Elevated Serum Levels of Pro-inflammatory Markers are Associated with Glucose Intolerance in Metabolic Syndrome Patients from Jordan

Amal A. Akour[*1], *Violet N. Kasabri*[1], *Nailya Y. Bulatova*[1], *Yasser Bustanji*[1], *Munther Momani*[2], *Ayman Zayed*[2], *Mais Al-Nuoaimi*[1], *Hiba Fahmawi*[1], *Rula Al-Selawi*[1]

Abstract

Objective: Metabolic syndrome (MetS) is tightly associated with cardiovascular atherosclerosis development and diabetes. However, the association between these markers and glucose intolerance and other clinical parameters in Jordanian MetS patient is not clear. Therefore, the objective of this study was to evaluate the potential association of atherosclerotic/metabolic inflammatory markers in Jordanian MetS patients with their glucose tolerance and other clinical parameters.

Methods: A total of 190 MetS obese or overweight subjects (men = 61, women = 129) were enrolled. ELISA assays of plasma hs-CRP, MCP-1, PAI-1, MMP-9, resistin, adiponectin, leptin, MIF, TNF-α, TSP-1, IL-10, and IL-6 were performed.

Results: It was found that hs-CRP and TNF-α were significantly and positively correlated with HbA1c (r=0.274; and 0.406; p<0.0001)and FPG (r=0.272; p<0.0001 and r= 0.163; p<0.05) , while IL-10 was negatively correlated with HbA1c (r=-0.264; p<0.001). MIF positively correlated with FPG (r=0.207; p<0.001), and along with TSP-1(r=0.580; p<0.0001), it was linked positively to insulin resistance as measured by HOMA-IR (r=0.252; p<0.001).

Conclusions: This study showed that most of proinflammatory markers have direct association with indicators of glucose tolerance parameters, namely, FPG and HbA1c. Therefore, these markers can be used as indicators for glucose intolerance and disease progression in patients with metabolic syndrome.

Keywords: Metabolic Syndrome, Inflammatory markers, Glucose intolerance.

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Introduction

The escalating increase in metabolic syndrome (henceforth MetS) prevalence globally is alarming[(1)] The mainstay of MetS is the interplay of insulin resistance, visceral adiposity, atherogenic dyslipidemia, endothelial dysfunction, genetic susceptibility, as well as elevated blood pressure[(2).] The proinflammation in association with visceral

1. Department of Biopharmaceutics and Clinical Pharmacy, School of Pharmacy, The University of Jordan, Amman, Jordan.
2. Endocrinology and Diabetes Unit, Jordan University Hospital and School of Medicine, The University of Jordan, Amman, Jordan.
*** *Correspondence should be addressed to:***
Amal A. Akour
School of Pharmacy (Office 324), The University of Jordan E-mail: h.hawari@ju.edu.jo
Queen Rania Street, Amman 11942, Jordan.
E-mails: amalakour@gmail.com; a.akour@ju.edu.jo

obesity and insulin resistance inevitably leads to the substantial adipocytokines production such as tumor necrosis factor α (TNF-α), interleukin-6 (IL-6), leptin, and adiponectin. Crucially MetS is a progressive condition encompassing detectable abnormalities via serum biomarkers; including adipokines (leptin, adiponectin), proinflammatory cytokines (IL-6, TNF-α), antiinflammtory cytokines, interleukin-10(IL-10) and prothrombotic factors, Plasminogen Activator Inhibitor-1 (PAI-1). Importantly the concentrations of pro-inflammatory cytokines (IL-6, TNF-α), and prothrombic factors (PAI-1) were elevated in MetS but leptin concentrations were found to be elevated likely due to leptin resistance. In contrast, concentrations of anti-inflammatory cytokines (IL-10), and adiponectin were decreased in MetS, and these decreases also correlated with specific disorders within the MetS cluster [(2)]. Furthermore, where plasminogen activator inhibitor-1 (PAI-1), leptin and adiponectin were promoted as markers to predict MetS among adolescents[(3)]; Lower circulating levels of leptin and PAI-1, but not adiponectin or resistin, were significantly associated within a working population's Westernized dietary patterns[(4)]. Noticeably adiponectin and TNF- α reciprocally inhibit production of each other in adipose tissue [(5)] Thus, serum high sensitivity C-reactive protein (hs-CRP) concentrations were decreased whereas adiponectin levels increased significantly, among the beneficial effects of weight loss in MetS patients[(6-8)]. CRP and fibrinogen[(9-10)], resistin, nisfatin, and insulin like growth factors (IGF)[(11-12)] are also validated as metabolic prognostic and predictive biomarkers in metabolic syndrome related complications and disturbances.

Considering the MetS biochemical background, its clinical significance and anthropometric profile; these factors can be interrelated to each other and act in a concerted, antagonistic, synergistic or modulating way [(13-14)]. While multiple interventional studies accentuated the associations of MetS-related inflammatory and oxidative status with its biochemical derangements [(15-16);] scarcity of reports could principally underpin the correlations between MetS clinical features with inflammatory markers as prognostic indicators. Thus we aimed to investigate the potential correlations between MetS clinical and biochemical profile and these markers in a cross-sectional study, hence, providing a minimally-invasive means for early detection and specific treatment MetS. This can surely determine the efficacy of applying these biomarkers to diagnosis and treatment in a clinical setting. Subsequently prospective studies can be suggestively undertaken to establish causality and the effectiveness of pharmacological and non-pharmacological interventions in improving – or even better preventing- MetS and its complications.

Materials and Methods

Settings and Subjects

Approval for the study was obtained from the Clinical IRB (Institutional Review Board) Committees affiliated with the Jordan University Hospital (JUH) (18/2014/IRB) and National Center for Diabetes, Endocrinology, and Genetics (NCDEG) (1151, 1152, 1153/9/SM).

Informed written consent was obtained from each participant. All participants who attended the Diabetology and Endocrinology and Nutrition outpatient clinics at JUH and

NCDEG for the first time were screened for potential recruitment. Adult patients (> 18 year-old), either overweight (BMI ≥ 25 kg/m^2) or obese (BMI ≥ 30 kg/m^2), were included if they met at least 3 of these 5 metabolic syndrome criteria, as defined by the ATP III [17]: (1) Abdominal white adipose tissue (WAT) accumulation, waist circumference > 35 inches (85 cm) in women and > 40 inches (100 cm) in men; (2) Blood pressure (BP) > 130/85 mmHg; (3) Triglycerides (TG) > 150 mg/dL; (4) High density lipoprotein cholesterol (HDL-C) < 40 mg/dL in men or < 50 mg/dL in women, and (5) Fasting plasma glucose levels > 100 mg/dL.

All patients were newly diagnosed and did not receive any treatment including oral antidiabetic, hypolipidemic, and/or antihypertensive agents. In this study, subjects with: (1) acute complications of diabetes; (2) secondary obesity; (3) acute and chronic inflammatory diseases; (4) systemic corticosteroid treatments; (5) renal dysfunction; (6) hepatic dysfunction; or (7) women who were currently pregnant, breast feeding or taking contraceptive pills were excluded altogether.

Clinical and Biochemical Evaluation

Height and weight were measured with standardized techniques. BMI was expressed as weight per height squared (kg/m^2). Serum creatinine was obtained from the patient's data file and glomerular filtration rate (GFR) was calculated by Cockcroft-Gault equation ([(140-Age in years) * Mass (in kg)]/ [72 * Serum creatinine (in mg/dL)]). If the patient was female, multiply the above by 0.85 [18-19]. Participants were told to avoid stressful activities (sports, physical exercise) prior to blood sampling. Blood samples were drawn after a 10-hour overnight fast and put into lithium heparin for subsequent centrifugation and -80^{o}C storage until thawed immediately before plasma biomarker and hormonal analyses. The lipid TC, TGs, HDL-C, LDL-C concentrations were measured by appropriate enzymatic assays (Beckman® Coulter Inc., USA). Fasting blood glucose was determined by glucose oxidase-based assay and HbA1c was determined by turbidimetric inhibition immunoassay (COBAS C, Roche® Diagnostics GmbH Mannheim, Germany). Insulin sensitivity was assessed by homeostasis model assessment insulin resistance index (HOMA-IR) using the following equation:

[Fasting insulin (mIU/L) x Fasting glucose (mg/dL)]/ 405

Commercially available human Enzyme-linked Immunosorbent Assay (ELISA) assays of plasma insulin, leptin, macrophage chemo-attractant protein-1 (MCP-1) (Abcam®, UK), adiponectin, IL-6, IL-10, matrix metalloproteinase-9 (MMP-9), PAI-1, TNF-α, (eBioscience®, USA), hs-CRP (AccuBind®, USA), thrompospondin-1 (TSP-1), macrophage migration inhibitory factor (MIF) (AssayBiotech®, USA) and resistin (RayBiotech®, USA) were performed according to manufacturers' instructions. The leptin-to-adiponection-ratio (LAR) was calculated by dividing leptin levels by adiponectin ones.

Statistical Analysis

Anthropomorphic data, clinical data, and inflammatory biomarkers were described as mean and standard deviation or median and interquartile range, as appropriate. Pearson or Spearman correlation was used to correlate markers' levels with HbA1c, fasting plasma glucose, lipids, insulin, and inflammatory markers.

Results

I. Descriptive

All patients were Caucasians, the majority were females (68%), and the mean age was (51.2 ± 10.5) years. Almost half of patients were obese (48.8%), while the rest were either morbidLy obese with BMI ≥35 kg/m^2 (29.4%) or overweight (19.4%). Mean body mass index (BMI) was (33.3 ± 5.3) kg/m^2. Table 1 describes the population in term of their clinical parameters and levels of inflammatory markers.

II. The correlation between inflammatory markers and clinical parameters

The correlation between inflammatory markers levels and clinical parameters is illustrated in Table 2. Leptin positively correlated with BMI and waist circumference. Hs-CRP positively correlated with BMI, HbA1c and FPG. MMP-9 positively correlated with BMI, SBP, DBP, HbA1c and FPG. PAI-1 correlated with DBP, waist circumference, HbA1c, FPG and fasting insulin positively. TSP-1 positively correlated with DBP, HbA1c, and HOMA-IR. MCP-1 positively correlated with HbA1c, FPG, and HDL-C. TNF-α correlated with GFR, HDL-C, HbA1c and FPG positively. Resistin correlated with age, GFR, HbA1c and FPG positively. MIF positively correlated with FPG and HOMA-IR. Surprisingly, adiponectin positively correlated with SBP, HDL-C, and HbA1c. None of TC, LDL-C and TGs correlated to any of the inflammatory markers. Finally, LAR positively correlated with both HbA1c and FPG.

III. The correlation among inflammatory markers

The correlation among plasma inflammatory markers was also assessed (Table 3). hsCRP, PAI-1, MMP-9, resistin, adiponectin, leptin and TNF-α were positively and significantly correlated with all *other* markers with the exception of MCP-1 and IL-6, where a significant negative correlation was observed. MCP-1 had significant, though negative, correlations with all markers except IL-6. TSP-1 was not correlated to hsCRP, negatively correlated with IL-6, yet, significantly and positively correlated with all other markers. MIF was positively correlated with MMP-9 and TSP-1.

Discussion

MetS disorder is tightly associated with cardiovascular atherosclerosis development and diabetes. The objective of this study was to evaluate the potential association of atherosclerotic/metabolic inflammatory markers in MetS patients with their glucose tolerance and other clinical parameters. We demonstrated that hs-CRP and TNF-α were significantly correlated with HbA1c and FPG, while IL-10 was negatively correlated with HbA1c. MIF positively correlated with FPG and HOMA-IR. TNF-α correlated with GFR and HDL-C negatively. A previous study by Ghnaim et al.[20], showed a positive correlation between both hsCRP, and MIF levels with HOMA-IR. BMI significantly correlated with hsCRP but not with MIF. Here, there was no significant correlation between either marker or BMI, mostly due to differences in Ghnaim et al., [20] studied population vs. ours. Ghnaim et al. [20] compared levels of MIF and hsCRP in obese and lean patients, while _as shown in results section_ the majority of our population were obese. Haffner et al.[21] showed that Ln CRP levels were significantly and negatively correlated with Age; and like our study positively and significantly correlated with BMI, FPG and HbA1c. Except for TGs, neither LDL-C nor HDL-C was significantly correlated

with Ln CRP. Unlike results from our study where IL-6 was not significantly correlated with any parameter, Ln IL-6 was positively correlated with Age, BMI and HOMA-IR. While Ln MMP-9 was positively correlated with BMI, Ln LDL-C, and Ln TG according to Haffner et al. [21], we showed that it is positively correlated with SBP, DBP, BMI, waist circumference, FPG and HbA1c. Van Exel et al.[22] found an association between low IL-10 production capacity (a pro-inflammatory response) and total cholesterol, LDL-C, TGs, high serum glucose, high HbA1c. The later comes in harmony with our finding of a negative correlation of IL-10 levels and HbA1c. Unexpectedly, MCP-1 levels in our study correlated significantly and negatively with FPG and HbA1c, and positively with HDL-C. MCP-1 has been found to be significantly increased in patients with type 2 diabetes [23] which contrasts with our findings.

In a clinical study by Lim *et a*l. [24], 450 chronic kidney disease (CKD) cases versus 920 controls matched for age, gender and ethnicity were enrolled. HbA1c was significantly higher in case group (6.6 ± 1.3%) than in control group (6.3 ± 1.1%). Also, FPG was higher in case group (140.4 ± 72) mg/dL than in control group (124.2 ± 55.8) mg/dL (p<0.0001). Adipocytokines biomarkers (leptin and adiponectin) were notably comparable to our study where both leptin and adiponectin were positively correlated with both FPG and HbA1c, while LAR was positively correlated with both HbA1c and FPG. Moreover, leptin was found to be positively correlated with BMI, IR, TG, LDL, SBP and DBP while it was negatively correlated with HDL in case group of patients[24]. Adiponectin levels positively correlated to BMI and waist circumference[25]. Our study showed the positive correlation of adiponectin with each of SBP, HbA1c and FPG. Adiponectin correlated inversely with HDL. Leptin correlated directly with BMI and waist circumference. LAR had a direct relationship with FPG and HbA_1c. Collectively, these outcomes provide an augmenting evidence of adiponectin effect on cardiovascular diseases, atherosclerotic disorders and sugar profile disturbances in MetS patients. Overall, research suggested the beneficial effect of adiponectin in metabolic diseases and atherosclerosis, but some reports are less consistent. This may arise from differences between studies such as population variations, confounding factors and different isoforms of adiponectin (total vs. the high molecular weight form)[26]. Obviously adiponectin levels were consistently reported to decrease in diabetic MetS patients. Conversely our findings, in line with those of Aleidi et al.[27] showed the incremental increase in biomarker profile in association with MetS-related pre/diabetes. Principally as the inflammatory and immune biomarker profile varies notably with the development and progression of MetS[28] the shifts in biomarker profile collectively complement, rather than contradict, each other.

According to Varma et al.[29], TSP-1 was highly correlated with adipose inflammation; and is decreased by pioglitazone. TSP-1 is an important link between adipocytes and macrophagedriven adipose tissue inflammation and may mediate the elevation of PAI-1 that promotes a prothrombotic state. Similarly, our study showed that TSP-1 was positively correlated with DBP, FPG and HbA1c. While, in Coffey et al.[30], PAI-1 antigen levels were substantially associated with MetS BMI and insulin levels but not with either CRP or

urinary albumin excretion; we could present obviously that PAI-1 is positively correlated with DBP, waist circumference, FPG, HbA1c, and negatively correlated with fasting insulin.

Our study is *the first clinical study* to evaluate the relationship between inflammatory markers, glucose tolerance and clinical parameters in *Jordanian* metabolic syndrome patients. Patients were recruited from two large referral medical centers in Jordan which ensures the inclusion of enough number of patients and a fairly representative sample of Jordanian population. Still, we cannot say with confidence that the results are generalizable, due to lack of statistics about prevalence of metabolic syndrome in Jordanian population. Due to its cross-sectional nature, a causative relationship among levels of inflammatory markers themselves along with clinical parameters cannot be withdrawn.

Conclusion

In conclusion, this study showed that most of inflammatory markers are significantly and positively correlated with indicators of glycemic tolerance parameters, namely, FPG and HbA1c. Insulin resistance was positively correlated with TSP-1 and MIF. Waist circumference was positively correlated with PAI-1, MMP-9 and leptin. Therefore, these markers can be used as indicators for glucose intolerance and disease progression in patients with metabolic syndrome.

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إرتفاع مستويات العلامات ما قبل الالتهابية في المرضى الأردنيين الذين يعانون من خلل في الجلوكوز ومتلازمة التمثيل الأيضي

أمل عكور[*1]، فيوليت كسابري[1]، نائلة بولاتوفا[1]، ياسر بستنجي[1]، منذر مومني[2]، أيمن زايد[2]، ميس ناعومي[1]، هبة فحماوي[1]، رلى السيلاوي[1]

1- قسم الصيدلة الحيوية والصيدلة السريرية، كلية الصيدلة، الجامعة الأردنية، عمان، الأردن.

2- وحدة السكري والغدد الصماء، مستشفى الجامعة الأردنية، عمان، الأردن.

الملخص

الهدف: متلازمة الأيض ترتبط بشكل وثيق مع تصلب شرايين القلب والأوعية الدموية والسكري. ومع ذلك، فإن العلاقة مستويات العلامات ما قبل الالتهابية في المرضى الذين يعانون من خلل في الجلوكوز ومتلازمة الأيض الأردنيين ليست واضحة. لذلك، كان الهدف من هذه الدراسة هو تقييم الارتباط المحتمل من علامات التهابات الأيض/ تصلب الشرايين لدى مرضى متلازمة الأيض الأردنيين الذين يعانون من خلل في تحمل الجلوكوز والعلامات السريرية الأخرى.

الطرق: تم التحاق ما مجموعه 190 من مرضى متلازمة الأيض ممن يتسمون بالبدانة أو زيادة الوزن (الرجال = 61 والنساء = 129).

ثم أجريت قياسات العلامات ما قبل الالتهابية التالي بطريقة ELISA: (Hs-CRP)، MCP-1، PAI-1، MMP-9، رزيستين، اديبونيكتين، اللبتين، MIF، TNF-α, TSP-1, IL-10, and IL-6.

النتائج: تبين أن Hs-CRP وTNF-α مرتبطين بشكل طردي مع نسبة HbA1c (r = 0.274؛ و0.406؛ p <0.0001) وFPG (r = 0.272؛ p <0.0001 وr = 0.163؛ p <0.05)، في حين كان IL-10 يتناسب عكسيا مع نسبة HbA1c (r = −0.264؛ p <0.001). أما MIF يتناسب طرديا مع FPG (r = 0.207؛ p <0.001)، وجنبا إلى جنب مع TSP-1 (r = 0.580؛ p <0.0001)، الذي ارتبط أيضا ارتباط طردي مع مقاومة الأنسولين (r = 0.252؛ p <0.001).

الاستنتاجات: أظهرت هذه الدراسة أن معظم العلامات ما قبل الالتهابية لها ارتباط مباشر مع مؤشرات علامات أيض الجلوكوز، وهي FPG ونسبة HbA1c. لذلك، هذه العلامات يمكن أن تستخدم كمؤشرات لحساسية الجلوكوز وتطور المرض في المرضى الذين يعانون من متلازمة التمثيل الأيضي.

الكلمات الدالة: متلازمة التمثيل الأيضي، العلامات ما قبل الالتهابية، حساسية الجلوكوز.