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The role of immune metabolic mediators (IL-1β, visceral adiposity index and Apo- β lipoproteins) in the pathogenesis of pre-diabetic state in obese persons

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Abstract

Background: Pre-diabetes is the stage before Diabetes mellitus (DM) there are two forms of prediabetes Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). Many inflammatory markers have been found to be related to Pre-diabetes, such as interleukin-1β (IL-1β), visceral adiposity index, insulin resistance, and insulin secretory states and serum levels of Apo- β lipoproteins in the pathogenesis of pre-diabetic state in obese persons.

AIM OF THE WORK: To assess the role of Interleukin-1β, visceral adiposity index, insulin resistance, and insulin secretory states and serum levels of Apo- β lipoproteins in the pathogenesis of pre-diabetic state in obese persons.

Patients and Methods: This study is a prospective one that was carried out on one hundred and twenty (120) patients attending to internal medicine outpatient clinic and inpatient department of internal medicine, Al-Azhar university hospital, Damietta. The populations of the study were classified into (60) obese persons and (60) non obese persons. All were subjected to full history and Clinical examination, Laboratory tests include HbA1c, Fasting blood sugar, post prandial glucose level, Liver Function Test (ALT, AST, serum albumin, bilirubin, and GGT), Renal Function Test (Creatinine, Urea, Uric Acid), Lipid Profile (Cholesterol, Triglycerides, HDL Cholesterol, and LDL Cholesterol) and High sensitive C-reactive proteins, OGTT, Visceral adiposity index based on (WC, BMI,TG, and HDL-C, it estimates the visceral adiposity functionality, Male VAI=(WC/{39.68+(1.88×BMI)})×(TG/1.03)×(1.31/HDL-C), Female VAI=(WC/{36.58+(1.89×BMI)})×(TG/0.81)×(1.52/HDL-C), serum Interleukin-1β levels and Apo β-lipoproteins.

Results: Our study showed that there was statistically significant increase in VAI, IL-1β, Apo- β lipoproteins, ALT, AST, Cholesterol, TG, LDL, HDL, S. insulin, HOMA and HbA1c in group I in comparison to group III, on the other hand there was statistically significant increase in VAI, IL-1β, Apo- β lipoproteins, ALT, AST, Cholesterol, TG, LDL, HDL, S. insulin and HOMA in group II in comparison to group IV and there was statistically significant increase in IGT in group I subjects in comparison to group III subjects.

Conclusion: IL-1β and Apo- β lipoproteins consider as a risk factor in the pathogenesis of pre-diabetes in obese persons, which may progress to Diabetes So Therapy targeting IL-1β may ameliorate the condition and VAI is associated with insulin resistance.

Keywords: Pre-diabetes, Immune metabolic mediators, IL-1β, Apo- β lipoproteins, VAI.

Introduction

Pre-diabetes is the precursor stage before DM in which not all of the symptoms required to diagnose diabetes are present, but blood sugar is abnormally high. This stage is often referred to as the grey area [(1)]. T2DM is the most prevalent metabolic disease in the world and is characterized by defects in insulin secretion and insulin resistance in the skeletal muscle, adipose tissue and the liver [(2)]. Obesity in particular excess visceral adiposity is associated with insulin resistance (IR), hyperglycemia, dyslipidemia and hypertension which increase the risk of developing T2DM [(3)]. The pro- inflammatory markers are positively correlated with (IR) and features of metabolic syndrome [(4)].

Esser et al. [(5)] showed that Visceral adipose tissue has more macrophage, T-lymphocytes and inflammatory molecules than SC adipose tissue, moreover a low number of anti-inflammatory regulatory T- lymphocytes were recently found in the visceral adipose tissue, and this less favorable inflammatory role of visceral adipose tissue is in line with the belief that this tissue has an important

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role in metabolic derangement. Also ***Esser et al.*** [5] observed that adipose tissue inflammation was considered as a crucial event leading to metabolic syndrome, T2DM and atherosclerotic CVD. Beside total adiposity the pathogenic role of its location has a great role e.g. high visceral adipose tissue is more strongly correlated with metabolic syndrome.

White blood cells counts and plasma levels of coagulation factors (fibrinogen, and plasminogen activator inhibitor-1),acute phase proteins such as C- reactive protein and serum amyloid A, pro-inflammatory cytokines (TNF-α1, interleukin-1β and IL-6) and chemokines are elevated in obese and T2DM [6]**.** In addition ***Herder et al.*** [7] observed that Prospective studies have identified WBCs, and pro-inflammatory cytokines and other several indirect markers of inflammation such as fibrinogen, sialic acid and PAI-1, as predictors of T2DM. The progression from obesity related (IR) to T2DM implicates a failure of pancreatic β-cells to compensate for (IR). An inflammatory process was demonstrated in pancreatic islets of T2DM patients, as shown by the presence of amyloid deposits fibrosis, increase β- cell death and infiltration of macrophages along with increased levels of pro-inflammatory cytokines and chemokines [8].

Maedler et al. [9] showed that the increase of immune cells in pancreatic islets is described even before the onset of T2DM particularly the expression and local release of the pro-inflammatory cytokine IL-1β. also, ***Dinarello*** [10] found that this cytokine seems to be a master regulator of islet inflammation in T2DM by increasing its local expression.

Ehses et al. [11] found that this leads to immune cell recruitment in islets with reduced insulin secretion, apoptosis and decreased islet cell mass, those are critical events in the progression of T2DM, so interleukin-1β has been reported to contribute to β-cell failure. IL-1β consider as a risk factor in the pathogenesis of pre-diabetes in obese persons, which may progress to frank Diabetes. So, Therapy targeting IL-1β may ameliorate results.

AIM OF THE WORK

The aim of this study is to assess IL-1β, VAI and Apo- β lipoproteins as risk factors in the pathogenesis of pre-diabetic state in obese persons.

Subjects and methods

This study is a prospective one that was carried out on one hundred and twenty (120) individuals attending to internal medicine outpatient clinic and inpatient department of internal medicine, Al-Azhar university hospital, Damietta. The populations of the study were classified as follow:

Group I: Thirty (30) Obese with pre-diabetic state (IFG and/or IGT).
Group II: Thirty (30) Obese with normal glucose tolerance (NGT).
Group III: Thirty (30) Non-obese with pre-diabetic state (IFG and/or IGT).
Group IV: Thirty (30) Non-obese with normal glucose tolerance (NGT).

Exclusion criteria:

Patients with chronic liver disease including patients with HCV Ab-positive and HBs Ag-positive.
Patients with chronic renal disease.
Patients with malignancy.

Methods: All were subjected to full history and Clinical examination to assess history of hypertension, DM, history of drug intake, any chronic illness, and family history of DM. Anthropometric assessment; Weight, height, WC, W/H, BMI, and visceral adiposity index. Laboratory tests include: Liver function test (ALT, AST, Serum Albumin, Bilirubin, and GGT) and renal function test (Creatinine, Urea, Uric Acid). Lipid profile (Cholesterol, Triglycerides, HDL Cholesterol, and LDL Cholesterol) and High sensitive C-reactive proteins, OGTT through which we assess; FBS/PP. Serum insulin levels at 0 and 30 minutes post prandial to assess: Insulin resistance states (HOMA-IR), Insulinogenic index according to: I 0-I 30/G0-G30 (increment in plasma insulin ÷ increment in plasma glucose) during the first 30 min of the OGTT, Assessment of serum Interleukin-1β levels and Apo β-lipoproteins.

The study was approved by the Ethics Board of Al-Azhar University.

Statistical methods: Data were collected, coded, revised and entered to the Statistical Package for Social Science (IBM SPSS) version 20. The data were presented as number and percentages for the qualitative data, mean, standard deviations and ranges for the quantitative data with parametric distribution and median with inter quartile range (IQR) for the quantitative data with non parametric distribution. Chi-square test was used in the comparison between two groups with qualitative data and Fisher exact test was used instead of the Chi-square test when the expected count in any cell found less than 5. The comparison between more than two groups with quantitative data and parametric distribution were done by using One Way Analysis of Variance (ANOVA) test and Kruskall-Wallis test was used in

the comparison between more than two groups with quantitative data and non-parametric distribution.

Results

Table (1): Comparison between group I and group III as regards VAI, apo beta lipop and IL- 1 β

	Group **I** (No.=30)		Group **III** (No.=30)		Independent t test	
	Mean	SD	Mean	SD	T	P value
VAI	15.45	4.91	5.98	2.52	9.400	0.001
Apo beta lipop (mg/dl)	130.53	16.17	62.33	21.27	13.984	0.001
IL 1 beta(0.3-3.9pg/ml)	26.03	10.81	4.93	0.84	11.668	0.001

There was high statistically significant increase in VAI, apo beta lipop and IL- 1 β in group **I** in comparison to group **III**. The p-value was considered significant as the following: P > 0.05: Non significant (NS), P < 0.05: Significant (S) , P < 0.01: Highly significant (HS)

Table (2): Comparison between group II and group IV as regards VAI, apo beta lipop and IL- 1 β

	Group **II** (No.=30)		Group **IV** (No.=30)		Independent t test	
	Mean	SD	Mean	SD	T	P value
VAI	4.91	0.84	1.97	0.82	13.700	0.001
Apo beta lipop (mg/dl)	117.30	21.14	64.77	12.34	11.756	0.001
IL 1 beta(0.3-3.9pg/ml)	12.56	8.02	2.63	0.90	6.731	0.001

There was high statistically significant increase in VAI, apo beta lipop and IL- 1 β in group **II** in comparison to group **IV**.

Table (3): Comparison between studied groups as regards insulinogenic index

	Group **I** (No.=30)		Group **II** (No.=30)		Group **III** (No.=30)		Group **IV** (No.=30)		One way ANOVA	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	P value
Insulinogenic Index	0.11	0.09	4.98	2.81	0.14	0.11	8.05	2.23	141.421	<0.001

There was statistically highly significant increase in insulinogenic index as regards studied groups.

Table (4): Comparison between group I and group III as regards insulinogenic index

	Group **I** (No.=30)		Group **III** (No.=30)		Independent t test	
	Mean	SD	Mean	SD	T	P value
Insulinogenic Index	0.11	0.09	0.14	0.11	-1.279	0.206

There was no statistically significant increase in insulinogenic index as regards studied groups.

Table (5): Comparison between group II and group IV as regards insulinogenic index

	Group **II** (No.=30)		Group **IV** (No.=30)		Independent t test	
	Mean	SD	Mean	SD	T	P value
Insulinogenic Index	4.98	2.81	8.05	2.23	-4.682	0.001

There was high statistically significant increase in insulinogenic index as regards studied groups.

Table (6): Correlation between VAI, apo beta lipop and IL 1 beta as regards all parameters in group I (obese with pre diabetic state)

	VAI		Apo beta lipop (mg/dl)		IL 1 beta (pg/ml)	
	R	P value	R	P value	R	P value
Age (Years)	-0.093	0.624	0.211	0.264	-0.090	0.635
Weight (kg)	0.265	0.158	0.053	0.782	0.220	0.244
Height (m)	0.227	0.227	-0.377	0.040	0.273	0.145
BMI (Kg/m2)	0.137	0.472	0.341	0.065	-0.059	0.755
SBP (Mmhg)	-0.165	0.384	-0.079	0.676	0.108	0.570
DBP (Mmhg)	-0.311	0.095	-0.008	0.965	0.238	0.206
WC (cm)	0.177	0.348	-0.017	0.928	0.087	0.001
Wc (inch)	0.172	0.364	-0.017	0.931	0.092	0.630
HC (cm)	0.034	0.860	0.135	0.479	0.140	0.003
W/H ratio	0.181	0.338	-0.130	0.493	0.013	0.001
ALT (U/L)	-0.131	0.489	-0.530	0.003	-0.068	0.719
AST (U/L)	-0.238	0.206	-0.192	0.308	-0.128	0.501
Albumin (g/Dl)	0.006	0.976	0.157	0.407	-0.189	0.318
Bilirubin (mg/dL)	-0.052	0.785	-0.177	0.350	-0.265	0.157
GGT (ul)	0.110	0.561	0.060	0.753	0.287	0.124
Creat (mgldl	-0.182	0.335	-0.271	0.147	0.155	0.413
Uric Acid (mgldl)	0.174	0.359	0.204	0.281	0.118	0.534
FBS (mgldl)	-0.012	0.949	0.222	0.238	-0.117	0.540
PP (mgldl)	-0.045	0.814	0.194	0.305	0.199	0.292
Cholest (mgldl)	-0.381	0.038	-0.123	0.519	0.208	0.269
TG (mgldl)	0.345	0.062	-0.412	0.024	0.070	0.713
HDL (mgl dl)	-0.637	0.001	0.148	0.434	-0.251	0.181
LDL (mg/dl)	-0.206	0.275	-0.058	0.762	0.218	0.246
s. Insulin(mulml)	-0.133	0.484	0.218	0.246	-0.039	0.001
FBS(mmol)	-0.016	0.932	0.204	0.281	-0.117	0.537
HOMA	-0.136	0.473	0.222	0.239	-0.053	0.001
Hba1c	-0.178	0.347	0.291	0.119	0.291	0.119

This table shows that VAI has positive correlation with LDL and cholesterol. Apo-β lipop has positive correlation with TG, ALT and height but negative correlation with HOMA. IL- 1 β has positive correlation with WC, W/H ratio, S. insulin and HOMA in obese with pre diabetic state.

Table (7): Correlation between VAI, apo beta lipop and IL- 1β as regards all parameters in group II (obese with normal glucose tolerance)

	VAI		Apo beta lipop (mg/dl)		IL 1 beta (pg/ml)	
	R	P value	R	P value	R	P value
Age (Years)	0.169	0.373	0.066	0.727	-0.379	0.039
Weight (kg)	-0.317	0.088	-0.091	0.634	0.050	0.792
Height (m)	0.154	0.415	0.048	0.803	-0.091	0.632
BMI (Kg/m2)	-0.382	0.037	-0.050	0.792	0.125	0.510
SBP (Mmhg)	-0.009	0.962	-0.068	0.720	0.166	0.382
DBP (Mmhg)	0.105	0.579	-0.063	0.741	-0.041	0.831
WC (cm)	-0.030	0.873	-0.232	0.217	-0.118	0.536
Wc (inch)	-0.030	0.873	-0.232	0.217	-0.118	0.536
HC (cm)	0.121	0.524	-0.270	0.149	-0.451	0.012
W/H ratio	0.030	0.876	0.073	0.703	0.478	0.008
ALT (U/L)	-0.073	0.700	-0.454	0.012	-0.479	0.007
AST (U/L)	-0.026	0.891	-0.575	0.001	-0.331	0.074
Albumin (g/Dl)	0.254	0.176	0.156	0.410	0.468	0.009
Bilirubin (mg/dL)	-0.226	0.229	-0.167	0.377	0.135	0.478
GGT (ul)	0.032	0.865	0.502	0.005	0.382	0.037
Creat (mgldl	-0.293	0.116	-0.126	0.506	-0.224	0.234
Uric Acid (mgldl)	0.083	0.662	-0.069	0.717	-0.476	0.008
FBS (mgldl)	0.216	0.251	0.046	0.809	-0.191	0.313
PP (mgldl)	0.340	0.066	-0.098	0.605	-0.280	0.134
Cholest (mgldl)	-0.175	0.354	0.210	0.265	0.408	0.025
TG (mgldl)	0.069	0.718	0.164	0.387	-0.069	0.716
HDL (mgl dl)	-0.262	0.162	-0.023	0.906	0.215	0.254
LDL (mg/dl)	-0.414	0.023	0.138	0.468	0.386	0.035
s. Insulin(mulml)	-0.248	0.187	0.062	0.745	0.326	0.079
FBS(mmol)	0.240	0.201	0.064	0.739	-0.193	0.307
HOMA	-0.071	0.716	0.127	0.510	0.150	0.437
Hba1c	-0.049	0.798	-0.147	0.439	0.163	0.390

This table shows that VAI has positive correlation with BMI and LDL. Apo-β lipop has positive correlation with liver function test (ALT, AST and GGT). IL- 1 β has positive correlation with HC, W/H ratio, ALT, uric acid, cholesterol and LDL in obese with normal glucose tolerance

Table (8): Correlation between VAI, apo beta lipop and IL 1 beta as regards all parameters in group III (non obese with prediabetic state)

	VAI		Apo beta lipop (mg/dl)		IL 1 beta (pg/ml)	
	R	P value	R	P value	R	P value
Age (Years)	0.045	0.813	-0.110	0.562	-0.092	0.627
Weight (kg)	-0.066	0.728	-0.202	0.284	0.122	0.522
Height (m)	-0.054	0.778	-0.228	0.226	0.088	0.645
BMI (Kg/m2)	-0.141	0.456	0.068	0.722	0.155	0.415
SBP (Mmhg)	0.197	0.298	-0.315	0.090	-0.393	0.032
DBP (Mmhg)	0.079	0.679	-0.357	0.053	-0.305	0.101
WC (cm)	-0.358	0.052	0.081	0.669	-0.328	0.077
Wc (inch)	-0.358	0.052	0.023	0.902	-0.366	0.047
HC (cm)	-0.355	0.054	0.052	0.786	0.005	0.979
W/H ratio	0.093	0.627	0.141	0.456	-0.340	0.066
ALT (U/L)	-0.095	0.617	0.194	0.305	0.075	0.695
AST (U/L)	-0.298	0.110	-0.174	0.357	-0.361	0.050
Albumin (g/Dl)	0.029	0.878	-0.116	0.543	-0.181	0.339
Bilirubin (mg/dL)	0.075	0.692	0.009	0.963	0.013	0.944
GGT (ul)	-0.083	0.664	0.013	0.945	-0.083	0.662
Creat (mgldl	-0.166	0.381	-0.268	0.151	-0.182	0.336
Uric Acid (mgldl)	-0.010	0.959	-0.386	0.035	-0.020	0.915
FBS (mgldl)	-0.159	0.401	-0.344	0.062	-0.236	0.209
PP (mgldl)	0.104	0.583	-0.327	0.078	-0.218	0.248
Cholest (mgldl)	0.139	0.463	0.411	0.024	0.293	0.116
TG (mgldl)	0.328	0.077	0.168	0.376	0.090	0.637
HDL (mgl dl)	-0.657	0.001	-0.372	0.043	-0.184	0.331
LDL (mg/dl)	0.266	0.155	0.531	0.003	0.278	0.136
s. Insulin(mulml)	0.771	0.003	0.409	0.001	0.521	0.001
FBS(mmol)	-0.138	0.466	-0.361	0.050	-0.256	0.172
HOMA	0.784	0.001	0.388	0.001	0.500	0.001
Hba1c	0.069	0.716	-0.301	0.106	-0.105	0.579

This table shows that VAI has positive correlation with LDL, serum insulin and HOMA. Apo-β lipop has positive correlation with LDL, uric acid, cholesterol, serum insulin and HOMA. IL- 1β has positive correlation with systolic BP, wc, serum insulin and HOMA in non obese with prediabetic state.

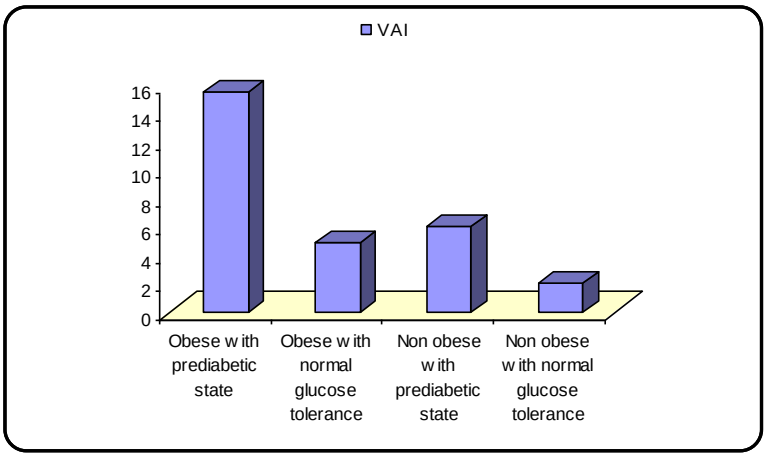

Figure (1): VAI regarding studied groups

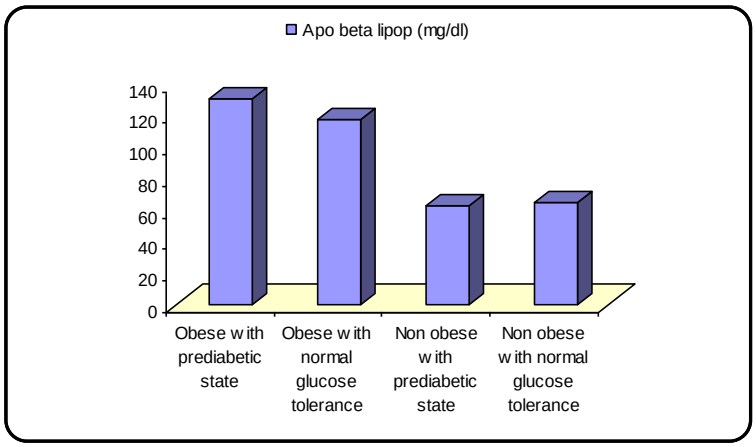

Figure (2): Apo- beta lipop regarding studied groups

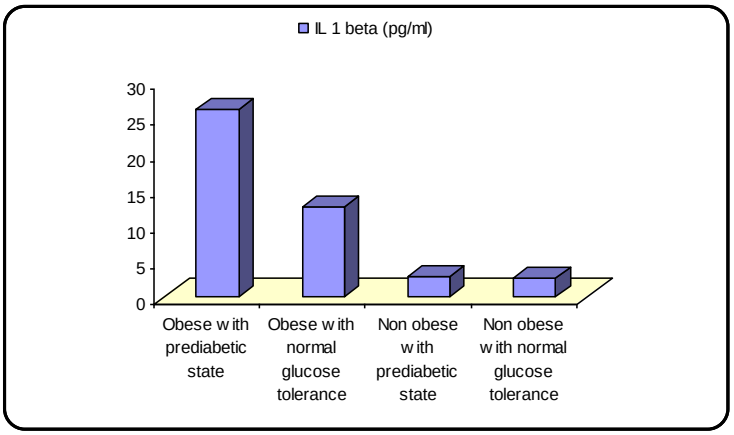

Figure (3): IL- 1 beta regarding studied groups

Discussion

In this study, there was statistically significant increase in VAI in group I in comparison to group III, on the other hand there was statistically significant increase in VAI in group II in comparison to group IV. ***Neeland et al.*** [12] showed that Increase visceral adiposity can lead to incident diabetes mellitus (DM) and atherosclerosis in the general population.

In this study, there was statistical significant increase in IL-1 β in group I in comparison to group III, while there was statistically significant increase in IL- 1 β in group II in comparison to group IV. In agreement with resultes ***Maedler et al.*** [9] Showed that the increase of immune cells (IL-1 β) in pancreatic islets is described even before the onset of T2DM particularly the expression and local release of the pro-inflammatory cytokine IL-1β. Also, ***Herder et al.*** [13] reported that the association between IL-1Ra levels in the circulation and pre-diabetes. IL-1Ra levels showed an accelerated increase during the last 6 years preceding diagnosis of diabetes.

In addition ***Mandrup-Poulsen*** [14] reported that it is unclear whether inflammatory responses are a primary cause or a secondary effect in T2DM progression, so in persons with pre-diabetic state they suggested that therapy targeting IL-1β has shown encouraging results. In this study, there was statistically significant increase in Apo- β lipoproteins in group I in comparison to group III , on the other hand there was statistically significant increase in apo- β lipoproteins in group II in comparison to group IV. ***Sierra et al.*** [15] found that the levels of ApoB were significantly increased in subjects with pre-diabetes.

Haffner et al. [16] showed that development of hyperglycaemia is closely associated with lipid disturbances. ApoB-containing lipoprotein particles undergo compositional changes, including the increase formation of LDL and large VLDL particles. These features were present in pre-diabetic patients with insulin resistance.

Also the results of this study showed that there was statistically significant increase in ALT and AST in group I in comparison to group III, on the other hand there was statistically significant increase in ALT and AST in group II in comparison to group IV, while there

are 17 patients in group I with elevated ALT and AST and 13 patients in group II with elevated ALT and AST, with no statistically significant between group I and group II. In agreement with results ***Balkau et al.*** [17] Showed that elevations in levels of liver enzymes ALT and AST related to incident pre-diabetes and type 2 diabetes in apparently healthy younger adults.

In this study there was statistically significant increase in frequency of HTN in group I in comparison to group III, and there was statistically significant increase in frequency of HTN in group II in comparison to group IV. ***American Heart Association,*** [18] Showed that pre-diabetes paired with high blood pressure increase the coronary artery disease, while pre-diabetes didn't increase cardiovascular risk by itself.

In this study, there was statistically significant increase in IGT in group I subjects in comparison to group III subjects, while no statistical significant between group II and group IV. IFG and IGT represent intermediate states of abnormal glucose regulation that exist between normal glucose homeostasis and diabetes [19]. In addition ***Brohall et al.*** [20] reported that, the majority of individuals with IFG or IGT appear to develop diabetes with poor reproducibility of the glucose tolerance test.

In this study, there was statistically significant increase in Cholesterol, TG, LDL, HDL, S. insulin, HOMA and HbA1c in group I subjects in comparison to group III , on the other hand there was statistically significant increase in Cholesterol, TG, LDL, HDL, S. insulin and HOMA in group II in comparison to group IV subjects. ***Antuna et al.*** [21] Showed that the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) is a tool for assessment of insulin resistance and increase level of (HOMA-IR) can lead to insulin resistance among subjects with metabolic syndrome.

These findings were in agreement with ***Despres et al.*** [22] who reported that the risk may be particularly great for individuals with more prominent upper body obesity, in whom triglyceride and cholesterol levels are high.

Also, these findings were in agreement with ***Despres et al.*** [22] who reported that increase in total cholesterol raised up the risk for CHD by 10% over a 5- to 10-year period.

In this study there was statistically significant increase in insulinogenic index in group II in comparison to group IV, while there was no statistically significant increase in insulinogenic index in group I in comparison to group III.

Faulenbach et al. [23] observed that this finding is in agreement with increased incidence of glucose intolerance in subjects with a nonpositive insulinogenic index. So could be useful for estimating the risk for developing diabetes.

In this study there was statistical significant increase of +ve CRP in group I subjects and group II in comparison to +ve CRP in group III, while in group IV subjects which was zero. These findings were in agreement with ***Hung et al.*** [24] who showed that CRP level was higher in subjects with increased level of VAI. Also, ***Yosef et al.*** [25] reported that C-reactive protein (CRP) is an extremely sensitive marker of systemic inflammation.

Conclusion

IL-1β& Apo- β lipoproteins consider as a risk factor in the pathogenesis of pre-diabetes in obese persons, which may progress to frank Diabetes ,So Therapy targeting IL-1β may ameliorate the condition, Insulinogenic index could be useful for estimating the risk for developing diabetes.

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