Original Article

Iranian Journal of Immunology

https://iji.sums.ac.ir

IL-18 Serum Level in Subjects with Obesity, Prediabetes, and Newly Identified Type 2 Diabetes

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ABSTRACT

Background: Obesity and diabetes are related to a chronic low-grade inflammation. As a pro-inflammatory cytokine, IL-18 stimulates various cell types and has pleiotropic functions.

Objective: To assess the levels of IL-18 in subjects from the entire spectrum of glycemic disorders.

Methods: This study included 387 Caucasians divided into four groups: healthy controls, obese subjects without carbohydrate issues, prediabetic patients, and recently discovered type 2 diabetics.

Results: Subject with body mass index ≥30kg/m2 and glycemic disorders showed significantly higher levels of IL-18 (249.77±89.96 pg/ml; 259.01±95.70 pg/ml; and 340.98±127.65 pg/ml) compared with that of the control group (219.47±110.53 pg/ml, P<0.05). IL-18 also had significant positive associations with some anthropometric parameters, liver enzymes, fasting, post-load glucose, insulin, uric acid, and triglycerides while negative with HDL. The circulating IL-18 levels for differentiating subjects with carbohydrate disturbances and those with metabolic syndrome were determined by ROC analysis. The AUC for the disturbances of the carbohydrate metabolism was 0.597 (P=0.001; 95% CI=0.539-0.654) and for MS AUC was 0.581 (P=0.021; 95 % CI=0.516-0.647).

Conclusion: Our data indicate that as the levels of IL-18 are increased the carbohydrate tolerance is deteriorated. However, the significance of IL-18 in the progression of diabetes mellitus and subsequent consequences requires further exploration.

Keywords: Carbohydrate disturbances, IL-18, Metabolic syndrome

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Cite this article as:
Nedeva I, Gateva A, Assyov Y, Karamfilova V, Hristova J, Yamanishi K, Kamenov Z, Okamura H. IL-18 Serum Level in Subjects with Obesity, Prediabetes, and Newly Identified Type 2 Diabetes. *Iran J Immunol.* 2022; 19(2):193-200, doi: 10.22034/IJI.2022.90095.1987.

Received: 2021-02-08
Revised: 2021-08-30
Accepted: 2021-09-09

INTRODUCTION

Various factors play a role in the pathogenesis of type 2 diabetes mellitus (T2DM), which accounts for more than 90 % of the diabetes cases (1, 2). Previous studies suggest that inflammation could be a potential cause of T2DM and other obesity-associated diseases (3). In T2DM it is also implicated as a causal factor for insulin resistance and dysfunction of the beta-cells (4). The inflammatory cytokines, tumor necrosis factor-alpha

(TNFα), and interleukins (ILs) are small, non-structural proteins that all nucleated cells can synthesize (5).

Interleukin-18 (IL-18), part of IL-1 superfamily, was initially discovered as an interferon-gamma (IFNγ)-inducing factor in the late 20th century (6). This is produced by various cell types and triggers the expression of adhesion molecules and chemokine receptors. Furthermore, this cytokine activates immune response through type 1 and 2 T-helper cells (7).

Besides its inflammatory role, IL-18 also participates in the pathogenesis of visceral obesity. Studies have reported an abnormal increase in IL-18 levels in individuals with obesity, supporting the hypothesis that adipose tissue regulates the secretion of the pro-inflammatory cytokine (8, 9). Furthermore, IL-18 is associated with atherosclerotic plaque as it is involved in the process of atherogenesis (10), affects plaque destabilization, and predicts cardiovascular mortality (11, 12). Certain oxidative mechanisms play a leading role in the acute increase of cytokines, suggesting a definitive association between hyperglycaemia and pro-inflammatory cytokines. Patients with T2DM had higher serum IL-18 levels and this cytokine have been associated with microangiopathies such as nephropathy (13, 14). Two prospective cohorts have reported that increased levels of IL-18 could predict incident type 2 diabetes (15, 16).

However, there is lack of information about the relation between IL-18 in the early disturbances of the glucose homeostatis and namely this was the focus of our study.

MATERIALS AND METHODS

Patients**:** The current study included 388 Caucasian individuals. The people were divided into four groups: 158 obese subjects without glycemic disturbances (group 1); 127 prediabetic subjects (group 3) and 60 subjects diagnosed with diabetes within one month. The inclusion criteria were: age (35–74 years), fasting glucose between 6.1 and 6.9 mmol/l and/or on 120 min of OGTT between 7.8 and 11.0 mmol/l, and/or newly diagnosed diabetes mellitus type 2, without therapy and/or body mass index≥30 kg/m^2. The exclusion criteria were: therapy with antidiabetic drugs, neoplastic disease, and liver or kidney dysfunction. The current project was approved by the Medical University of Sofia's clinical research ethics committee.

Anthropometric measurements*:* height, weight, the circumference of hip and waist, body mass index (BMI), and arterial blood pressure. BMI, a measure of general obesity, was calculated as weight (kg) divided by height squared (m^2). The midpoint between the inferior costal margin and the superior border of the iliac crest on the midaxillary line was used for measuring the waist circumference. The level of the greater trochanter was used for measuring the hip circumference. VAI (visceral adiposity index) was estimated using the following formula: VAI=(WC/(36.68+(1.88 x BMI) x (TG/1.03) x (1,31/HDL) for men. VAI=(WC/(36.58+(1.89 x BMI) x (TG/0,81) x (1,52/HDL) for women; TANITA™ TBF-215 GS Body Composition Analyzer in fasting state was used to evaluate the percentage of body fat (body fat %).

Investigation of glycemic homeostatic: An oral glucose tolerance test (OGTT) with 75 g of glucose was performed by determining the glucose and immunoreactive insulin (IRI) at 0, 60, and 120 min. Patients were considered insulin resistant if the HOMA index was >2.5.

Metabolic syndrome *(MS)* was determined based on the IDF criteria (Alberti et al. 2009).

Measurement of serum IL-18*:* Enzyme-linked immunosorbent assay (ELISA) was used for performing IL-18 levels with a detection limit of 12.5 pg/ml. The blood samples for determining serum IL-18 levels were centrifuged and stored at –80 °C until the assay was performed.

Statistical Analysis

For statistical analyses, the statistical

package SPSS 25.0 (IBM™) was used. The statistical methods applied were: descriptive analysis, variation analysis, Student's t-test, and Kolmogorov– Smirnov test. Differences between more than two groups were analyzed using one-way analysis of variance between groups ANOVA or Kruskal-Wallis tests. The odds ratios and 95% confidence intervals were performored using multivariate logistic regression analyze. The level of significance for rejecting the null hypothesis was P<0.05

RESULTS

Subjects were divided into four groups: 42 healthy volunteers -group 1; 158 obese patients- group 2;127 prediabetic subjects-group 3 and 60 subjects with diabetes mellitus-type 2, diagnosed within one month- group 4. The group with prediabetes consisted of 62 patients with only IFG, 35 patients with only IGT, and 30 patients with IFG+IGT. Females were 296 (63.2%) in the study group. The mean age of the participants was 53.3±10.78 years.

Table 1 shows the baseline characteristics of all the study groups. When compared with the healthy controls, with lower BMI, WHR, WSR, and waist circumference, patients from groups 2, 3, and 4 (obesity, prediabetes, diabetes respectively) did not significantly differ in BMI and waist circumference.

Table 2 shows the currency of the risk factors associated with cardiovascular disease among the study participants. Patients with diabetes had significantly high levels of triglycerides and low HDL compared with the other two groups. Blood pressure and other lipid parameters showed not to be significantly difference between subjects of all four groups.

IL-18 levels in subjects with obesity and glucose disturbances, were higher compared with those of the healthy control group

Table 1. Baseline parameters of the four groups

Parameters	Controls			Obesity			Prediabetes			Diabetes		
	n	$\bar{X}$	SD	n	$\bar{X}$	SD	n	$\bar{X}$	SD	n	$\bar{X}$	SD
Age (years)	42	48.90	12.68	158	52.07	10.26	127	54.98*●	9.97	60	55.80*●	10.96
BMI (kg/m^2)	42	23.07	1.30	158	35.43*	4.52	127	34.54*	5.16	60	34.62*	5.54
Waist (cm)	42	82.71	6.85	140	106.36*	11.93	125	104.77*	11.77	54	108.11*	13.95
WHR	42	0.84	0.03	130	0.96*▪	0.75	123	0.91*▪	0.08	41	3.68*	17.34
WSR	42	0.49	0.03	130	0.65[a]	0.07	123	0.63*●	0.07	47	0.65*	0.07

*P<0.05 compared with controls; •P<0.05 compared with obesity; ▪P<0.05 compared with diabetes; BMI-Body mass index; WSR- waist to stature ratio; WHR-waist to hip ratio

Table 2. Comparison of the mean cardiovascular risk factors between the three pathologic groups

Parameters	Group 2 Obesity			Group 3 Prediabetes			Group 4 Diabetes		
	n	$\bar{X}$	SD	n	$\bar{X}$	SD	n	$\bar{X}$	SD
SBP (mmHg)	158	132.13	17.68	127	131.47	16.60	60	136.22	20.62
DBP (mmHg)	158	83.31	10.70	127	83.62	9.97	60	83.62	12.81
Tchol (mmol/l)	156	5.39	1.22	122	5.48	1.12	59	5.62	1.36
LDL (mmol/l)	149	3.41	1.11	119	3.44	1.15	59	3.24	1.10
HDL (mmol/l)	157	1.33	0.33	124	1.23*	0.34	59	1.08*•	0.30
TG (mmol/l)	156	1.43	0.93	124	1.74*	0.80	58	2.71*•	2.15
Hypertension (%)	69.6%				69.3%			85%	
Dyslipidemia(%)	47.1%				61.6%			79.7%	
Smoking (%)	38%				76%			57%	

*P<0.05 compared with obesity; •P<0.05 compared with prediabetes

(249.77±89.96; 259.01±95.70; 340.98±127.65 *vs* 219.47±110.53, respectively, P<0.05; Figure 1). Diabetic subjects had the highest levels of IL-18 and revealed a gradual progression from obesity to prediabetes to diabetes. Gender differences were also observed as males showed significantly high levels of IL-18 (303.94±128.60 *vs* 249.92±94.85; P=0.001). Additionally, patients with MS and dyslipidemia had elevated levels of IL-18 in comparison with those without this pathological states (277.75±110.15 *vs*

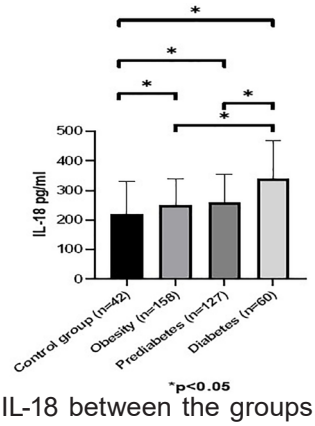

Figure 1. IL-18 between the groups. Shown p value is the result of the Mann Whitney U-test.

Table 3. Spearman correlations of circulating serum IL-18 (pg/ml) with different parameters of the study population.

Parameters	Correlation coefficient	P value
Age (years)	-0.032	NS
BMI (kg/m^2)	0.108	0.035
Waist (cm)	0.132	0.013
WHR	0.097	0.102
WSR	0.120	0.021
VAI	0.219	0.003
Leu (G/l)	0.244	0.000
ASAT (U/l)	0.153	0.008
ALAT (U/l)	0.170	0.002
GGT (U/l)	0.190	0.001
Tchol (mmol/l)	0.009	NS
LDL (mmol)	0.006	NS
HDL (mmol/l)	-0.314	0.000
TG (mmol/l)	0.205	0.000
Creatine (mkmol/l)	0.061	NS
Uric acid (mkmol/l)	0.207	0.001
CRP (mg/l)	0.156	0.037
Glu 0 min (mmol/l)	0.188	0.001
Glu 60 min (mmol/l)	0.116	0.043
Glu 120 min (mmol/l)	0.154	0.007
Insulin 0 min (mIU/ml)	0.240	0.000
Insulin 60 min (mIU/ml)	0.122	0.020
Insulin 120min (mIU/ml)	0.193	0.003
HOMA	0.235	0.000
QUICKI	-0.104	NS
HbA1c (%)	0.122	NS
Met.comp	0.197	0.006
SBP (mmHg)	0.046	NS
DBP (mmHg)	-0.001	NS

NS-not significant; BMI- body mass index; WHR- waist-to-hip ratio; WSR-waist-to-stature ratio ; VAI-visceral adiposity index; Leu-leukocyte; ASAT-aspartate aminotransferase; ALAT-alanine aminotransferase; GGT-gamma-glutamyl-transferase; Tchol- total cholesterol; LDL-low-density lipoprotein; HDL- high-density lipoprotein; TG-triglycerides; CRP-C-reactive protein; Glu0- glucose at the 0 min; Glu60-glucose at the 60 min; Glu120-glucose at the 120 min; Insulin0-insulin at the 0 min; Insulin60- insulin at the 60 min; Insulin120-insulin at the 120 min; HOMA-IR, homeostatic model assessment of insulin resistance; Met. Comp-metabolic components; SBP-systolic blood pressure; DBP- diastolic blood pressure

244.34±84.82; P=0.02) (282.15±114.48 *vs* 250.84±85.62; P=0.03). Spearmen correlation analysis determined positive correlation between IL-18 and some of the anthropometric parameters; BMI (r=0.108; P=0.035), waist circumference (r=0.132; P=0.013), VAI (r=0.219; P=0.003), WHR (r=0.097; P=0.102), WSR (r=0.120; P=0.021), as well as hepatic enzymes- ASAT (r=0.153; P=0.008), ALAT (r=0.170; P=0.002), GGT (r=0.190; P=0.001); TG (r=0.205; P=0.000); fasting glucose (r=0.188; P=0.001), 60 min (r=0.116; P=0.043), 120min (r=0.154; P=0.007) and fasting insulin (r=0.240, P=0.000), 60min (r=0.122; P=0.020); 120min (r=0.193; P=0.003) , HOMA index (r=0.235; P=0.000), CRP (r=0.156; P=0.037) and the number of metabolic components (r=0.197; P=0.006) and negative to HDL-cholesterol r=-0.314; P=0.000). Table 3 presented Spearman correlations between IL-18 levels and different parameters of the study population**.** We performed ROC curve analysis for determining whether IL-18 could be used as a marker, differentiating subjects with glycemic disorders and those with MS. By means of the ROC-curve analysis (AUC=0.597; P=0.001; 95% CI=0.539-0.654; Figure 2) we determined that IL-18 ≥ 235 pg/ml had 63% sensitivity, 51% specificity for determining subjects with disturbances of glycemic regulation and a 62 % sensitivity and 54 % specificity for determining those with MS (AUC=0.581; P=0.021; 95% CI=0.516-0.647; Figure 3**)**. Binary logistic regression analysis showed that patients with levels of IL-18 > 235 ng/ml had an OR of 1.607 for carbohydrate disturbances (P=0.021, 95% CI=1.073-2.406) and an OR of 1.780 for MS (P=0.007, 95% CI=1.173-2.700).

DISCUSSION

T2DM and obesity, due to their increasing prevalence, are recognized as epidemics by the World Health Organization. The term "diabesity" was conceived due to the strong association of obesity and diabetes, suggesting a causal pathophysiological relationship between both diseases (17, 18).

Low-grade inflammation, related to both the conditions, is suggested to be a potential mediator for the evolution of endothelial dysfunction and cardiovascular diseases. The inflammatory state motivator is thought to

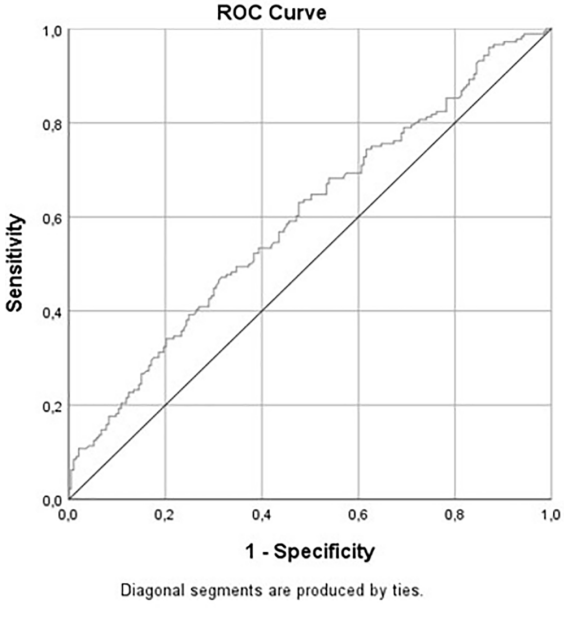

Figure 2. ROC curve (AUC 0.597, P=0.001; 95% CI=0.539-0.654) for determining the cut-off value of IL-18 in differentiating the patients with and without glycemic disorders.

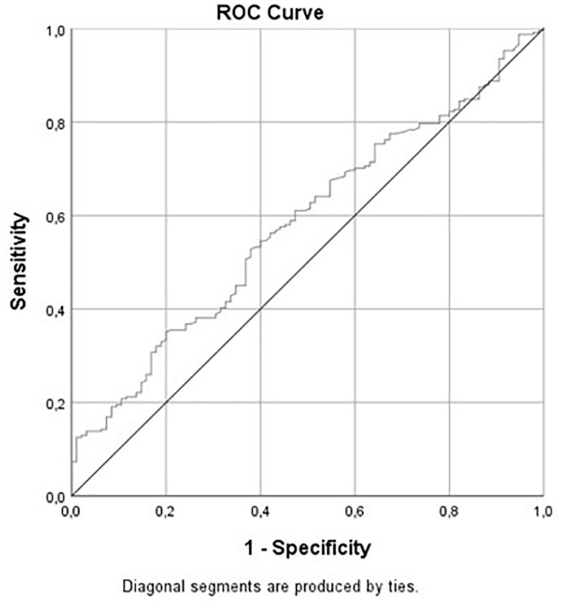

Figure 3. ROC curve (AUC 0.581, P=0.021; 95% CI=0.516-0.647) for determining the cut-off value of IL-18 in differentiating the patients with and without MS.

be the visceral adiposity, due to its ability to synthesize many adipocytokines. One such pro-inflammatory cytokine is IL-18, the product of various cell types (6, 19). It has also been shown that IL-18 concentration drops with weight reduction (20) suggesting that IL-18 could affect the risk of T2DM development and insulin resistance.

Previous research found that obese patients and those with T2DM had considerably higher levels of IL-18 (21, 22). Zilverschoon et al. (2008) suggested one possible explanation for the elevated serum levels of IL-18 in those patients (23). Leukocytes, which were isolated from patients with obesity or T2DM had a poor response to IL-18 stimulation. The authors also hypothesized that the resistance to IL-18 could elucidate the relationship between obesity, diabetes and high IL-18 circulating concentrations. Higher levels of serum IL-18 in obese and diabetic subjects in comparison to that of the healthy controls, was also found in our study. In previous studies, subjects with diabetes mellitus had long-standing diabetes and most of them were on a treatment with glucose lowering drugs and/or insulin, which couldhave influenced the IL-18 concentrations. However, in our study, patients with T2DM were newly diagnosed and drug-naïve.

Currently, this is the first study, which followed the values of IL-18 in all stages of glucose tolerance. Correlation analysis in our study revealed a positive relation between IL-18 levels BMI, waist circumference, WSR, and VAI. Similar findings were reported by Sun et al. who observed the correlations in normal weight and overweight/obese subjects between serum IL-18 levels, BMI and waist circumference (24). Similar to previous reports (25, 26), a positive correlation between IL-18, fasting and post-load glucose, between IL-18 and HbA1, and negative with HDL was observed in this study. Our results also correlate to the reported increased IL-18 in fasting and post-load insulin, as well as the HOMA index (27, 28).

There was located, for the first time, in this examination a positive relation between ASAT, ALAT, GGT, and circulating serum IL-18 in patients with early carbohydrate disorders. Different mechanisms are included in the liver cytotoxic response, causing hepatocyte apoptosis and nuclear factor-kB activity modulation (29). It can be assumed that the increased IL-18 levels in insulin-resistant subjects, such as obesity or T2DM has the potential to cause fatty liver disease.

Besides, limited information about the relation between IL-18 levels and the early stages of carbohydrate disturbances is available. This study evaluated the IL-18 levels in obese individuals and those with the earliest glucose abnormalities. We suggested that the progressive increase of IL-18 level could cause a deterioration in glycaemia, as IL-18 would be tightly associated with the natural evaluation of T2DM.

Coupled with this, among patients with prediabetes, those with combinate carbohydrate disturbances had the highest IL-18 levels, although the results were not statistically significant. Subjects with metabolic syndrome had elevated IL-18 levels and corresponded to the number of components of the syndrome (25, 30). Similar data were observed in our study.

The binary logistic regression analysis revealed a potential predictive value of IL-18 for determining those with disorders of the carbohydrate metabolism as well as with MS. Subjects with IL-18≥235 ng/ml had about 1.6 higher risk for developing dysglycemia, while this figure would increase to 1.7 for the risk of developing MS.

Still, we are mindful that our work has several drawbacks, including the tiny size of the control group, gender distribution, and cross-sectional design.

CONCLUSION

Here, we have demonstrated a progressive increase in IL-18 levels alongside the worsening of glucose tolerance in our study

population. A positive association was found between IL-18 levels and various metabolic parameters, such as hepatic enzymes, lipid profiles, estimates of insulin sensitivity, and could be used to predict metabolic risk. The potential involvement of IL-18 in the cardiometabolic syndrome is further correlated in our study. Furthermore, deeper insight and prospective analyses could also provide light on the potential role of IL-18 in glucose metabolism.

ACKNOWLEDGMENTS

The Bulgarian Ministry of Education and Science funded this project under the National Program for Research "Young Scientists and Postdoctoral Students." IL-18 ELISA kits were provided by Hirakata Ryōikuen, Osaka

Conflict of Interest: None declared.

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