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ORIGINAL ARTICLE

Observational Study

Interleukin-18 polymorphism as an inflammatory index in metabolic syndrome: A preliminary study

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Abstract

AIM

To assess circulatory levels of interleukin-18 (IL-18) and determine whether the presence of IL-18 promoter polymorphism influences metabolic syndrome phenotypes.

METHODS

This study recruited one hundred and eighty individuals divided into three groups with sixty subjects each as: Normal weight (18.0-22.9 kg/m^2), overweight (23.0-25.9 kg/m^2) and obese (> 26.0 kg/m^2) according to South Asian criteria of BMI. Fasting blood glucose (FBG), Lipid profile, insulin, IL-18 and tumor necrosis factor (TNF)α were measured using ELISA kits, whereas low density lipoprotein (LDL)-cholesterol, insulin resistance (HOMA-IR) and insulin sensitivity (QUICKI) were calculated. The body fat percentage (BF) was measured through bioelectrical impedance analysis; waist and hip circumference were measured. Genotyping of IL-18 -607 C/A polymorphism was performed by using tetra-primer amplification refractory mutation system. Student *t* test, One-way analysis of variance, Hardy-Weinberg equilibrium, Pearson's χ^2 test and Pearson's correlation were used, where a P value < 0.05 was considered significant.

RESULTS

In an aged matched study, obese subjects showed higher levels of FBG, cholesterol, triglycerides and LDL levels as compared to normal weight (P < 0.001).

Highest levels of IL-18 and TNF levels were also seen in obese subjects (IL-18: 58.87 ± 8.59 ng/L) (TNF: 4581.93 ± 2132.05 pg/mL). The percentage of IL-18 -607 A/A polymorphism was higher in overweight and obese subjects *vs* normal weight subjects ($P < 0.001$). Moreover, subjects with AA genotype had a higher BF, insulin resistance, TNFα and IL-18 levels when compared with subjects with AC (heterozygous) or CC (wild type) genotypes. However, we did not find any difference in the lipid profile between three subgroups.

CONCLUSION

This preliminary data suggests that IL-18 polymorphism affects IL-18 levels that might cause low grade inflammation, further exacerbated by increased TNFα. All these increase the susceptibility to develop MetS. Further studies are required to validate our findings.

Key words: Metabolic syndrome; Interleukin-18; Polymorphism; Obesity; Body fat; High density lipoprotein; Low density lipoprotein; Insulin

Core tip: Interleukin-18 (*IL-18*) gene polymorphisms may influence the expression of its levels. This in turn increases the risk of metabolic syndrome (MetS). Therefore, we aimed to assess the circulatory levels of IL-18 and determine whether the presence of IL-18 promoter polymorphism influences MetS phenotypes. Subjects with AA genotype had a higher body fat, insulin resistance, tumor necrosis factor α and IL-18 levels when compared with subjects with AC (heterozygous) or CC (wild type) genotypes. This preliminary data suggests that IL-18 polymorphism affects IL-18 levels that might cause low grade inflammation. All these increase the susceptibility to develop MetS. Further studies are required to validate our findings.

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INTRODUCTION

Interleukin-18 (IL-18), also known as interferon-gamma inducing factor, is a pro-inflammatory cytokine that belongs to the IL-1 superfamily. It is not only produced by immune cells like macrophages but is also express by keratinocytes, osteoblasts cells, pituitary gland and adrenal cortical cells[1]. IL-18 serves as a mediator of immune response by stimulating T-helper cells (Th-1) against infections[2]. In healthy individuals, its production by the host is in line to utilization as a defense and healing mechanism, maintained in a fine balance. However, it has been established that its over-production results in autoimmune inflammatory disorders[3]. Apart from its role in inflammation, IL-18 has also been associated with increased visceral adiposity and obesity. Studies report abnormally elevated circulating IL-18 levels in obese individuals while reduction in body weight is found to results in a concomitant reduction in IL-18 levels, supporting the fact that reduction in adipose tissue leads to a decline in secretion of pro-inflammatory cytokines[4]. Furthermore, IL-18 mediated inflammation is associated with cardiovascular disorders suggesting its role in atherosclerotic diseases[5]. In the context of hyperglycemia, there are certain oxidative mechanisms that increase circulating cytokines including IL-18, thereby linking high blood glucose to the pro-inflammatory cytokines[6]. Various studies have reported elevated serum IL-18 in patients with type 2 diabetes[7].

As the presence of risk factors for cardiovascular disease and type 2 diabetes mellitus increases the threat of developing metabolic syndrome (MetS), IL-18 has been implicated to play a critical role in such conditions[8]. In terms of polymorphism in the IL-18 gene, various SNP are reported in association with diseases like type 1 diabetes[9], chronic hepatitis B virus infection[10], asthma[11].

The *IL-18* gene is located on chromosome 11 (11-q22.2-22.3), and contains many polymorphism, especially in the promoter region[12]. One such polymorphism is the -607 A/C that seems to affect the expression level of IL-18 at transcription level[13]. In addition, it has been associated with the development of cardiovascular disease such as vascular endothelial damage and formation of atherosclerosis[14]. The relationship between the promoter region polymorphism of IL-18 and MetS phenotypes is scarce. Therefore, we aimed to assess the circulatory levels of IL-18 and determine whether the presence of IL-18 promoter polymorphism influences MetS phenotypes.

MATERIALS AND METHODS

Patient recruitment

This cross-sectional study recruited 180 healthy male individuals from the waiting areas of outpatient department of Aga Khan University. The subjects were divided into three groups. Group A: normal weight (18.0-22.9 kg/m^2), Group B: overweight (23.0-25.9 kg/m^2), Group C: obese (> 26.0 kg/m^2) according to South Asian criteria of BMI[15]. Subjects with diabetes mellitus, hypertension [resting blood pressure (BP) 170/100 mmHg], dyslipidemia, body weight fluctuation of 5 kg in the recent 6 mo, smokers, alcoholics, any acute illness during last one month, as well as those taking anti-inflammatory medications were excluded. This study was approved by the institutional ethical committee and all participants gave a written and informed consent to participate in this study. The sample size was calculated

in order to achieve 80% power to detect an odds ratio of at least 2 among obese, with a two sided alpha value of 95% (NCSS/PASS version 11 software for power analysis and sample size).

Anthropometric data

The weight and height of all the subjects were measured in kilograms and meters respectively, using a weight scale with a built-in Stadiometer (ZT-120 Health Scale, Nanjing Everich China). Waist circumference and hip circumference was measured using the WHO protocol[16]. Subjects were asked to stand in an erect posture wearing light clothing. BMI was calculated by dividing weight by height squared (kg/m^2)[17]. While body fat percentage was measured using Diagnostic Scale BG55 (Beurer Germany) through bioelectrical impedance matching/analysis.

Biochemical profile

Six milliliter of blood was collected from the study participants after an overnight fast of 12 h. Fasting plasma glucose and Lipid profile were measured using commercially available kits as per the vendor's instruction (Merck, France). Low density lipoprotein (LDL)-cholesterol levels were calculated using the Friedewald equation[18]. Fasting insulin, IL-18 and TNFα levels were measured using an ELISA kit (DIA source Immuno Assay S.A., Belgium). Insulin resistance was calculated using the homeostasis model assessment of insulin resistance (HOMA-IR) index [fasting insulin (units per milliliter) × fasting glucose milligram/deciliter)/405][19], and insulin sensitivity was calculated by (QUICKI) {1/[log(fasting insulin) + log(fasting glucose)]}[20].

Genotyping

DNA extraction was performed using commercially available Qiagen DNA extraction kit (Cat. #51185, Valencia, CA United States). Genotyping of IL-18 -607 C/A polymorphism was performed by using tetra-primer amplification refractory mutation system (TARMS-PCR) using the GoTaq® Hot Start Green Master Mix (Cat. # M5122, Promega Corporation, United States) as per the manufacturer's instructions with the following cycling conditions for PCR: 1 cycle for 5 min at 95 ℃ for initial denaturation followed by 35 cycles at 95 ℃ for 30 s, 55 ℃ for 30 s, 72 ℃ for 30 s followed by a final extension of 10 min at 72 ℃. PCR products were electrophoresed in 2% agarose gel. Genotyping quality control was performed in 10% of the samples by duplicate checking (rate of concordance in duplicates was > 99 %). Tetra arms primers used for amplifying IL-18 -607 (C/A) were as follows: Control Band (Outer forward: CCTACAATGTTACAACACTTAAAAT; Outer reverse: ATAAGCCCTAAATATATGTATCCTTA) (product size 440 bp); A allele [Inner forward: GATACCATCATTAGAATTTTGTG (product size 278 bp)] and C allele [Reverse inner GCAGAAAGTGTAAAAATTATCAA (product Size 208 bp)] (Figure 1). The study was approved by the institutional ethical review board (3597-BBS-ERC-15), and all subjects gave a written and informed consent.

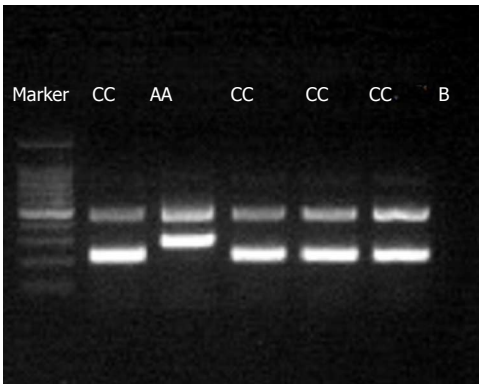

Figure 1 Genotype distribution of selected samples for the tetra arms PCR. Marker is 100 bp DNA ladder and B is blank.

Statistical analysis

A descriptive statistical analysis of continuous variables was performed using SPSS (version 21; SPSS Inc., Chicago, IL, United States). Data on continuous variables were calculated as mean ± SD, whereas data on categorical variables was presented as frequencies and percentages. Statistical comparisons were computed using a student *t* test, one-way analysis of variance (ANOVA) and Pearson's χ^2 test of independence. Pearson's correlation (r) were used to determine the correlation between serum IL-18 levels and lipid profile, fasting blood glucose, insulin and body fat parameters. Hardy-Weinberg equilibrium (HWE) was calculated for IL-18 SNP. Significance and effect size of minor allele with study parameters were determined under an additive model of inheritance. In all statistical analysis performed *P* values < 0.05 were considered significant.

RESULTS

Table 1 shows the biophysical and biochemical data of the study subjects. All three groups were aged matched, therefore no significant difference was observed amongst the groups. Considerable difference was observed in terms of raised BMI and BF in obese group as compared to controls ($P < 0.001$). Similarly, obese group had a higher FBG, insulin, cholesterol, triglycerides and LDL levels as compared to controls ($P < 0.001$). Interestingly no differences were seen in the high density lipoprotein (HDL) levels of our study groups. IL-18 and TNF levels showed an increasing trend from normal weight to obese, with the highest levels seen in obese group (IL-18: 58.87 ± 8.59) (TNF: 4581.93 ± 2132.05). We next performed the correlation of IL-18 levels with the study parameters and report a strong positive correlation of IL-18 with BMI, Waist circumference, FBG, insulin, HOMA-IR, QUICKI, Choles-

Table 1 Biophysical and biochemical data of the study subjects

Variables	Normal weight (18-22.9 kg/m^2) (n = 60)	Overweight (23-25.9 kg/m^2) (n = 60)	Obese (>26 kg/m^2) (n = 60)	P value
Age (yr)	26.21 ± 3.876	25.76 ± 4.059	27.30 ± 5.389	NS
BMI (kg/m^2)	20.48 ± 1.30	24.20 ± 0.91[1]	28.59 ± 3.34[1,2]	< 0.001
Body fat (%)	19.26 ± 7.17	28.70 ± 9.10[1]	34.89 ± 4.47[1,2]	< 0.001
Waist circumference (cm)	88.03 ± 10.53	88.46 ± 7.69	1.9.26 ± 11.47	< 0.001
Hip circumference (cm)	77.69 ± 11.78	84.43 ± 0.69	100.41 ± 12.89	< 0.001
WHR (cm)	0.87 ± 0.05	0.871 ± 0.054	0.91 ± 0.073	< 0.001
Fasting blood glucose (mg/dL)	89.31 ± 15.23	105.59 ± 12.50[1]	119.00 ± 25.71[1]	< 0.001
Insulin (uIU/mL)	20.48 ± 7.95	34.96 ± 4.47[1]	41.13 ± 7.81[1,2]	< 0.001
HOMA-IR	4.70 ± 2.66	9.05 ± 1.34[1]	11.88 ± 2.81[1,2]	< 0.001
QUICKI	0.31 ± 0.02	0.27 ± 0.00[1]	0.27 ± 0.01[1]	< 0.001
Cholesterol (mg/dL)	145.72 ± 30.08	147.44 ± 37.91	209.06 ± 55.51[1,2]	< 0.001
Triglyceride (mg/dL)	124.82 ± 43.92	137.58 ± 65.60	167.03 ± 55.99[1,2]	< 0.001
HDL(mg/dL)	39.96 ± 9.38	38.37 ± 8.00	36.40 ± 6.40	NS
LDL(mg/dL)	75.43 ± 30.03	79.57 ± 40.01	134.78 ± 58.99[1,2]	< 0.001
TNFα (pg/mL)	810 ± 1233	4455 ± 2390[1]	4581 ± 2132[1]	< 0.001
IL-18 (ng/L)	25.34 ± 6.57	41.96 ± 4.50[1]	58.87 ± 8.59[1,2]	< 0.001

Values are expressed as mean ± SD. Comparison between groups was tested by One way analysis of variance followed by Tuckey's *post hoc* test. [1]Statistically significant as compared to normal weight; [2]Statistically significant as compared to overweight. Significance set at P value < 0.05. HOMA-IR: Homeostasis model of insulin resistance; QUICKI: Quantitative insulin sensitivity check index; HDL: High density lipoprotein; LDL: Low density lipoprotein; TNF: Tumor necrosis factor; WHR: Waist to hip ratio.

Table 2 Correlation of interleukin-18 with metabolic syndrome phenotypes

Variable	Unadjusted r	Adjusted r (age, BMI and body fat %)
Age (yr)	0.302	--
BMI (kg/m^2)	0.751	--
Body fat (%)	0.518	--
Waist circumference (cm)	0.333	0.413
Hip circumference (cm)	0.695	-0.110[NS]
Fasting blood glucose (mg/dL)	0.559	0.376
Insulin (uIU/mL)	0.655	0.205[NS]
HOMA-IR	0.699	0.344
QUICKI	-0.600	-0.496
Cholesterol (mg/dL)	0.514	0.265
LDL(mg/dL)	0.464	0.245
TNFα	0.577	0.491

Pearson Correlation was applied. All associations remained significant after adjustment except insulin ([NS]non-significant), statistically significant P value < 0.01. HOMA-IR: Homeostasis model of insulin resistance; QUICKI: Quantitative insulin sensitivity check index; LDL: Low density lipoprotein; TNF: Tumor necrosis factor.

Table 3 Genotype frequency among study subjects

Genotype distribution				
	CC	AC	AA	P value
Normal weight	27	23	10	< 0.001
Overweight	11	25	24	
Obese	12	24	24	
Allele frequency				
	A allele	C allele	OR (95%CI)	P value
Normal weight	42 (35.0)	78 (65.0)	-	-
Overweight	47 (39.17)	73 (60.83)	2.81 (1.66-4.68)[1]	< 0.001
Obese	48 (40.00)	72 (60.00)	2.91 (1.72-4.94)[2]	

In all divisions the HWE was > 0.05. [1]Normal weight *vs* overweight and [2]normal weight *vs* obese calculated by Pearson's χ^2 test. Allele frequencies are given as absolute values with percentage given in parentheses.

terol, and TNFα while a moderate correlation was seen for LDL and BF. All these associations remained significant after multiple adjustments for confounding factors like age, BMI and BF, except insulin (Table 2 and Figure 2).

The genotype distributions was in accordance with HWE in total study subjects (P = 0.222) and in subgroups (Normal Weight: P = 0.281; Overweight: P = 0.663; Obese: P = 0.196). The percentage of IL-18 -607 A/A genotype was higher in overweight and obese subjects *vs* normal weight subjects (P < 0.001 Table 3). Moreover, subjects with AA genotype had a higher BF, insulin resistance, TNFα and IL-18 levels when compared with subjects with AC or CC genotypes. However, we did not find any difference in the lipids profile between three subgroups (Table 4).

DISCUSSION

IL-18 is pleiotropic cytokine acting in both acquired and innate immunity. Additionally it also acts to stimulate the production of TNFα[1] which is also a key player associated with higher BMI[21,22]. These cytokines in turn predispose an individual to develop MetS phenotypes.

In an age matched study group, we observed a positive association of serum IL-18 concentration with BMI, FBG, and serum TG, where body fat percentage contributed most to the variation of serum IL-18 concentration. Furthermore, our study shows circulating IL-18 levels were associated with measures of insulin resistance (HOMA-IR) and decreased insulin sensitivity (QUICKI) in apparently healthy obese subjects. Among other factors causing a rise in IL-18 levels, nutritional

Table 4 Stratification of study subjects according to genotype distribution

Variables	CC (n = 57)	AC (n = 72)	AA (n = 51)	P value
BMI (kg/m^2)	23.36 ± 4.05	24.60 ± 4.137	25.25 ± 3.35[1]	0.05
Body fat (%)	24.70 ±10.30	28.70 ± 8.59[2]	29.31 ± 9.46[1]	< 0.001
Waist circumference(cm)	92.78 ± 16.61	96.48 ± 13.21	97.32 ± 13.82	0.085
Hip circumference (cm)	74.18 ± 4.23	67.40 ±3.99	64.51 ± 4.84	0.694
WHR (cm)	0.88 ± 0.069	0.88 ± 0.061	0.89 ± 0.06	0.490
Fasting blood glucose (mg/dL)	103.41 ± 23.43	101.79 ± 21.01	110.32 ± 21.97	> 0.05
Insulin (uIU/mL)	28.83 ± 11.91	32.76 ± 11.39[2]	34.67 ± 9.61[1]	0.002
HOMA-IR	7.75 ± 4.34	8.44 ± 3.71	9.47 ± 3.00[1]	0.007
QUICKI	0.29 ± 0.02	0.28 ± 0.02	0.28 ± 0.01[1]	0.046
Cholesterol (mg/dL)	161.01 ± 39.01	165.12 ± 55.03	177.42 ± 60.72	> 0.05
Triglyceride (mg/dL)	135.66 ± 42.29	145.61 ± 61.45	146.78 ± 64.08	> 0.05
HDL(mg/dL)	38.29 ± 8.84	38.48 ± 56.32	37.17 ± 6.75	> 0.05
LDL(mg/dL)	88.99 ± 5.38 (SEM)	94.73 ± 6.63 (SEM)	107.77 ± 7.89 (SEM)	> 0.05
TNFα (pg/mL)	2521 ± 353.9 (SEM)	3403.08 ± 313.25 (SEM)	3760.35 ± 336.55[1] (SEM)	0.008
IL-18 (ng/L)	37.16 ± 19.35	43.00 ± 13.19[2]	46.311 ± 13.07[1]	0.001

[1]AA *vs* CC; [2]AC *vs* CC. HDL: High density lipoprotein; LDL: Low density lipoprotein; TNFα: Tumor necrosis factor alpha; IL-18: Interleukin-18.

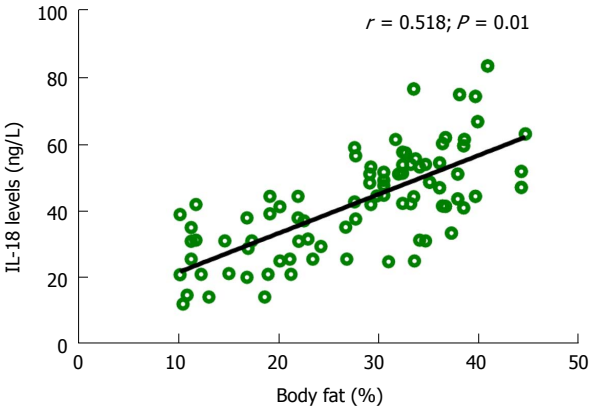

Figure 2 Correlation of interleukin-18 levels with body fat percentage. IL-18: Interleukin-18.

states, such as hyperglycemia, and fat mass increase[23] have been validated the most. In particular, adipocytes from obese individuals were found to secrete a threefold higher IL-18 *vs* lean ones[24], identifying an essential role of IL-18 in regulating fat distribution[25]. Though, an animal study demonstrated that deficiency of IL-18 resulted in obesity and insulin resistance in mice and the phenotype could be rescued by exogenous administration of IL-18[26].

We further evaluated the presence of a promote gene polymorphism in these subjects. Interestingly, we report that subjects with AA genotype had a higher BMI, BF, insulin resistance and IL-18 levels. Moreover, raised IL-18 increased the chances of developing of MetS in our study subjects (OR = 2.72, 95%CI: 1.28-5.74, P = 0.008). Results regarding the association of -607 SNP and MetS phenotypes are not consistent. One study reported a decreased proportion of A/A genotype in type 1 diabetic patients relative to control subjects[9]. However, another[27] found higher proportion of A/A genotype in type 1 diabetic patients but no risk association could be identified. Another study, conducted in Chinese population reported a higher proportion of A/A genotype in patients with type 2 diabetes, which is somewhat similar to our report. Therefore, it is empirical to identify the different genetic influences among different races when considering genotype data and risk association. For instance, A allele at position of -607 was a protective allele from type 1 diabetes in a Polish population[9], while in a population from United Kingdom, the significant association was not found[27].

These seemingly conflicting results suggested that IL-18 probably acts as a feedback signal for obesity, hyperglycemia, and positive energy balance. Alternatively, it might be a consequence of sensitivity in those subjects to the effect of IL-18. This may prove that inflammatory marker (IL-18) may just not be an indicator for chronic inflammation and obesity but has a role in pathway leading to MetS. Another outcome of our study was the relation of IL-18 with increased levels of cholesterol and LDL. This opens up another avenue about the role of IL-18 in atherosclerosis and presents a great opportunity to work further in this field. Some of previous studies have shown association of circulating IL-18 levels with cardiovascular mortality among patients with coronary artery disease[5]. However, contrasting data also exists which states no or weak association of IL-18 levels with BMI and lipid profile in European men[28], this may suggest that association may vary according to the population. In addition to Interleukin 18, recent repost suggested that other variants such as Interleukin-23/IL-17 axis has also been independently affiliated with obesity in women especially related to increase visceral fat, insulin resistance, and leptin levels[29] as well as in causing hypertension and increased cardiovascular risk[30].

One of the limitations of this study rests in the study-design. As this was a cross sectional study the association of IL-18 with all of these metabolic traits could not be established, further more we were unable to record the nonalcoholic fatty liver disease through

ultra sonographic analysis. Nevertheless our results clearly show that IL-18 can be used a marker for obesity and supports the hypothesis that IL-18 may be involved in pathway of MetS and form a link between metabolic risk factors, diabetes, and cardiovascular diseases specially in south Asian population.

COMMENTS

Background

Cytokines are implicated for causing lipid derangement and insulin resistance. Furthermore, polymorphisms in the interleukin-18 (*IL-18*) genes influences expression levels and may increase the risk of metabolic syndrome (MetS).

Research frontiers

The authors' results clearly show that IL-18 can be used a marker for obesity and supports the hypothesis that IL-18 polymorphism may be involved in pathway of MetS and form a link between metabolic risk factors, diabetes, and cardiovascular diseases specially in south Asian population. This can lead to precision treatments to reduce the burden of obesity.

Innovations and breakthroughs

The literature suggests a mixed role of *IL-18* gene polymorphisms in MetS or diabetes. However, the present study suggests a new role promter gene polymorphisms in modulating MetS phenotypes.

Applications

The authors' study provides a preliminary report of association of IL-18 levels and its polymorphism though at this stage no therapeutic role can be elucidated.

Terminology

MetS: It is a cluster of conditions such as diabetes, hypertension, increased waist circumference and lipid levels in in individual; Polymorphism: The presence of genetic variation within a population.

Peer-review

Preliminary results of this work are very interesting.

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