RESEARCH ARTICLE

The potential effects of metformin and/or sitagliptin on leptin/adiponectin ratio in diabetic obese patients: a new therapeutic effect

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Abstract

Objective: To explore how metformin, alone or in conjunction with sitagliptin, affects the leptin/adiponectin ratio in obese type 2 diabetes mellitus patients.

Method: The case-control study was conducted from March to August 2021 at the Department of Clinical Pharmacology, College of Medicine, Mustansiriyah University, Baghdad, Iraq, and comprised adult, obese type 2 diabetes mellitus patients of either gender and age-matched healthy controls. The MT group included patients taking metformin 1g/day, MTS group had patients taking metformin 1g/day plus sitagliptin 100mg/day, and the control group comprised healthy subjects. Serum levels of human leptin and adiponectin were recorded along with body mass index, blood pressure, lipid profile and glycaemic indices. Data was analysed using SPSS 20.

Results: Of the 90 subjects, 62(69%) were patients; 36(40%) in MT group and 26(29%) in MTS. The control group had 28(31%) individuals. The mean age of the patient groups was 48.62±8.17 years, and male: female ratio was 49:41, mean age of controls was 47.64± 5.77 years with the same male to female ratio as that of the patients. Leptin levels were higher in patients compared to controls (p=0.002), and leptin levels were lower in MTS (89.93±9.51) than MT group (93.69±13.69). Patients in MT (30.57±6.31) and MTS (32.99±7.10) groups had lower adiponectin levels than controls (48.83±9.21) (p=0.001). MT and MTS patients had a greater leptin-to-adiponectin ratio than controls (p=0.0001).

Conclusion: Leptin-to-adiponectin ratio could be a viable marker for assessing risks related to type 2 diabetes mellitus and other health conditions.

Key Words: Leptin, Adiponectin, Diabetes, Blood Pressure, Obesity, Metformin, Lipids, Sitagliptin Phosphate

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Introduction

Adipocytokines are bioactive proteins and hormones produced by the adipose tissue, such as leptin and adiponectin, as well as inflammatory mediators. Adipocytokines are also produced by immune cells implanted in the adipose tissue, such as macrophages, monocytes and endothelial cells.[1] Obesity is linked to chronic inflammatory reactions that are characterised by irregular adipokine production and activation of certain pro-inflammatory cytokines, all of which trigger a number of inflammatory and biological markers. Obesity is associated with increased fat cell mass that secrets substances that cause low-grade inflammation.[2] Obesity also increases macrophage and other immune cell infiltration in the adipose tissue, which drives chronic low-grade inflammation through altered adpokine synthesis. This has been suggested to be a pathogenic link between insulin resistance (IR) and obesity.[1,2]

IR and cellular dysfunction are both signs of type 2 diabetes mellitus (T2DM). The development of IR in T2DM is influenced by a number of genetic, environmental and host-related variables.[3] By increasing the transcription nuclear factor-kappa B (NF-kB) and stress-activated Jun-N (JUN) terminal kinase inflammatory pathways in peripheral tissues, cytokines disrupt insulin signalling, leading to IR.[4,5]

Adiponectin is a collagen-like protein found in the adipose tissue. In healthy humans, it makes up 0.01% of the circulating proteins in plasma, with levels ranging 5-30mg/ml. It is the only adipose-specific protein that is linked to obesity, heart disease and diabetes.[6] It increases nitric oxide (NO) production, accelerates fatty acid oxidation via AdipoR1 and AdipoR2 receptors, which, in turn, activates 5' adenosine monophosphate (AMP)-activated protein kinase (AMPK)and peroxisome proliferator-activated receptor (PPAR), which regulates cellular malonyl-coenzyme A (CoA) levels through regulation of mitochondrial acetyl CoA carboxylase (ACC) enzyme, and thus reduces the apoptotic effect of free fatty acids (FFAs) on cells.[7]

Leptin is an anorexigenic hormone that is structurally connected to cytokines and is produced by adipocytes. It regulates hunger and energy expenditure by conveying

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nutritional status to the hypothalamus via neurotransmitters and neuropeptides.[6,7] Leptin deficiency leads to increased food intake, IR and obesity. Adiposity, on the other hand, reduces leptin sensitivity, diminishing leptin's appetite suppressant effect and leading to leptin resistance, which is caused by diminished leptin sensitivity in the brain melanocortin circuit.[6,7]

Notably, the leptin-adiponectin ratio (LAR) predicts IR and metabolic syndrome better than adiponectin or leptin alone.[7] Metformin is a commonly prescribed hypoglycaemic medicine that improves insulin sensitivity in the hepatic and peripheral tissues, lowering or even preventing T2DM, especially when combined with lifestyle changes. Sitagliptin is a dipeptidyl peptidase-4 inhibitor that increases insulin secretion and has been demonstrated in T2DM patients to reduce oxidative stress (OS), inflammation and cell death.[8,9]

Studies have highlighted the differential effects of metformin and sitagliptin on adipocytokines in different metabolic disorders, including T2DM.[4,10]

The current study was planned to explore how metformin, alone or in conjunction with sitagliptin, affects LAR in obese T2DM patients.

Patients and Methods

The case-control study was conducted at the Department of Clinical Pharmacology, College of Medicine, Mustansiriyah University, Bagdad, Iraq, from March to August 2021. After approval from the institutional ethics review committee, the sample size was calculated using the Andrew Fisher formula:[11]

Sample size = (z-score)^2 * Std Dev (1-Std Dev)+(confidence interval)^2

Those included were adult, obese T2DM patients of either gender and age-matched healthy controls according to randomized sampling technique. The MT group included patients taking metformin 1g/day, MTS group had patients taking metformin 1g/day plus sitagliptin 100mg/day, and the control group comprised healthy subjects.

Patients with T1DM, those on other antidiabetic agents, those having renal disease, chronic liver disease, thyroid disease, or cardiac disease, as well as pregnant or breastfeeding women were excluded.

Data was collected after taking written informed consent from the participants. Body mass index (BMI) was computed after taking weight and height measurements using the standard equation.[12,13]

The waist: hip ratio (WHR) was estimated on the basis of waist and hip measurements. Mean arterial pressure (MAP) and pulse pressure (PP) were calculated using digital sphygmomanometer and equations mentioned in literature.[14]

Blood samples 5mL were taken from each subject and placed in a gel tube before being centrifuged at 3000 rpm and frozen at -20°C for lipid profile analysis, including triglycerides (TGs), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL) and very low density lipoprotein (VLDL) in Architect C4000 using an instant cholesterol kit (Abbott, A.S.A- Germany), where applicable, on the basis of formulas defined in literature.[14]

Using Architect C4000, fasting blood glucose (FBG) was tested with an instant kit (Abbott, Glucose, Germany), and glycated haemoglobin (HbA1c) was assessed using an enzyme0linked immunosorbent assay (ELISA) kit (Kono Biotech, China). Insulin levels were measured using an immediate insulin ELISA kit (My BioSource, United States), and Homeostatic model assessment for insulin resistance (HOMA-IR) was calculated as per literature.[14]

Adiponectin and leptin were quantified in a sandwich approach using an ELISA kit (My BioSource, US). Log TG/HDL value was used to calculate the atherogenic index of plasma (AIP) and cardiovascular risk index (CVRI), while TC/HDL value was used for the cardiac risk ratio (CRR).[14]

Data was analysed using SPSS 20. Unpaired student t-test was used to compare the control and treatment groups, and one-way analysis of variance (ANOVA) with a post-hoc test was used to examine the significance of differences between the groups. $P<0.05$ was considered significant.

Results

Of the 90 subjects, 62(69%) were patients; 36(40%) in MT group and 26(29%) in MTS. The control group had 28(31%) individuals. The mean age of the patient groups was 48.62±8.17 years, and male: female ratio was 49:41, mean age of controls was 47.64± 5.77 years with the same male to female ratio as that of the patients. There were 26(41.93%) smokers, dyslipidaemia was found in 17(27.41%), hypertension in 10(16.12%), and ischaemic heart disease in 3(4.83%). Besides, 27(43.54%) T2DM patients had a positive family history.

MT and MTS patients had a higher BMI compared to the controls (p=0.01). WHR was higher in patients compared to controls (p=0.05), and it was also higher in the MT

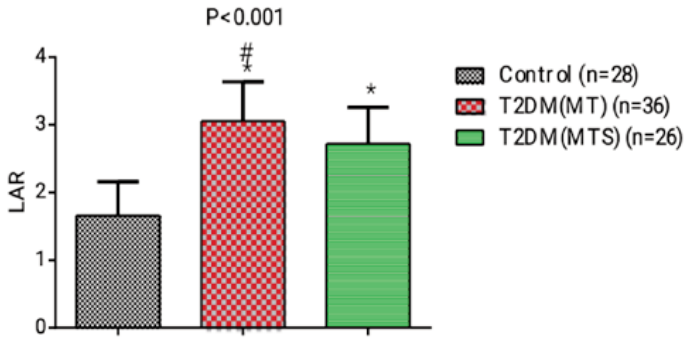

Figure-1: Leptin-adiponectin ratio (LAR.
*P <0.05 compared to control group
#P<0.05 compared to the MTS group
MT: Metformin, MTS: Metformin plus sitagliptin

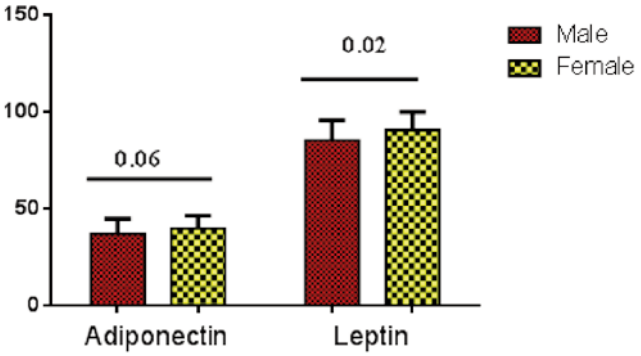

Figure-2: Gender distribution related to adiponectin and leptin serum levels in diabetic patients.

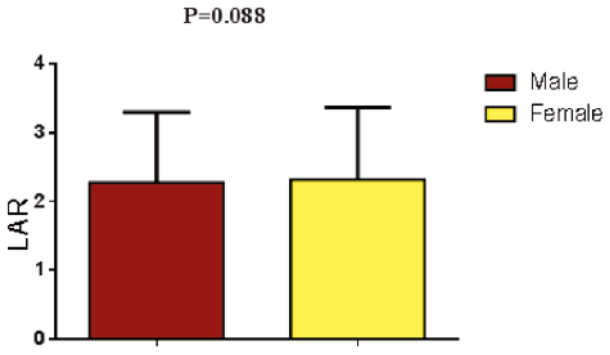

Figure-3: Gender differences related to leptin-adiponectin ratio (LAR) in diabetic patients.

group (0.93±0.03) than MTS group (0.90±0.03) (p=0.05). T2DM patients had higher BP profile than controls (p=0.05), but only systolic BP (SBP) and diastolic BP (DBP) values were higher (p=0.03) in the MT group. Both T2DM groups had increased lipid profiles compared to controls (p=0.0001). MT patients had greater TC, TG, LDL and VLDL, but not HDL (p=0.03) than MTS patients. T2DM patients showed higher AIP than controls (p=0.01), and MT group (0.391±0.05) which had a higher AIP than MTS group (0.238±0.03) (p=0.02). The patients had higher CRR and CVRI than controls (p=0.03, p=0.04, respectively), as well as lower T2DM MTS compared to MT group (p=0.04).

There were no significant differences between MT and MTS groups (p>0.05) with respect to glycaemic indices, while fasting serum insulin (FSI) was higher in MT group than MTS group (p=0.02). HOMA-IR was higher in patients than the controls (p=0.001), but it was lower in MTS group compared to MT group (p=0.02). MTS group had better HOMA and insulin sensitivity than MT group (p<0.05), but HOMA in MTS group did not differ significantly from the control group (p=0.06).

MT (30.57±6.31) and MTS (32.99±7.10) patients had lower adiponectin serum levels than controls (48.83±9.21) (p=0.001). The patients had greater leptin levels than controls (p=0.002), but no significant difference in current diabetic treatment was seen (p>0.05). T2DM patients had a greater LAR than controls (p=0.0001). LAR in MT group was 3.06±0.58, in MTS group it was 2.72±0.54, and it was 1.66 ±0.50. LAR in MTS differed significantly from MT (p=0.04) (Figure 1).

In terms of leptin and adiponectin serum levels, female T2DM patients had higher levels (39.75±6.52) than males (36.82±7.33), but the difference was not significant (p=0.06). Female T2DM patients showed a statistically significant higher leptin serum level (90.67±9.52) than male patients (85.441±0.42), and the females had a higher LAR (2.32±1.05) than the males (2.28±1.02) (Figures 2,3).

Discussion

Because it correlates with IR and central obesity, improves lipid profile and insulin sensitivity, and has anti-inflammatory and cardioprotective qualities, adiponectin has been recommended as a predictor of favourable cardiac and metabolic outcomes.[6] Low adiponectin serum levels have been connected to cardiometabolic disorders, and in the current study, it was found to be inversely correlated with HbA1c and HOMA-IR, which was in line with previous recommendations, since adiponectin levels are dropped following IR, metabolic syndrome and T2DM.[12] The metformin group had lower adiponectin serum levels than the metformin plus sitagliptin group in the current study. During a six-month period of daily metformin treatment, previous research indicated that metformin monotherapy induced elevation of adiponectin gene expression, as well as weight-loss and anti-inflammatory properties.[14] Compared to metformin alone, a combination of metformin plus sitagliptin was connected to a significant increase in adiponectin levels. Liu et al. discovered that sitagliptin increased adiponectin

serum levels by lowering OS, and that increased glucagon-like peptide 1 (GLP-1) production and AMPK pathway activation is a promoter for higher adiponectin secretion.[15] Females showed higher adiponectin levels than males in the current study, which was consistent with previous findings. Because androgen hormone lowers adiponectin production, while oestrogen has no effect, Day et al. discovered comparable results as a result of the action of sex hormones on adiponectin expression.[16]

Leptin is a protein that controls appetite, weight and energy expenditure. It is also linked to IR and a high BMI, and a lack of it makes one more likely to develop obesity and metabolic syndrome. In this study, the amount of leptin was found to be higher in T2DM patients than in healthy controls. Greater leptin levels have been linked to obesity, and HOMA-IR, HbA1c, and the development of T2DM.[17]

Significant changes in serum leptin were identified in metformin monotherapy participants in the current investigation. Metformin upregulates leptin receptors in the liver and peripheral tissues via stimulation of the AMPK pathway, enhances hepatic lipid oxidation by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, and so points to metformin as a novel treatment for leptin insensitivity.[18] Leptin levels were substantially lower in the sitagliptin group, which was consistent with previous studies, as it promotes weight-loss and lowers both BMI and visceral fat.[18] Female patients also had considerably higher amounts of leptin, which was consistent with a previous study that demonstrated a link between sex hormone-binding globulin and leptin.[19]

As a result, the female group had a higher LAR, which is a helpful indicator for dysfunctional adipose tissue. Chronic inflammatory indicators have an inverse connection with it as well.[20] The negative association between leptin and adiponectin has been demonstrated in several substantial studies, and it is regarded to be a critical pathogenic link between obesity and metabolic disorders.[19,20]

As a result, LAR changes are more strongly linked to total fat and BMI than changes in individual adiponectin and leptin levels. LAR also had a larger connection with IR and the HOMA index than either leptin or adiponectin alone.[21]

The significance of LAR as a novel marker for assessing cardiovascular disease, chronic renal disease, T2DM and metabolic syndrome has been highlighted in studies.[19,20] Despite this, diabetic individuals on metformin plus sitagliptin had lower LAR than diabetic patients on metformin alone, probably due to sitagliptin's potential effect on leptin reduction and adiponectin gene activation.[22-26]

Conclusion

LAR was higher in female T2DM patients than control subjects, and was favourably associated with HOMA-IR when compared to metformin alone. However, it was lower in diabetic patients on metformin + sitagliptin. LAR may be a new biomarker for cardiovascular disease, T2DFM and metabolic syndrome.

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