Estimation of Preptin Serum level, Insulin Resistance and other biochemical parameters in Pre-diabetic and Newly Diagnosed Type 2 Diabetic Mellitus

Amal Rasheed Farhan[1], Manal K. Rasheed[2]
[1] MSC Clinical Biochemistry (Medical Technical Institute –Al-Mansour, Middle of Technical University/Iraq
[2] PhD Clinical Biochemistry (Department of Clinical Biochemistry, College of Medicine, University of Baghdad, Iraq
Email: rasheedamal96@gmail.com

Abstract

Background: The term diabetes mellitus (DM) describes metabolic disorder of multiple causes characterized by high levels of blood glucose resulting from defects in insulin secretion, insulin action, or both. Preptin is a recently isolated 34-amino acid peptide hormone that is co-secreted with insulin, amylin and pancreastatin from the pancreatic β-cells. Preptin heighten glucose-mediated insulin secretion. There are few studies on preptin in Type2DM patients and this is the first study observed on plasma preptin in pre-diabetic subjects and done to compare plasma preptin levels in patients with newly diagnosed and pre-diabetic with control groups. Objectives: To study the relationship between serum preptin and some biochemical parameters in pre-diabetes and newly diagnosed type 2 diabetes mellitus subjects as compared with control healthy groups. Subjects, material and methods: This case control study have included 180 subjects, matched for age ranged (36-75 years) and sex ratio were enrolled male (90) and female(90) those subjects divided into three sub groups, 60 subjects having per-diabetic, 60 patients having newly-diagnosed and 60 healthy control group. Serum insulin and preptin levels were measured by using commercial ELISA kits, and Homeostatic Model Assessment for Insulin Resistance (HOMO IR) was calculated. The anthropometric measured BMI, and biochemical serum (FBS, Lipid profile) levels measured by automated method by using Abbott Architect 4000. Serum HbA1c level was measured by boronated affinity assay by using NYCOCARD TM reader II. Results: The preptin showed a significant increased levels in pre-diabetic, but non-significant increased levels in newly-diagnosed as compared with control groups(132.2±14.8 vs. 83.5±8.6 pg /ml, p≤ 0.004) ,(89.3.0±8.0 vs. 83.5I±8.6 pg /ml p≤0.09) respectively, Serum preptin levels in all three groups showed a significant decreased in males than females (69±11.6 , 128±10.9 , 79±12.91 vs. 97.19±12.39 , 132.9±17.9 , 89.1±18 , p≤0.01) respectively..Preptin levels showed a significant negative correlation with age in control groups (r= - o.29,p≤0.03) and non-significant positive correlation in pre-diabetic and in newly diagnosed patients,(r=0.163 ,p≥0.23, r= -0.18 , p≥0.191).BMI level showed non-significant negative correlation with preptin in pre-diabetic and control groups (r = - 0.24 ,p≥0.07 ,r = - 0.01 p≥0.93),while non-significant positive correlation in newly diagnosed (r= 0.12 , p≥0.39). Sugar were non-significant positive correlation with preptin in control, pre-diabetic groups (r= 0.02, 0.031, p≥ 0.87, 0.82) while significant positive correlation with newly –diagnosed (r= 0.35, p≤ 0.01). HbA1c showed significant positive correlation with preptin in newly diagnosed groups (r = 0.28, p≤ 0.04) and non-significant positive correlation with pre-diabetic subjects (r = 0.81, p≥ 0.19), while non-significant positive correlation in controls (r = 0.14, p ≥ 0.32). Insulin showed non-significant positive correlation in all three groups (control r=0.20, p≥0.15, pre-diabetic r=0.04, p≥0.79) and newly diagnosed r=0.11, p≥0.41). HOMA-IR correlate with preptin positive non-significantly in the controls (r=0.12, p ≥0.374), and significant positive correlation in pre-diabetic and newly diagnosed groups (r= 0.28, 0.38, p≤ 0.04, ≤0.001). Conclusion: The current study conclude that the insulin level is higher in pre-diabetic cases while HOMA-IR is higher in newly diagnosed cases and that's results accompanied with higher level of preptin, this result can show a positive relation between preptin and insulin resistance.

Keywords: Preptin, Insulin Resistance, Pre-diabetic, newly diagnosis Diabetic Mellitus type 2.

1. Introduction

The term diabetes mellitus describes metabolic disorder of multiple causes characterized by high levels of blood glucose with disturbances of carbohydrate, fat and protein metabolism

doi.org/10.31838/hiv23.02.32 Received: 14.10.22, Revised: 16.11.22, Accepted: 14.12.22

resulting from defects in insulin secretion, insulin action, or both (Paradis et al., 2013). In Iraq last update in 2020, mentioned that Iraq is one of the 21 countries and territories of the IDF MENA (International Diabetes Federation Middle east and north Africa) 463 million people have diabetes in the world and 55 million people in the MENA region by 2045 this will rise to 108 million (Abusaib et al., 2020). Many epidemiological studies have demonstrated a marked increase in prevalence of DM with age (Forouhi & Wareham, 2014). Prediabetes is an intermediate state of hyperglycemia with glycemic parameters above normal but below the diabetes threshold. Globally, the occurrence of prediabetes is about 7.3% (4.8-11.9%) of adults (20-79) years and the vast majority (72.3%) of these individuals lives in low and middle-income countries. The statistics of National Diabetes in the U.S. in 2017 have reported that 33.9% of the adult U.S. population has prediabetic characteristics and those characteristics include fasting glucose or hemoglobin A1C (HbA1c) levels. And they also mentioned that the people with age higher than 65 shown higher prevalence (Zand et al., 2018).

Preptin is a recently isolated 34-amino acid peptide hormone that is co-secreted with insulin, amylin and pancreastatin from the pancreatic β-cells (CM et al., 2001). Its precursor is pro-IGF-II secreted simultaneously with insulin, acting to augment glucose– mediated insulin release for regulating energy metabolism , while the infusion of isolated pancreas significantly diminished glucose –mediated insulin secretion ;thus preptin seem to act as a physiological amplifier of glucose –mediated insulin secretion(Holly et al., 2019).

Some studies have reported that serum preptin levels in type II diabetes and overweight \obese patients are higher than those of healthy subjects. (El- Eshmawy, 2015) Circulating levels of preptin were found to be higher in diabetic patients compared to patients with impaired glucose tolerance and controls, suggesting a potential role for preptin in the pathogenesis of type-2 diabetes mellitus (Mehmet Kalayci1,(2019). Similar to the other beta-pancreatic hormones, preptin has anabolic activity in bone,

These data demonstrate that preptin, is anabolic to bone and may contribute to the preservation of bone mass observed in hyperinsulinemia states such as obesity,(Naot,Dorit,2014).

Preptin is also involved in bone metabolism and osteoblastogenesis (J et al., 2007). Preptin corresponds to Asp69-Leu102 of the proinsulin-like growth factor II E-peptide, which has been termed 'preptin'. Increased circulating levels of a pro-IGF-II peptide complexes with IGF-binding protein-2 have been implicated in the high bone mass phenotype observed in patients with chronic hepatitis C infection. That have assessed preptin's activities on bone (Doorn, 2020).

2. The aim of the study

To study the relationship between serum preptin and some biochemical parameters in pre-diabetes and newly diagnosed subjects type 2 DM as compared with control groups, This study measured for the first time with explored the correlations between its serum levels and various metabolic parameters in humans

3. Subjects, Materials and Methods

This case control study was included 180 subjects, with age range (36-73) years and sex were enrolled male (90) and female (90) those subjects divided into three subgroups, 60 subjects having pre-diabetic, 60 patients having newly diagnosed and 60 healthy control group. Newly diagnosed and pre-diabetic groups of patients are sub-divided according to the BMI into three groups:

1-BMI less than 24.9 (Normal weight).
2-BMI ranging 25-29.9 (overweight).
3-BMImore than 30 (obesity). (WHO) (2021).

Samples were obtained from Al-Kadhimiya Teaching Hospital in Baghdad- Iraq, September 2019 - Januarys 2020).

The samples collection were done during the fasting status(8-12h)of the subjects using disposable syringe. The drawn blood divided into two parts, the first one (2ml) kept in the EDTA tube (in order to do the HbA1c) was measured by boronated affinity assay by using NYCOCARD TM while the second part kept in the gel tube (3ml) for about 15 minutes then centrifuged at 1500- 2000 Xg for 5 minutes and then transferred into a new plane tube and stored at (-20˚C) until analysis for (preptin, Insulin, FBS and lipid profile). preptin, Insulin and were measured by using commercial ELISA kits,HOMA-IR was calculated using the formula:(R.Matthews, 1985)

$$HOMO - IR = \frac{\left\{\text{glucose}\left(\frac{\text{nmol}}{\text{L}}\right) * \text{insulin}\left(\mu\frac{\text{U}}{\text{mL}}\right)\right\}}{22.5}$$

Fasting blood sugar and lipid profile levels were determined enzymatically which by automated method by using Abbott Architect 4000.

4. Results

A distribution was achieved in response to subject's gender between the pre-diabetic, newly diagnosed and control groups, as the results in table (1) showed non-significant, p≥0.147. While in another hand, the distribution of age group showed significant differences between the studied groups, p≤0.05.

Table 1; demographic characterizations frequencies and percentages of control, pre-diabetic and newly diagnosed groups represented by:										
Group		Control n=60	Frequency	Percentage	Pre diabetic n=60	Frequency	Percentage	Newlydi-agnosed n=60	Frequncy	Percentage
Age (years)	20-30	33	0.6	56.4	17	0.3	29.1	6	0.09	9.09
	31-40	14	0.2	21.8	16	0.3	27.3	8	0.13	12.73
	41-50	10	0.2	18.2	18	0.3	30.9	19	0.33	32.73
	51-60	0	0.0	0.0	6	0.1	9.1	16	0.25	25.45
	61-70	3	0.003	3.6	3	0.0	3.6	11	0.20	20.00
Chi-square		53.4						23.4		
P. Value		0.001								
Male		27			39			24		
Female		33			21			36		
Chi-square		3.8								
P. Value		0.147								

The serum levels of the studied parameters by this study are summarized in the table (2). The results of the serum BMI of the prediabetes showed a significant higher level followed by newly-diagnosed subjects as compared with control (32±1.2, 29.6±0.8, 26.9±1.0, P≤ 0.01)

The results of the serum sugar of the newly-diagnosed subjects showed a significant higher level (107.9±10.8) mg/dl but non-significant when compared to both control (90.7±0.8) mg/dl and pre-diabetic subjects (90.4±2.4 mg/dl , p≥0.17).

The HbA1c serum level was higher in the newly-diagnosed patients than pre-diabetic (7.8±0.2 v.s. 5.8±0.1, p≤ 0.01) and also higher than control group also (5.1±0.1, p≤ 0.04) the pre-diabetic also showed a significant higher level than control (p≤ 0.04).

Insulin serum levels recorder a significant differences among all the studied groups, higher levels were shown in pre-diabetic subjects (29.1±3.5 µIU/ml) followed by newly-diagnosed (20.7±2.4 µIU/ml) and then control group showed the lower level (14.3±2.0 µIU/ml).

Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) results showed the insulin resistance was higher in the newly diagnosed subjects (10.1±1.5) followed by the pre-diabetic (6.3±0.7) with a significant difference between them (p≤0,007) and the lower results were recorded in the control group (4.0±0.8) with a significant difference with newly diagnosed (p≤0.03)

Table 2: comparison of studied parameters among the control, pre-diabetic and newly-diagnosed subjects					
Factors	Control	Pre-diabetic	Newly diagnosed	P. Value	
BMI	26.9±1.0	29.6±0.8	32±1.2	Control vs. Pre-diabetic	0.01
				Control vs. Newly diagnosed	0.01
				Newly diagnosed vs. Pre-diabetic	0.01
Sugar (mg/dl)	90.7 ± 0.8	90.4±2.4	107.9±10.8	Control vs. Pre-diabetic	0.172
				Control vs. Newly diagnosed	0.002
				Newly diagnosed vs. Pre-diabetic	0.002
HbA1c (%)	5.1±0.1	5.8±0.1	7.8±0.2	Control vs. Pre-diabetic	0.04
				Control vs. Newly diagnosed	0.04
				Newly diagnosed vs. Pre-diabetic	0.01
Insulin (µIU/ml)	14.3±2.0	29.1±3.5	20.7±2.4	Control vs. Pre-diabetic	0.04
				Control vs. Newly diagnosed	0.05
				Newly diagnosed vs. Pre-diabetic	0.03
HOMA-IR	4.0±0.8	6.3±0.7	10.1±1.5	Control vs. Pre-diabetic	0.021
				Control vs. Newly diagnosed	0.03
				Newly diagnosed vs. Pre-diabetic	0.007
Preptin (pg /ml)	283.9±29.2	449.7±50.1	303.6±27.2	Control vs. Pre-diabetic	0.004
				Control vs. Newly diagnosed	0.09
				Newly diagnosed vs. Pre-diabetic	0.005

The correlations of preptin level with the other parameters are shown in table 3 in all groups (control, pre-diabetic, and newly-diagnosed type 2 DM). The preptin level showed significant negative correlation with age (r=-0.289, p≤0.032) in the control group only and non-significant correlation in the other groups in pre-diabetic, and newly-diagnosed groups. The BMI and Insulin correlate with preptin non-significantly in all the groups control, pre-diabetic and newly diagnosed The correlation of preptin with sugar were non-significant positive in the control, pre diabetic groups while in the newly-diagnosed preptin showed a significant negative correlation with sugar (r=-.354, p≤0.008). HOMA-IR correlate with the preptin non-significantly in the control group and correlate significantly negative in pre-diabetic group (r=-.283, p≤0.036), and significantly negative also in the newly-diagnosed group (r=-0.384, p≤0.004).

Table **Error! No text of specified style in document.**: Correlation of preptin with the all the studied parameters within the control, pre-diabetic, and newly-diagnosed						
Factor	Control		Pre-diabetic		Newly diagnosed	
	r.	P. Value	r.	P. Value	r.	P. Value
Age	-0.29	0.03	0.16	0.23	-0.18	0.19
BMI	-0.01	0.94	-0.25	0.07	0.12	0.39
Sugar (mg/dl)	0.02	0.87	0.03	0.82	0.35	0.01
HbA1c(%)	0.14	0.32	0.18	0.19	0.28	0.04
Insulin (µIU/ml)	0.20	0.15	0.04	0.79	0.11	0.41
HOMA-IR	0.12	0.37	0.28	0.04	0.38	0.001
Preptin (pg /ml)	1	1	1	1	1	1

The results of receiver operator characteristic (ROC) curve analysis of HOMA-IR, insulin and preptin for prediabetic s are shown in table (4) and figure (1). The cut off value of preptin was >181.5, that of HOMA-IR was >2.5 and that of insulin was >10.4. The area under the curve was highest in preptin (0.727) followed by insulin (0.700) and then by HOMA-IR (0.693).

Table 4: pre-diabetic Results of receiver operator characteristic (ROC) curve analysis of preptin, insulin and HOMA-IR			
Characteristic	HOMA-IR	Insulin	Preptin
Cutoff	>2.5	>10.4	>181.5
AUC	0.693	0.700	0.727
95% CI	0.602 to 0.774	0.609 to 0.781	0.638 to 0.804
P	< 0.001	< 0.001	< 0.001
Sensitivity	93.33	100	63.33
Specificity	53.33	50.85	100
Accuracy	69.3	70	72.7
AUC: area under the curve; CI: confidence interval			

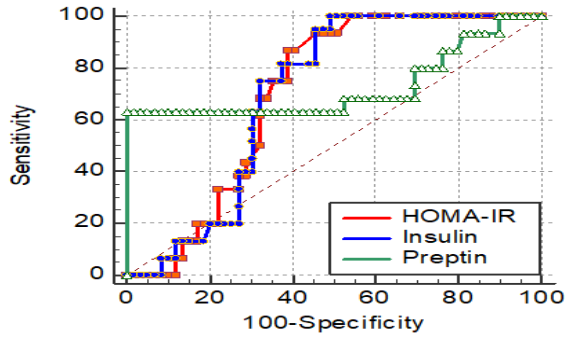

Figure 1: The receiver operator characteristic curve to find the best cutoff values of HOMA-IR, insulin and preptin in the diagnosis of pre-diabetic state

The Results of receiver operator characteristic (ROC) curve analysis of HOMA-IR, insulin and preptin for newly diagnosed diabetes are shown in table (5) and figure (2). The cut off value of preptin was > 188.7, that of HOMA-IR was >5.6 and that of insulin was >25. The area under the curve was lowest in preptin (0.538) and in insulin (0.538) and highest in HOMA-IR (0.678); however, in all cases it was lower than 0.7 and hence all these markers can be considered as poor predictors of diagnosis of diabetes mellitus.

Table 5: Newly diagnosis Diabetic Results of receiver operator characteristic (ROC) curve analysis of preptin, insulin and HOMA-IR			
Characteristic	HOMA-IR	Insulin	Preptin
Cutoff	>5.6	>25	> 188.7
AUC	0.678	0.538	0.538
95% CI	0.604 to 0.745	0.462 to 0.612	0.462 to 0.612
P	< 0.001	0.440	0.408
Sensitivity	53.33	35	13.33
Specificity	80.83	85.71	97.5
Accuracy	67.8	53.8	53.8
AUC: area under the curve; CI: confidence interval			

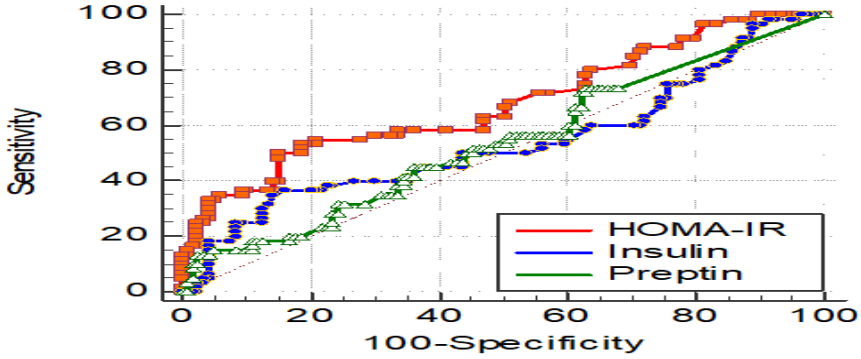

Figure 2: The receiver operator characteristic curve to find the best cutoff values of HOMA- IR, insulin and preptin in the diagnosis of diabetic state

5. Discussion

The results for preptin showed higher levels present in females than males in all study groups and these results corroborated a previous study which showed that, preptin levels were significant drastically lower in men than in women. (Yang et al., 2009). Preptin heightens glucose-mediated insulin secretion, while the binding of endogenous preptin through antipreptin antibodies lessens glucose-mediated insulin secretion. Consequently, it seems to act as a physiological amplifier of glucose-mediated insulin secretion.

In the current research concentrations of preptin levels are significantly higher in pre-diabetic, followed with newly diagnosed T2DM when compared with control groups. These results validate other results done by (Yang et al. 2013) who found higher levels of preptin in T2DM patients when compared to the control group. Increased preptin levels have also been found in studies of patients with gestational DM and polycystic ovary syndrome (Mierzwicka et al., 2018). Preptin is a physiological enhancer of insulin secretion generated by glucose.

The study carried out by Gupta et al uncovered the potential association between preptin and insulin resistance in humans. When it comes to diabetes mellitus, this association was also significant and this is further confirmed in literature where it was shown that the concentration of preptin levels were higher in DM patients (Gupta et al., 2015).

A past study investigated whether plasma preptin levels are different in non-diabetic subjects and patients suffering with impaired glucose tolerance (IGT) or type 2 diabetes mellitus (T2DM). The findings showed that serum preptin levels were elevated in patients with T2DM compared to patients with IGT and controls (456±14 versus 416±13 and 398±13 ng/l, $P<0.05$ and $P<0.01$, respectively) (Yang et al., 2009). The findings of this investigation also indicated higher preptin level in T2DM patients and even higher levels were exhibited in the pre-diabetic subjects.

In the current study, preptin showed significant negative correlation with age and this observation is in line with the observation of Şentürk et al., 2018 who reported significant negative correlation between age and preptin level; however, this observation was made in women with PCOS, but they were certainly non-diabetic or pre-diabetic. Preptin is a peptide containing 34 amino acids and is secreted from pancreatic beta cells together with insulin, amylin, and pancreostatin in response to glucose (Şentürk et al., 2018; Buchanan et al., 2001; Yang et al., 2009; Celik et al., 2011); therefore, we suggest that the lower levels of preptin with increasing age are due to aging effect on pancreas which is also associated with the appearance of glucose intolerance and frank diabetes as age is very well known risk factor for these health issues. Pancreas has a complex histology and is characterized by a combination of endocrine and exocrine cells. Pancreas undergoes various pathological changes with aging characterized by increased fatty replacement, fibrosis, lymphoplasmacytic infiltration, amyloid deposition, a decreased weight as well as development of intra-epithelial neoplastic changes. These age-related alterations lead to diabetes mellitus and can predispose the individual to pancreatic ductal adenocarcinoma. In this review, we summarize age-related morphological and pathological changes of aging in pancreas (Matsuda, 2018).

In addition in the present study, we noticed significant positive correlation between preptin and HOMA-IR in pre-diabetics in addition to significant positive correlation of preptin to FBS, HbA1c and HOMA-IR.in newly diagnosed T2DM. Indeed, our study is consistent with the results demonstrated by Yang et al in 2009 who found positive correlation of preptin to blood glucose, HbA1c, HOMA-IR in simple regression analysis; however, multiple regression analysis deny such correlations. Indeed, Kalayci et al in 2019 found significant positive correlation of serum preptin to FBS, HbA1c, HOMA-IR in diabetic patients and these results are in accordance to the current study finding.

Studies of patients with gestational DM and polycystic ovary syndrome also found a positive correlation between the preptin level, HOMA-IR, and the insulin level (Aslan et al., 2011; Celik et al., 2011). Bringing all these data together, it is suggested that preptin is directly related to glucose-mediated insulin secretion. An important question is the degree of the association between preptin concentrations and the insulin that is increased in circulation due to insulin resistance in T2DM. It is still controversial whether the cause of the increased insulin level seen as a result of resistance is due to increased capacity of the pancreatic cells or stimulation of insulin secretion by preptin (Kalayci et al., 2019).

The results of receiver operator characteristic (ROC) curve analysis of HOMA-IR, insulin and preptin for pre-diabetic are shown in table 4 and figure 1. The cut off value of preptin was >181.5, that of HOMA-IR was >2.5 and that of insulin was >10.4. The area under the curve was highest in preptin (0.727) followed by insulin (0.700) and then by HOMA-IR (0.693); Insulin and HOMA-IR more sensitive that predictor of diagnosis of pre-diabetes that comparison to prepertin

The results of receiver operator characteristic (ROC) curve analysis of HOMA-IR, insulin and preptin for newly diagnosed diabetes are shown in table 5 and figure 2. The cut off value of preptin was > 188.7, that of HOMA-IR was >5.6 and that of insulin was >25. The area under the curve was lowest in preptin (0.538) and in insulin (0.538) and highest in HOMA-IR (0.678); however, in all cases it was lower than 0.7 and hence all these markers can be considered as poor predictors of diagnosis of newly diabetes mellitus

The preptin serum markers appear to be poor predictors of diagnosis of prediabetic and newly diagnosed diabetic state. Despite, the presence of significant difference in preptin levels between patients and control group and this in agreement with previous authors (Yang G,2009); but this difference was enough to segregate diabetics from those who are prediabetic probably because of significant overlap in serum levels between control subjects and prediabetic subjects. For that reason we suggest a role for preptin in the pathogenesis of diabetes but no diagnostic role can be assured. Both, HOMA-IR and insulin levels were also poor predictors probably because of the wide variation of insulin sensitivity, basal insulin level and insulin resistance depending on stage and chronicity of the condition (Galicia-Garcia,2020).

6. Conclusion

From the results of this study ,we can conclude that the preptin level is higher in prediabetic cases and a accompanied with higher level of insulin while HOMA-IR is higher in newly diagnosed cases, these results can show a positive relation between preptin and insulin resistance it is suggested that preptin is directly related to glucose-mediated insulin secretion. An important question is the degree of the association between preptin concentrations and the insulin that is increased in circulation due to insulin resistance in newly diagnosed T2DM. It is still controversial whether the cause of the increased insulin level seen as a result of resistance is due to increased capacity of the pancreatic cells or stimulation of insulin secretion by preptin.

Insulin and HOMA-IR more sensitive that predictor of diagnosis of pre-diabetes that comparison to prepertin . while the results of HOMA-IR, insulin and preptin for newly diagnosed diabetes showed that all these markers can be considered as poor predictors of diagnosis of diabetes mellitus.

Despite, the presence of significant difference in preptin levels between patients and control group but, this difference was enough to segregate diabetics from those who are prediabetic probably because of significant overlap in serum levels between control subjects and prediabetic subjects. For that reason we suggest a role for preptin in the pathogenesis of diabetes but no diagnostic role can be assured. Both, HOMA-IR and insulin levels were also poor predictors probably because of the wide variation of insulin sensitivity, basal insulin level and insulin resistance depending on stage and chronicity of the condition.

References

Abusaib, M., Ahmed, M., Nwayyir, H. A., Alidrisi, H. A., Al-Abbood, M., Al-Bayati, A.et al (2020). Iraqi Experts Consensus on the Management of Type 2 Diabetes/Prediabetes in Adults. In Clinical Medicine Insights: Endocrinology and Diabetes (Vol. 13). SAGE Publications Ltd.

-CM, B., AR, P., & GJ, C. (2001). Preptin derived from proinsulin-like growth factor II (proIGF-II) is secreted from pancreatic islet beta-cells and enhances insulin secretion. The Biochemical Journal, 360(Pt 2), 431–439.

Doorn, J. van. (2020). Insulin-like growth factor-II and bioactive proteins containing a part of the E-domain of pro-insulin-like growth factor-II. Biofactors (Oxford, England), 46(4), 563.

Forouhi, N. G., & Wareham, N. J. (2014). Epidemiology of diabetes. Medicine (Abingdon, England : UK Ed.), 42(12), 698.

Gupta, A., Singh, S. K., Padmavathi, B. N., Rajan, S. Y., Mamatha, G. P., Kumar, S., Roy, S., & Sareen, M. (2015). Evaluation of correlation of blood glucose and salivary glucose level in known diabetic patients. Journal of Clinical and Diagnostic Research, 9(5), ZC106–ZC109.

Holly, J. M. P., Biernacka, K., & Perks, C. M. (2019). The Neglected Insulin: IGF-II, a Metabolic Regulator with Implications for Diabetes, Obesity, and Cancer. Cells, 8(10).

J, C., KE, C., U, B., M, W., X, X., JM, L., VA, C., AB, G., D, N., CM, B., GJ, C., & IR, R. (2007). Preptin, another peptide product of the pancreatic beta-cell, is osteogenic in vitro and in vivo. American Journal of Physiology. Endocrinology and Metabolism, 292(1).

.(Mehmet Kalayci1 , Ihsan Halifeoglu , Hatice Kalayci1 , Kader Ugur , Musa Yilmaz, Plasma preptin levels in patients with type 2 diabetes mellitus: DOI: 10.14744/ijmb.2018.74946 Int J Med Biochem 2019;2(1):1-5)

Mierzwicka, A., Kuliczkowska-Plaksej, J., Kolačkov, K., & Bolanowski, M. (2018). Preptin in women with polycystic ovary syndrome. Gynecological Endocrinology, 34(6), 470–475.

Paradis, R., Lazar, N., Antinozzi, P., Perbal, B., & Buteau, J. (2013). Nov/Ccn3, a Novel Transcriptional Target of FoxO1, Impairs Pancreatic β-Cell Function. PLoS ONE, 8(5).

Yang, G., Li, L., Chen, W., Liu, H., Boden, G., & Li, K. (2009). Circulating preptin levels in normal, impaired glucose tolerance, and type 2 diabetic subjects. Annals of Medicine, 41(1), 52–56.

Zand, A., Ibrahim, K., & Patham, B. (2018). Prediabetes: Why Should We Care? Methodist DeBakey Cardiovascular Journal, 14(4), 289.

Galicia-Garcia, U., Benito-Vicente, A., Jebari, S., Larrea-Sebal, A., Siddiqi, H., Uribe, K. B., Ostolaza, H., & Martín, C. (2020). Pathophysiology of Type 2 Diabetes Mellitus. International journal of molecular sciences, 21(17), 6275.

World Health Organization (WHO) (2021), Obesity and Overweight; 9

R.Matthews,JP.Hosker,AS.Rudenski,BA.Naylor,DF.Treacher,RC.Turner(1985)"Homeostasis model assessment:insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man"Diabetologia; Springer-Verlag ,28(7):412-419.