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Study of Serum Concentrations of Omentin-1 in Children with Type 1 Diabetes as Indicator of Insulin Resistance at Zagazig University Hospital

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Abstract

Background:*Diabetes mellitus (DM) is characterized by a set of metabolic disorders which are related to high blood sugar levels over a lengthy interval of time and may cause many complications. Omentin-1 is an important anti-inflammatory adipokine produced preferentially in visceral adipose tissue. It has been reported that circulating levels of omentin-1 are related to insulin resistance, obesity, dyslipidemia, endothelial dysfunction, arterial hypertension and so on.*

The aim was to assess omentin-1 in serum of children with type 1 diabetes, relevant to the disease duration. ***Methods:*** *This case control prospective study that carried out in endocrinology unit and outpatient clinic at Pediatric Department, Zagazig University Hospital on 85 (17 in every group). Serum omentin-1 level was measured.* ***Results:****Regard omentin control group were significantly lower than other groups and group 4 were significantly higher than other groups also group 2&3 were sig higher than group1.Significant AUC with cutoff >191.7 and 100.0% sensitivity and specificity****.*** *Regard FBS & PPBS control group were significantly lower than other groups but group 4 were significantly higher than other groups regard PPBS, Regard HA1C control group were significantly lower than other groups but group 1&4 were significantly higher than other groups .****Conclusion:*** *increased omentin-1 levels are associated with increasing obesity hormonal disturbance state (early puberty) and insulin resistance. Therefore, omentin-1 levels may be predictive of the metabolic consequences or co-morbidities associated with type 1 DM. The mechanism and physiological role of omentin-1 in glucose metabolism is not well understood. Further investigation is needed to determine whether omentin-1 can act as a link between obesity and diabetes. Omentin-1 serum levels act as a predictor of development of insulin resistance and diabetes and should be further investigated.*

Key words: *Omentin-1- Type 1 Diabetes- Insulin Resistance.*

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I. Introduction:

Diabetes mellitus (DM) is characterized by a set of metabolic disorders which are related to high blood sugar levels over a lengthy interval of time and may cause many complications. DM is classified into three types: gestational diabetes mellitus (GDM), type 1 diabetes mellitus (T1DM), and type 2 diabetes mellitus (T2DM). The development of DM has been a prominent global public health issue. However, it has been observed that the etiology of DM is complex, in the sense that it is influenced by numerous genetic, life-styles, psychosocial, and other environmental factors **(1).**

Recently, many adipocyte-secreted proteins as well as adipokines (omentin 1) have been introduced as novel links to DM. It is widely accepted that the adipokines participate in many metabolic processes, including energy expenditure, appetite control, insulin sensitivity, and regulation of adipogenesis**(2).**

Omentin-1 is an important anti-inflammatory adipokine produced preferentially in visceral adipose tissue. It has been reported that circulating levels of omentin-1 are related to insulin resistance, obesity, dyslipidemia, endothelial dysfunction, arterial hypertension and so on **(3).**

Overall, a substantial number of recent studies on the association between concentrations of omentin-1 and DM found contradictory results. For example, concentrations of omentin-1 were lowered in patients with DM in many clinical studies. However, other studies find that DM had higher concentration levels of omentin-1 than controls **(4).**

The aim of our study is to evaluate the concentrations of selected gastric peptide omentin-1 in serum of children with type 1 diabetes, relevant to the disease duration.

II. Patients and Methods

This study case control study was carried out in endocrinology unit and outpatient clinic at Pediatric Department, Zagazig University Hospital.

Target population: Children with Type 1 DM visiting the outpatient clinic and endocrinology unit in Zagazig university hospitals

Inclusion criteria:

- ***Cases***: Male and female children with T1DM aging from 1 to 18 years (n: 68) divided into four groups (see sample size page56)
- ***Healthy control***: age and sex matched healthy children (n: 17)

Exclusion criteria:

acute or chronic systemic disorders. adipose tissue diseases. autoimmune diseases. Patient or caretakers or guardian did not consent to participate in the study.

Sample size:

The sample size was calculated by Community medicine Department, Faculty of Medicine, Zagazig University according to the following: Assuming that level of omentin-1 in diabetic patients is 124.8 +/- 40, in

control group is 157 +/- 50 , at confidence level 95% , power 80% so, total sample size is 85 (17 in every group) .

Group 1: Children with newly diagnosed type 1 diabetes after D.K.A. attack (17 child)

Group 2: Children with type 1 diabetes for less than five years (17 child)

Group 3: Children with type 1 diabetes for a period of five to ten years (17 child)

Group 4: Children with type 1 diabetes for more than 10 years (17 child)[5]

II. Operational design

Methods:

Full history:

Clinical examination:

Laboratory Investigations:

1. **HbA1c: -**
2. **Fbs and 2h Ppbs: -**
3. **Measure serum omentin-1 level by ELISA (Sandwich technique): -**

III. Administrative design

Approvals obtained for performing the study from Institutional review board (IRB)

STATISTICAL ANALYSIS: Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) (Statistical Package for the Social Sciences) software for analysis. According to the type of data qualitative represent as number and percentage, quantitative continues group represent by mean ± SD, the following tests were used to test differences for significance;.difference and association of qualitative variable by Chi square test (X^2). Differences between quantitative independent groups by t test. P value was set at <0.05 for significant results.

III. Results:

Table and figure 1: Age and anthropometric measures distribution between cases and control

	Case (N=68)	Control (N=17)	t	P
Age	**10.35±3.42**	**9.17±2.95**	**0.996**	**0.322**
Weight	**32.89±10.58**	**28.0±8.91**	**1.491**	**0.140**
BMI	**25.61±2.71**	**24.71±1.07**	**1.321**	**0.190**

There was no significant difference between cases and control regard age or anthropometric measures

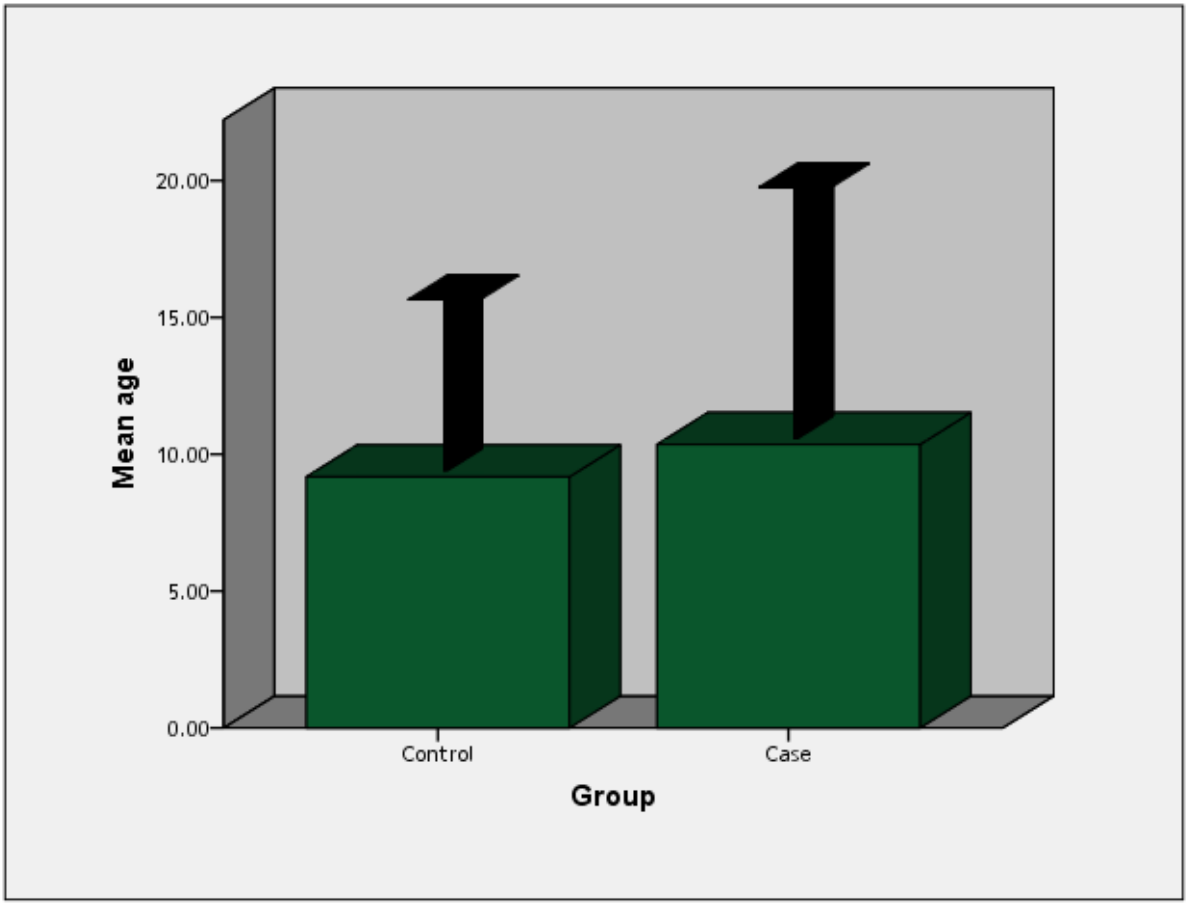
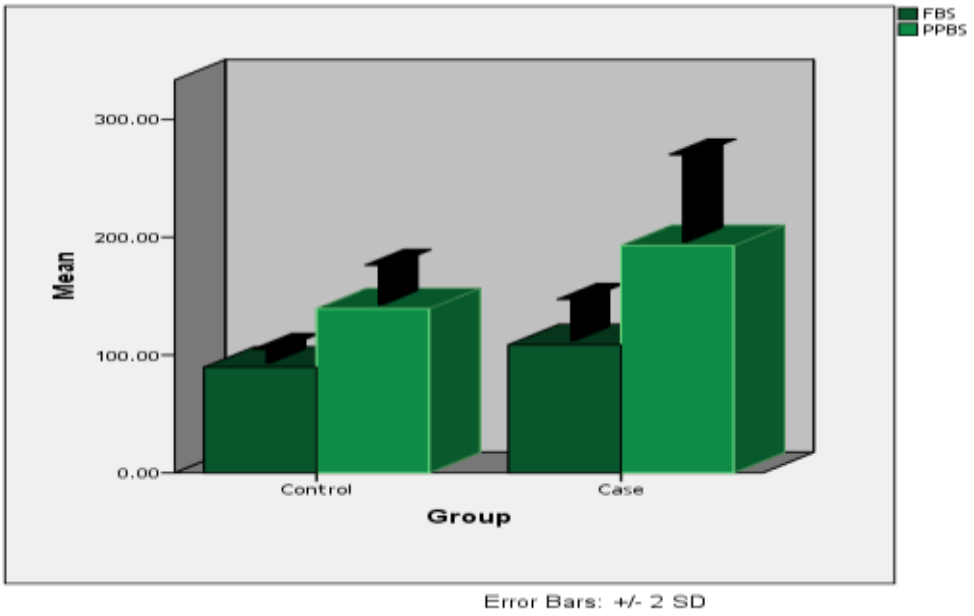


Table and figure 2 (a and b): FBS, PPBS (a) and HA1C (b) distribution between cases and control

	Case (N=68)	Control (N=17)	t	P
FBS	**108.66±18.15**	**89.64±6.49**	**4.235**	**<0.001****
PPBS	**192.6±37.71**	**139.17±17.51**	**5.670**	**<0.001****
HA1C	**7.83±1.87**	**4.69±0.47**	**6.805**	**<0.001****

Cases were significantly higher than control regard FBS, PPBS and HA1C



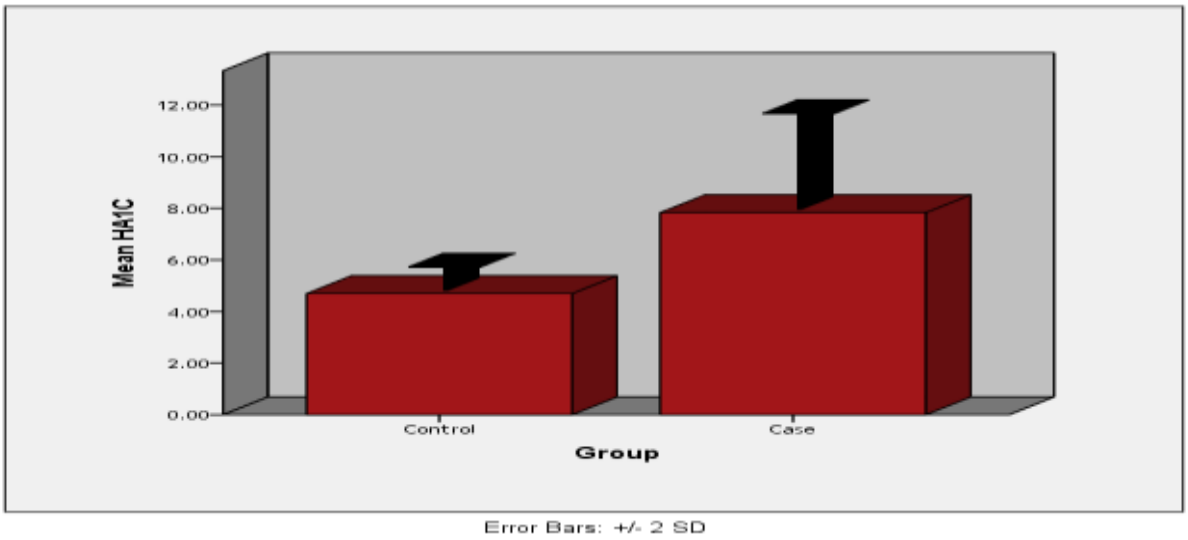
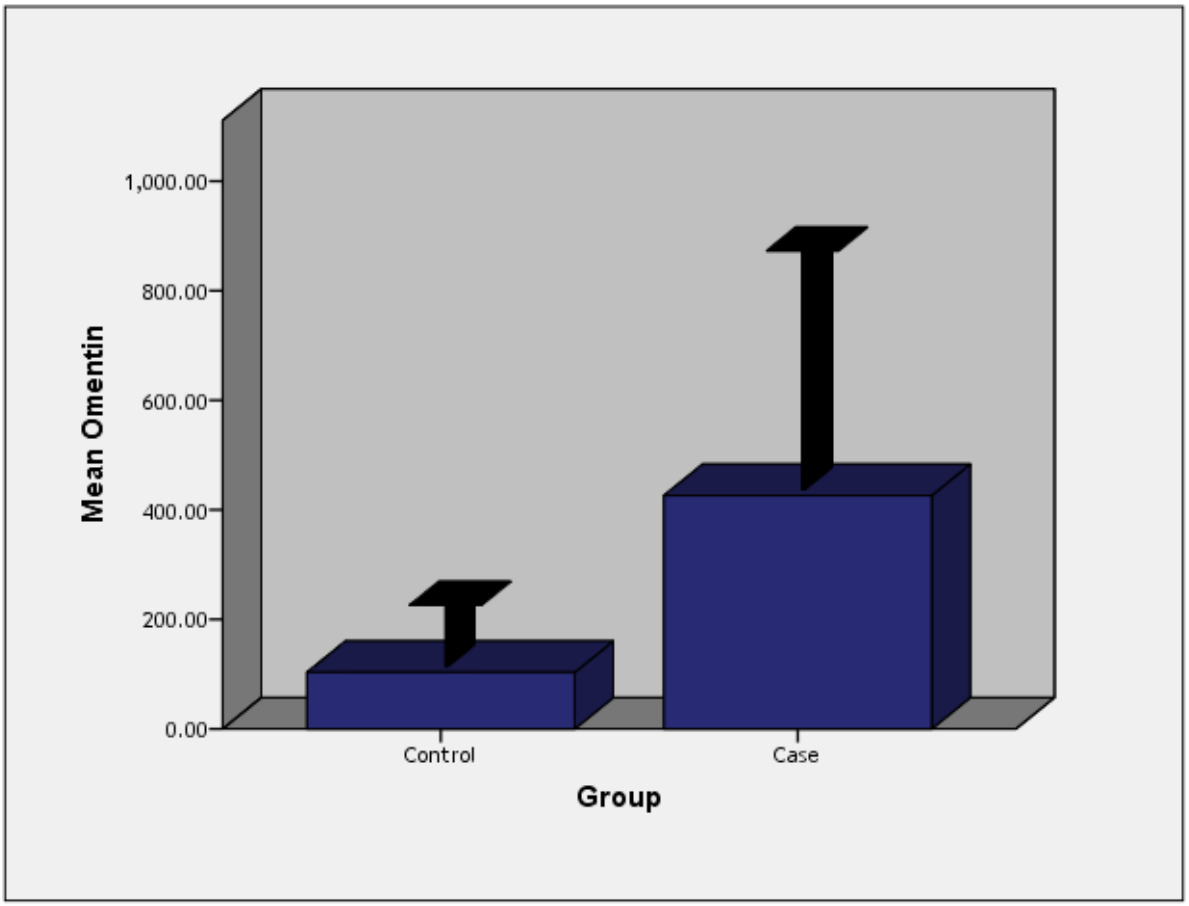


Table and figure 3: Omentin distribution between cases and control

	Case (N=68)	**Control (N=17)**	**t**	**P**
Omentin	**426.04±137.6**	**103.21±32.5**	**5.977**	**<0.001****

Cases were significantly higher than control as it was distributed as 426.04±137.6 and 103.21±32.5 respectively



Omentin distribution between cases and control

Table 4: Area under curve with cutoff and vlidity

Area	Cutoff	P	95% Confidence Interval		Sensitivity	Specificity
			Lower Bound	Upper Bound		
1.000	>191.7	0.00**	1.000	1.000	100.0%	100.0%

Significant AUC with cutoff >191.7 and 100.0% sensitivity and specificity

Table5: Age and anthropometric measures distribution among studied groups

	Control	Group1	Group2	Group3	Group4	F	P
Age	9.17±3.05@	5.62±1.87#	7.36±1.34#	12.27±2.48!	16.17±1.6*	56.400	<0.001**

Weight	**28.0±8.91**	**26.41±8.51**	**28.82±9.41**	**34.47±8.36!**	**45.88±11.57***	**15.149**	**<0.001****
BMI	**24.71±1.07**	**25.01±2.26**	**26.38±2.81**	**24.99±1.55**	**26.0±3.71**	**1.486**	**0.214**

 # Similar group @, !and * significant different groups

Age was significantly higher among group 3& 4, and 4 sig higher than 3 and control group were significantly higher than group 1&2, also weight was significantly higher at group 4 than other groups and group 3 was significantly higher than control, group 1 and group 2

LSD (Least Significant Difference)

Dependent Variable	**Group**	**Group**	**P**
Age	Control	Group1	**<0.001****
		Group2	**0.024***
		Group3	**<0.001****
		Group4	**<0.001****
	Group1	Group2	**0.030***
		Group3	**<0.001****
		Group4	**<0.001****
	Group2	Group3	**<0.001****
		Group4	**<0.001****
	Group3	Group4	**<0.001****
Weight	Control	Group1	**0.088**
		Group2	**0.800**
		Group3	**0.049***
		Group4	**<0.001****
	Group1	Group2	**0.051**
		Group3	**0.000**

		Group4	**<0.001****
	Group2	Group3	**0.005***
		Group4	**<0.001****
	Group3	Group4	**<0.001****

Age was significantly higher among group 3& 4, and 4 significantly higher than 3 and control group were significantly higher than group 1&2 also weight was significantly higher at group 4 than other groups

Table6: FBS, PPBS and HA1C distribution measures distribution among studied groups

	Control	**Group1**	**Group2**	**Group3**	**Group4**	**F**	**P**
FBS	**89.64±6.49***	**118.29±5.84**	**116.94±16.94**	**118.52±14.5**	**117.88±23.09**	**11.210**	**<0.001****
PPBS	**139.17±17.51!**	**182.41±11.99#**	**180.29±39.62#**	**180.58±27.2#**	**220.11±48.7***	**13.850**	**<0.001****
HA1C	**4.69±0.47***	**9.29±1.5#**	**6.9±0.76!**	**6.55±1.24!**	**8.57±2.21#**	**29.216**	**<0.001****

 # and! Similar group and * significant different groups

Regard FBS & PPBS control group were significantly lower than other groups but group 4 were significantly higher than other groups regard PPBS, Regard HA1C control group were significantly lower than other groups but group 1&4 were significantly higher than other groups

LSD (Least Significant Difference)

Dependent Variable	Group	Group	P
FBS	Control	Group1	**<0.001****
		Group2	**<0.001****
		Group3	**0.013***
		Group4	**<0.001****
	Group1	Control	**<0.001****

		Group2	**0.089**
		Group3	**0.091**
		Group4	**0.390**
	Group2	Control	**<0.001****
		Group1	**0.099**
		Group3	**0.078**
		Group4	**0.178**
	Group3	Group4	**0.121**
PPBS	Control	Group1	**<0.001****
		Group2	**<0.001****
		Group3	**<0.001****
		Group4	**<0.001****
	Group1	Control	**<0.001****
		Group2	**0.409**
		Group3	**0.424**
		Group4	**0.007***
	Group2	Group3	**0.979**
		Group4	**<0.001****
	Group3	Group4	**<0.001****
HA1C	Control	Group1	**<0.001****
		Group2	**<0.001****
		Group3	**<0.001****
		Group4	**<0.001****

	Group1	Group2	**<0.001****
		Group3	**<0.001****
		Group4	**0.133**
	Group2	Group3	**0.473**
		Group4	**<0.001****
	Group3	Group4	**<0.001****

Regard FBS & PPBS control group were significantly lower than other groups but group 4 were significantly higher than other groups regard PPBS, Regard HA1C control group were significantly lower than other groups but group 1&4 were significantly higher than other groups

Table7: Omentine distribution among studied groups

	Control	**Group1**	**Group2**	**Group3**	**Group4**	**F**	**P**
Omentin	**103.21±31.8@**	**248.09±27.3!**	**332.27±24.9#**	**390.23±24.4#**	**733.59±235.9***	**76.55**	**<0.001****

 # Similar group @, !and * significant different groups

Regard omentin control group were significantly lower than other groups and group 4 were significantly higher than other groups also group 2&3 were sig higher than group1

LSD (Least Significant Difference)

Dependent Variable	Group	Group	P
Omentin	Control	Group1	**<0.001****
		Group2	**<0.001****
		Group3	**<0.001****
		Group4	**<0.001****
	Group1	Group2	**0.029***
		Group3	**<0.001****

		Group4	**<0.001****
	Group2	Group3	**0.130**
		Group4	**<0.001****
	Group3	Group4	**<0.001****

Regard omentin control group were significantly lower than other groups and group 4 were significantly higher than other groups also group 2&3 were sig higher than group1

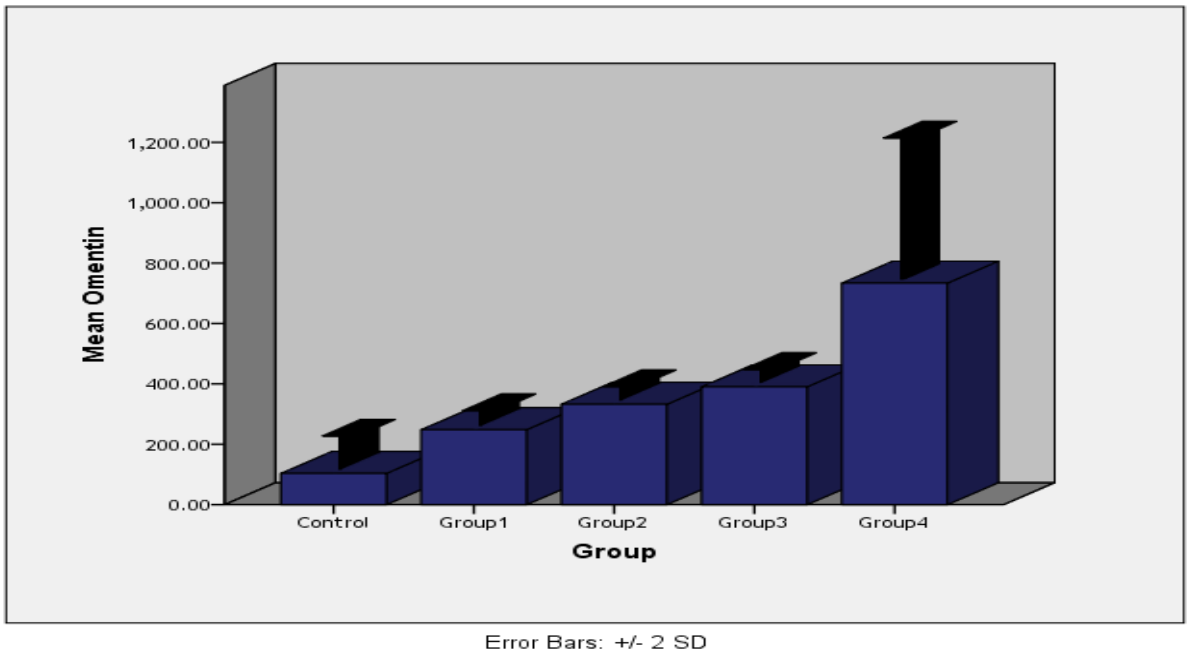


Figure 4: Omentine distribution among studied groups

Group 8: Units and duration distribution among studied group

	Group2	**Group3**	**Group4**	**F**	**P**
Units	**18.52±3.42!**	**29.23±9.8@**	**84.17±25.8***	**16.54**	**<0.001****
Duration	**2.51±0.81!**	**7.16±1.24@**	**10.94±1.25***	**200.63**	**<0.001****

@,! and * significant different groups

Units and duration significantly different among groups

LSD

Dependent Variable	Group	Group	P

Units	Group2	Group3	**0.002***
		Group4	**<0.001****
	Group3	Group4	**<0.001****
Duration	Group2	Group3	**<0.001****
		Group4	**<0.001****
	Group3	Group4	**<0.001****

All groups significantly different from each others

Group 9: resistance distribution among studied groups

			Group			**Total**	**X^2**	**P**
			Group2	**Group3**	**Group4**			
Resistance	**No**	**N**	**17**	**12**	**7**	**36**	**14.16**	**0.001****
		%	**100.0%**	**70.6%**	**41.2%**	**70.6%**		
	Yes	**N**	**0**	**5**	**10**	**15**		
		%	**0.0%**	**29.4%**	**58.8%**	**29.4%**		
Total		**N**	**17**	**17**	**17**	**51**		
		%	**100.0%**	**100.0%**	**100.0%**	**100.0%**		

Resistance was significantly associated with group 4 then group 3

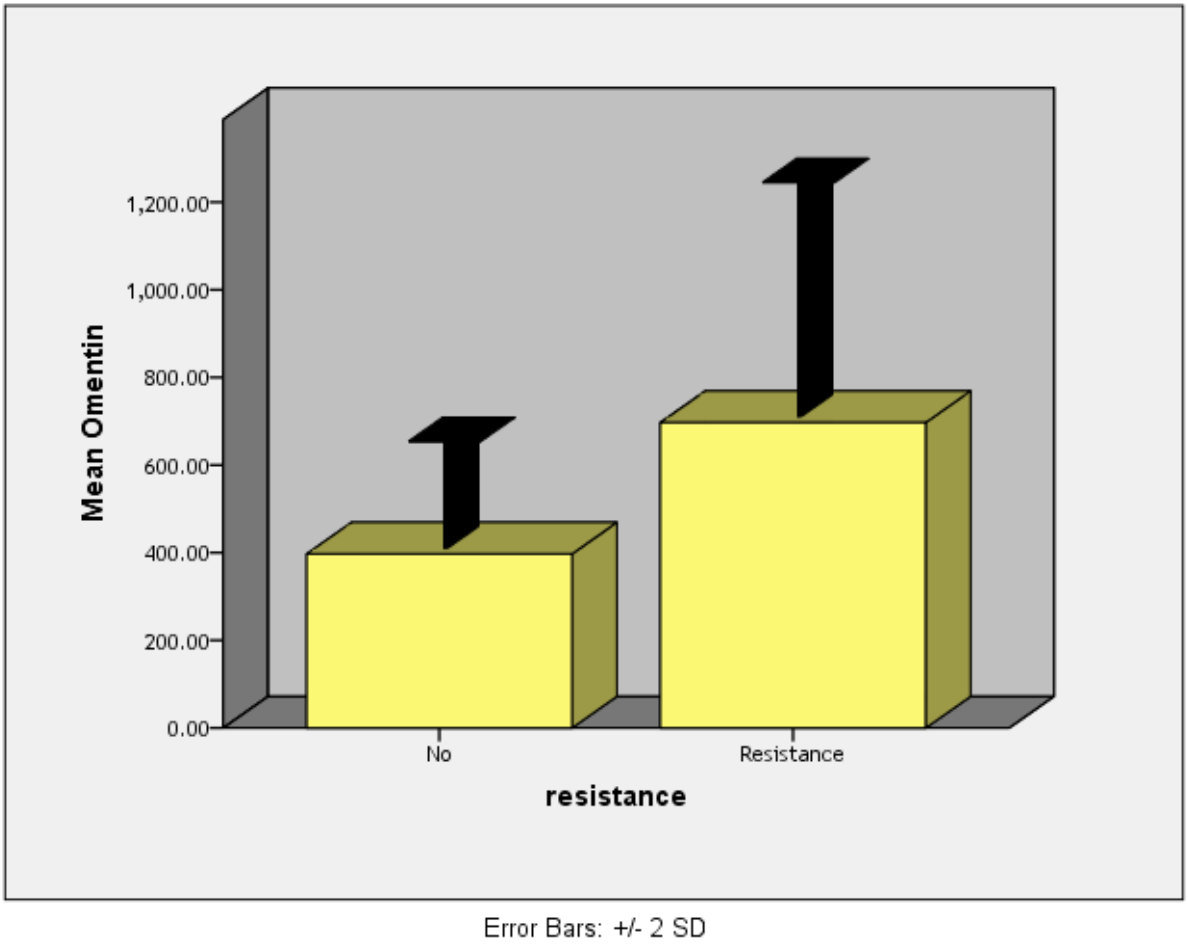


Figure 5 :Omentin in relation with resistance

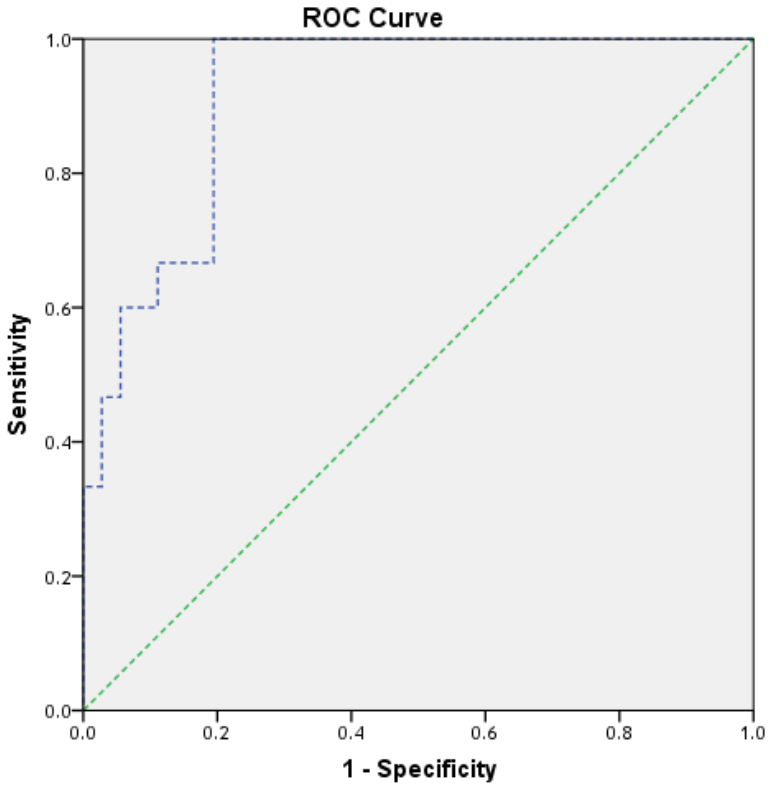
Table 10: Univariate analysis of predictors of resistance

	Resistance	No	t	P
Age	**14.46±3.13**	**10.88±3.25**	**3.096**	**0.003***
Weight	**41.33±12.5**	**34.33±10.22**	**1.944**	**0.058**
BMI	**25.82±3.55**	**25.78±2.54**	**.038**	**0.970**
FBS	**111.46±24.46**	**102.94±17.14**	**1.421**	**0.162**
PPBS	**211.86±52.59**	**186.08±36.65**	**2.006**	**0.49***
HA1C	**8.82±2.27**	**6.73±0.97**	**4.634**	**<0.001****
Omentin	**697.06±213.5**	**397.16±124.15**	**5.473**	**<0.001****

Units	**84.4±27.85**	**21.94±8.3**	**7.912**	**<0.001****
Duration	**9.66±2.52**	**5.71±1.78**	**3.982**	**<0.001****

Higher age, high PPBS& HA1C also Higheromentin, units and duration were significant dependent predictors for insulin resistance

Figure 6 :ROC Curve for omentin cutoff regard resistance



Area	Cutoff	P	95% Confidence Interval		Sensitivity	Specificity
			Lower Bound	Upper Bound		
0.917	**>445.2**	**0.00****	**.843**	**.990**	**75.5%**	**83.3%**

Significant AUC with cutoff >445.2 and 75.5% sensitivity and 83.3%specificity

Table 11: Correlations with omentin among cases (N=68)

	Omentin

Age	**r**	**0.651****
	P	**<0.001****
Weight	**r**	**0.620****
	P	**<0.001****
BMI	**r**	**0.226**
	P	**0.112**
Units	**r**	**0.863****
	P	**<0.001****
Duration	**r**	**0.646****
	P	**<0.001****
PPBS	**r**	**0.522****
	P	**<0.001****
FBS	**r**	**0.446****
	P	**0.004***
HA1C	**r**	**0.683****
	P	**<0.001****

r = Pearson's correlation (critical value=0.375)

Omentin was sig positive correlated with Age, Weight, units, duration, PPBS, FBS and HA1C

Table 12: Logistic Regression for independent predictors of resistance

	Wald	P	OR	CI 95%
Age	**3.369**	**0.066**	**0.471**	**(0.21-1.155)**
HA1C	**2.655**	**0.133**	**1.852**	**(0.88-3.88)**
PPBS	**1.589**	**0.215**	**1.054**	**(0.75-2.98)**

	Omentin	**2.322**	**0.148**	**1.255**	**(0.99-1.01)**
	Duration	**4.622**	**0.032***	**2.382**	**(1.08-5.23)**

Duration was the only significant independent predictor of insulin resistance

IV. Discussion

As regarding Age, weight and BMI distribution between cases and control, there was no significant difference between cases and control regard age or anthropometric measures.

Regarding weight, height and BMI there was a great difference between cases and matched control of same age; cases tend to be either underweight or obese unlike healthy control of same age and sex. On the other hand height where cases are noted to be shorter than control of same age and sex that's duo to the nature of the disease which impact normal growth of children

In the study of **Baltadjiev et al.**[(6)]Weight and height were significantly affected by diabetes in cases unlike healty control which come to agree with our results

Regarding FBS, PPBS and HA1C distribution between cases and control, there were significantly higher than control regard FBS, PPBS and HA1C. group 4 were significantly higher than other groups regard PPBS, Regard HA1C control group were significantly lower than other groups but group 1&4 were significantly higher than other groups.

Regarding univariate analysis of predictors of resistance. We figured out that higher age, high PPBS& HA1C also higher omentin, units and duration were significant dependent predictors for insulin resistance. ROC Curve analysis for omentin cutoff regard resistance declaired that, Significant AUC with cutoff >445.2 and 75.5% sensitivity and 83.3% specificity for resistance.Omentin was significantly positive correlated with Age, Weight, units, duration, PPBS, FBS and HA1C. Duration was the only significant independent predictor of insulin resistance.

Regarding Omentin-1 distribution between cases and control, there was a statistically significant difference between cases and control groups. Cases were significantly higher than control. The median Omentin-1level was (426.04±137.6 SD) and (103.21±32.5 SD) respectively. Regarding ROC Curve analysis for Omentin cutoff regard cases, Significant AUC with cutoff was >191.7 and 100.0% sensitivity and specificity.

In the study of **Tichá et al., [(7)]**omentin 1 levels were found to be high in cases and significantly high with longer duration this agrees with our results

In another study by **Panel Hong-Yan et al., [(8)]** also omentin 1 levels were found to be higher in cases than control which indeed agrees with our results

In the study of **Abd El Dayem et al., [(9)]**, Omentin was significantly lower than controls in T1DM patients. Which come in disagreement with our results.

In contrast our results were consistent with **Nurten et al., [(10)]**, they reported that omentin-1 levels were elevated ($p < 0.001$) in type 1 diabetic children than controls. omentin-1 were elevated in longstanding patients

compared to healthy controls ($p < 0.001$). omentin-1 levels were higher than in any group of longstanding type 1 diabetes ($p < 0.025$). they concluded that omentin-1 in pediatric type 1 diabetes patients indicate metabolic changes caused by adipose tissue dysregulation which do not normalize during insulin therapy.

In the study of **Habi et al., [11]**, they made a systematic review and meta-analysis of observational studies on the association between omentin and diabetes, they concluded that: Our analysis failed to show any significant association between omentin-1 and T1DM. The results of previous studies in this sub-group are inconsistent. In other words, some evidence proved lower level of omentin in T1DM subjects but **Nurten et al., [10]**revealed higher levels of this adipokine in these populations. Another sub-group of our study included T2DM patients. The analysis proved lower levels of omentin in these populations which is consistent with previous report but was not confirmed by some.

Another systematic review and meta-analysis was done by **Pan et al., [12]**to asses Omentin-1 in diabetes mellitus, they conclude that; Forty-two eligible studies were included in the final meta-analysis. There was no significant difference in omentin-1 concentration between patients with type 1 diabetes mellitus and the controls. On the other hand, lower concentration levels of omentin-1 were observed in patients with gestational diabetes mellitus (standardized mean difference:-0.44, 95% confidence interval:-0.76; -0.12, $p = 0.007$), or type 2 diabetes mellitus (standardized mean difference: -1.74, 95% confidence interval: -2.31; -1.16, $p< 0.001$) than in the controls. Which is also come in disagreement with our results.

For all this data we can conclude that, T1DM is a common health problem in the pediatric age group, Omentin-1 level was significantly high in T1DM and its level is strongly correlated to duration, units and insulin resistance. Although in literature there is diversity in analysis of Omentin-1 level in T1DM patients which varies between high and low. Further work up should be done especially on ethnicity of the studied population to figure out if it has a role in this variation.

V. Conclusion:

Increased omentin-1 levels are associated with increasing obesity hormonal disturbance state (early puberty) and insulin resistance. Therefore, omentin-1 levels may be predictive of the metabolic consequences or co-morbidities associated with type 1 DM. The mechanism and physiological role of omentin-1 in glucose metabolism is not well understood. Further investigation is needed to determine whether omentin-1 can act as a link between obesity and diabetes. Omentin-1 serum levels act as a predictor of development of insulin resistance and diabetes and should be further investigated.

VI. Recommendations

From our study we can recommend the following

1. Type 1 DM incidence is rapidly increasing in developing countries especially middle east countries so impaction of the disease makes it a must to increase studies done about it

2. The disease impacts on individual’s health and abilities are major and can even be handicapping

3. Duration of the disease is the most dependent factor when it comes to developing insulin resistance

4. Omentin-1 levels were significantly higher in patient with insulin resistance and it almost were specific to insulin in our study

5. Further studies must be held in larger scales to determine the exact relation between omentin-1 and insulin resistance

6. We recommend adding omentin1 serum level in patient with long standing DM and in patients with criteria of insulin resistance

7. Following up type 1 diabetic patients with HbA1C only is not enough to predict insulin resistance it should be verified with insulin resistance markers as omentin-1

8. Routine screening of omentin-1 levels in people at risk of developing type1 DM as (positive family history, obesity, hormonal disorders.

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