, it was significantly higher among the diabetic group compared to the control group (p=0.001).

Likewise, **Grzelak et al. (2019)** illustrated that adiponectin showed higher levels of adiponectin than in the control group ($p < 0.006$).

This could be explained by the exposure to high level of glucose which increases HbA1c level and affects the process of glycosylation raising serum adiponectin level in T1DM persons and that low level of insulin cause future expression of adiponectin gene and more adiponectin secretion **(Karamifar et al., 2013).**

As regards MDI group, we found a significant positive correlation between NPW and leptin (r=0.36, p=0.04). As for CSII group, we found a significant positive correlation between NPB and NPW (r=0.51, p=0.004), NPB and leptin (r=0.55, p=0.002), NPW and leptin (r=0.77, p=0.001), while there was a was significant negative correlation between NPW and WH ratio (r=-0.45, p=0.01).

In agreement, **Grzelak et al. (2019)** found a positive correlation between levels of NPB and NPW in both sub-groups of T1DM patients treated using MDI ($r = 0.45$; $p < 0.02$) and the CSII ($r = 0.79$; $p < 0.0001$)·

Limitaton of the study

Some of the limitations encountered in this study include the small sample size, where larger cohort would give better review on the metabolic state of different participants. Also, biomarkers assessment was conducted in one setting, which leads to lack of generalization and lack of follow up results.

CONCLUSION

- The lower levels of NPB, NPW and leptin among both MDI and CSII groups could be attributed to decreased body fat, and lower BMI which could be used as indicator of their metabolic control. Similarly, elevation in adiponectin among both MDI and CSII groups compared to the control group might be a result of hyperglycemia and impaired glycosylation process. Further studies on larger scale are warranted to confirm our data.

- Some of the limitations encountered in this study include the small sample size; larger cohort would have given better review on the metabolic state of different participants. Also, biomarkers assessment was conducted in one setting, which leads to lack of generalization and lack of follow up results.

RECOMMENDATIONS

Biomarkers namely, NPB, NPW, leptin and adiponectin can be used to assess metabolic state of diabetics expressing hyperglycemia, glycosylation process and their reflection on BMI.

More expanded studies are needed at different disease durations and age of onset of diabetes.

Further studies are needed to assess the biomarkers in different metabolic states during fasting and postprandial, during exercise and rest. Including T1DM, T2DM or may be other diseases like inborn errors of metabolism.

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