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Renin-angiotensin System Blocking Antihypertensive Therapy Effect on Surrogate Glycemic and Lipid Markers in Metabolic Syndrome Patients

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Abstract

BACKGROUND: Metabolic syndrome (MetS) is a constellation of metabolic disorders, that together, aggravate the cardiovascular, and atherosclerotic risks. ACE inhibitors class, used for managing hypertension in MetS, induces favorable effects on glycemic control and insulin action on tissues as well as reducing all-cause mortality in HT patients. However, exploring changes associated with ACEI use and the exact impact of ACE inhibitors in hypertensive MetS patients on surrogate lipid and glycemic markers has not been reported in previous research extensively, if any.

AIM: The aim of the study was to assess metabolic impact of ACE inhibition in MetS patients in terms of surrogate glucose-, insulin-, and lipid fraction-based markers.

METHODS: A case–control study involving subjects diagnosed with MetS was conducted. Two study groups were involved: Hypertensive MetS patients maintained on Enalapril (n = 27), and normotensive control patients (n = 24). Triglyceride and glucose index (TyG index), triglyceride glucose-body mass index (TyG-BMI), serum insulin by TG (InsuTAG), atherogenic index of plasma (AIP), Castelli risk index-I (CRI-I) and -II (CRI-II), were calculated.

RESULTS: Compared to controls, InsuTAG and TyG index were non-significantly different, AIP was significantly lower, TyG-BMI was significantly higher and CRI-I was significantly lower while CRI- II was non-significantly higher, in the treatment group.

CONCLUSION: Despite controversy and scarcity of evidence in the literature, benefits of using enalapril on important components of MetS, indirectly assessed by surrogate markers, were shown in the current study and using ACE inhibitor in hypertensive MetS patients probably minimized metabolic and cardiovascular risk.

Introduction

Metabolic syndrome (MetS) is a constellation of metabolic anomalies that encompasses arterial hypertension, central obesity, impaired sensitivity to insulin, and a range of dyslipidemias. Taken together, these factors entail an enhanced risk for atherosclerotic, cardiovascular (CV) incidents [1] as well as type 2 diabetes mellitus (T2DM) [2]. Each of the syndrome's pathophysiologic elements constitutes a known CV disease risk factor *per se*, but when clustered together, the risk of CV incidents increases dramatically [3]; hence, management becomes essential.

The diagnostic criteria (and thus the definition) of MetS have been modified several times over the past decades by expert panels, the earliest definition was put forward by the World Health Organization (WHO) (1999); later, other definitions, of National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) (2002), modified NCEP-ATP III [4], [5], [6] and International Diabetes Federation (IDF) (2005), were proposed. The most recent diagnostic criteria, Joint Interim Statement on MetS (JIS) [7], were issued jointly by several major medical and health organizations. MetS, as defined by any of these different criteria, is a major atherosclerotic CV risk factor [8], thus requiring management. The global prevalence of MetS was estimated to be one quarter of the entire population of the world, that is, more than a billion may be affected [9]. The MetS prevalence worldwide varies widely based on gender, age, and ethnicity [10]; the prevalence also varies with different definitions [11].

Obesity and specifically central obesity is a major pathophysiological factor in MetS [3]. Elevated blood pressure (BP) is a key feature in MetS, with a reported incidence of over 30% of the latter in HT patients [12], [13]. Resistance to insulin, a major pathophysiologic factor in MetS, is a major cause for co-existing (HT) [14]. Renin-angiotensin system (RAS) is a major player in BP regulation; and several components of the system are extensively expressed in human adipose tissue [15]; furthermore, production of angiotensin II (Ang II) and angiotensinogen is enhanced in obese patients. Activation of RAS is etiologically linked to HT and MetS (especially its hypertensive component) [14], [16], making it a prime target for management approaches.

Intensive and strict BP control in MetS patients may prevent future CV events. Asymptomatic damage to organs linked to HT was shown in MetS patients with concurrent HT [17], this indicates importance of controlling HT, especially given the high prevalence of MetS in patients with HT. Guidelines are still ambiguous regarding managing MetS patients with mild to moderate HT [18]. Antagonists of RAS, inhibiting either the angiotensin converting enzyme (ACE) or Ang II receptors, are widely employed for HT management, in addition to reducing its mortality [19]. Such drugs have recently been put forward for their potential to improve insulin sensitivity (IS) or alleviate obesity [16]. This class induces favorable effects on glycemic control and insulin action on tissues [20] as well as reducing all-cause mortality in HT patients [19], Thus, ACE inhibitors (ACEIs) are considered drugs of choice in MetS patients.

The variability in MetS criteria probably affects the ability to diagnose and interpret the condition accurately [21]. In addition, whether insensitivity to insulin or obesity is the major hallmark of the syndrome is still a matter of debate [2]; the need to unify diagnostic standards is still unresolved; and developing sensitive surrogate markers may be warranted. Studies assessing metabolic consequences of ACEI class in hypertensive MetS patients are lacking. The complex multifactorial nature of MetS, different and variable definitions adopted for it in literature all add to the burden of quantifying appropriately its different pathological aspects and monitoring/assessing outcome targets, with the resultant arising need to find new markers. Potential biomarkers in this respect are an area of major interest and a necessity [18]. As obesity is at the core of pathophysiology of MetS, assessing obesity-related biomarkers could serve as a surrogate for MetS itself and be a sensor for its clinical improvement/outcome. Given the novelty of some of surrogate biomarkers used in the current study, and hence the scarcity of data on their relevance, exploring changes associated with ACEI use and the exact impact of ACE inhibitors in hypertensive MetS patients on surrogate lipid and glycemic markers has not been reported in previous research extensively, if any. We hypothesized that ACE inhibition may improve surrogate lipid and glycemic markers in hypertensive MetS subjects. The objective of the current study was to investigate whether use of ACEI (Enalapril) in hypertensive MetS patients is associated with clinical improvement in MetS in terms of these surrogate markers.

Patients and Methods

Study design, subjects, and sampling

The current study follows a case–control design. The study was conducted in Mosul, Iraq, and sample collection took place during the period of April 2021 through September 2021. For the purpose of this study, identification of MetS cases was based on Joint Interim Statement on MetS (JIS) [7] criteria (Appendix 1). A total of 51 subjects diagnosed with MetS were recruited, assigned into either of two groups (treatment and control). Eligibility criteria for patients in the study included diagnosis of MetS. In addition, hypertension was an add-on criterion for assigning patients to either group for this purpose. Subjects enrolled in the study were MetS patients who were either hypertensive (treatment group) or normotensive (control). Cutoff values for HT were based on JIS criteria (systolic BP greater than or equal to 130 mmHg and/or or diastolic BP greater than or equal to 85 mmHg or taking antihypertensive drug), which roughly corresponds to American Hypertension Association (AHA) cutoff points for stage 1 HT [22]. To be assigned to treatment group, patients should be hypertensive patients receiving antihypertensive treatment with a fixed regimen of Enalapril (an ACEI) for at least 4 months before enrollment in the study. Those with other underlying conditions or receiving other treatments were excluded from the study. Written informed consent was obtained from all participants. Patient data including age, height, weight, and gender were obtained by filling a questionnaire for the subjects participating in the study. Blood sample collection was done in the morning after overnight fasting, by standard venipuncture procedure. Blood was collected in plain tubes and was left to clot at room temperature, and serum was separated by centrifugation.

Estimation of serum insulin

Serum insulin was measured by enzyme linked immune sorbent assay (ELISA) sandwich technique [23], using the Human Insulin ELISA kit manufactured by Elabscience, Inc. (USA) (*Elabscience kit*, cat#E-EL- H2665). Sandwich ELISA procedure was performed according to the manufacturer's (*Elabscience*, Houston, Texas, USA) instructions.

Assessment of glucose and lipid parameters

All the measurements were done on fasting samples. Serum glucose (SG) was estimated by glucose-oxidase peroxidase colorimetric method [24]. Determination of serum total cholesterol (TC) concentration was done by the enzymatic colorimetric method [25]. For high-density lipoprotein cholesterol (HDL-C), other lipid fractions [very low-density lipoprotein cholesterol (VLDL-C), and low-density lipoprotein cholesterol (LDL-C)] were precipitated from the sample (in the presence of phototungistic acid and magnesium), after centrifugation, HDL-C in the supernatant that was separated was assayed similar to TC [26]. Determination of serum triglyceride (TG) was done by enzymatic colorimetric method [27]. While cutoff points for dyslipidemia are well established (TC, ≥ 5.2 mmol/L; LDL-C, ≥3.4 mmol/L; TG, >1.7 mmol/L; and HDL-C, <0.9 mmol/L) [28]; however,

the current study utilized cutoff values diagnostic for MetS based on JIS criteria (TG higher than/or equal to 1.7 mmol/L; HDL-C lower than 1 mmol/L for males and lower than 1.3 mmol/L for females) for diagnosing Metabolic syndrome (Appendix 1). All measurements were carried out spectrophotometrically using commercially available kits. LDL-C was calculated according the formula: LDL-C (mg/dL) =TC – HDL-C - [TG/5] [29]. Body mass index (BMI) was calculated according to the formula: Weight (kg)/height^2 (meter). BMI is not a MetS criterion, however, it is an adiposity index, Cutoff points of BMI of 25 and 30 kg/m^2 for overweight and obesity, respectively, are widely recognized globally [30] and long endorsed by the WHO [31].

Surrogate lipid and glycemic markers

The triglyceride and glucose index (TyG index) was calculated as: Ln [fasting triglycerides (mg/dL) × fasting glucose (mg/dL)]/2 [32]. Triglyceride glucose-body mass index (TyG-BMI) also called TyG with adiposity status was calculated using the formula: TyG index × BMI [33]. The product of serum insulin by TG (InsuTAG) was calculated using the formula: fasting insulin (mU/L) × fasting TG (mmol/L) [34]. Atherogenic index of plasma (AIP) was calculated using the formula: log(TG/HDL-C) (in mmol/L units) [35]. Castelli risk index-I (CRI-I), also known as cardiac risk ratio (CRR), was calculated according to the formula: CRI-I = TC/HDL-c, and Castelli's Risk Index-II (CRI-II) was calculated by the formula: CRI-II= LDL-C/HDL-C [36].

Statistical analysis

For all parameters, mean, standard deviation (SD), and standard error of the mean (SEM) were calculated. Shapiro–Wilk test was used to test normality of distribution of data. For normally distributed data, independent samples *t*-test was used to compare parameters' means in treatment versus control groups; same test was used for non-normally distributed data after log-transforming the data. To adjust for confounding contribution of age and gender to the differences seen in means, study parameters were analyzed through two-way ANCOVA. $p < 0.05$ was considered significant. IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, N.Y., USA) software package was used for statistical analysis.

Results

Characteristics of patients

The study group consisted of 27 (15 males and 12 females) patients. The control group included 24 (13 males and 11 females) subjects. Table 1 patient characteristics, including age, body mass index (BMI), and gender ratio, as well as biochemical parameters. Data are shown as mean ± standard error of the mean (SEM).

Table 1: Patient characteristics

	ACEI (n = 27)	Control (n = 24)
Age (Years)	53.11 ± 1.17	52.21 ± 1.91
BMI (kg/m^2)	33.64 ± 0.80*	29.48 ± 1.18
Gender (Male: Female)	15:12	13:11
TC (mg/dl)	204.54 ± 6.92	212.56 ± 8.08
TG (mg/dl)	205.39 ± 19.50	215.66 ± 21.30
HDL-C (mg/dl)	44.10 ± 1.81*	32.49 ± 1.159
SG (mg/dl)	175.07 ± 11.53	200.33 ± 13.94
Insulin (μU/ml)	13.99 ± 1.43	15.09 ± 1.15
LDL-C (mg/dl)	119.36 + 6.81	136.93 + 7.37

BMI: Body mass index, TC: Serum total cholesterol, TG: Serum triglyceride, HDL-C: Serum high-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, SG: Serum glucose. Data expressed as mean ± SEM. *Significant difference at $P < 0.05$.

InsuTAG, TyG index and insulin range in treatment versus control groups

InsuTAG was non-significantly lower in treatment group, compared to controls (Figure 1). Likewise, TyG index was non-significantly lower in treatment group, compared to controls (Figure 2). Range of insulin levels in control group was (5.7–27.9 μU/m) and for the treatment group the range was 3.8–39.15 μU/ml.

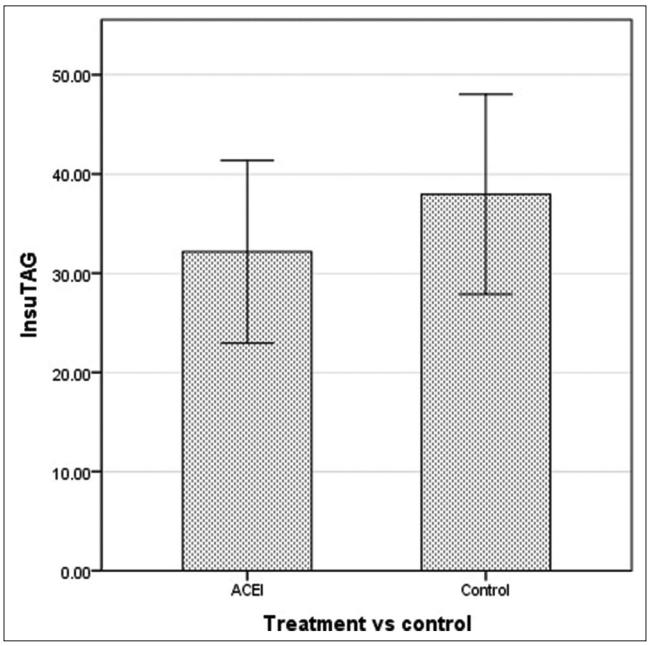

Figure 1: InsuTAG in treatment versus control groups. Higher value is demonstrated in control group but the difference is not statistically significant. Data are expressed as the mean ± 2 SEM

Atherogenic index of plasma and TyG - BMI in treatment versus control groups

Atherogenic index of plasma (AIP) was significantly lower ($p < 0.05$) in treatment group, compared to controls (Figure 3); while TyG-BMI was significantly higher ($p < 0.05$) in treatment group, compared to controls (Figure 4).

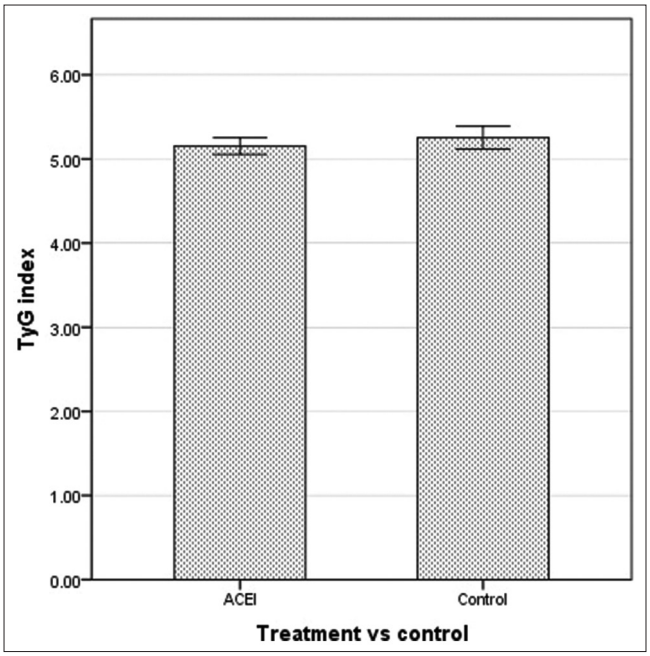

Figure 2: TyG index in treatment versus control groups. Higher value is demonstrated in control group but the difference is not statistically significant. Data are expressed as the mean ± 2 SEM

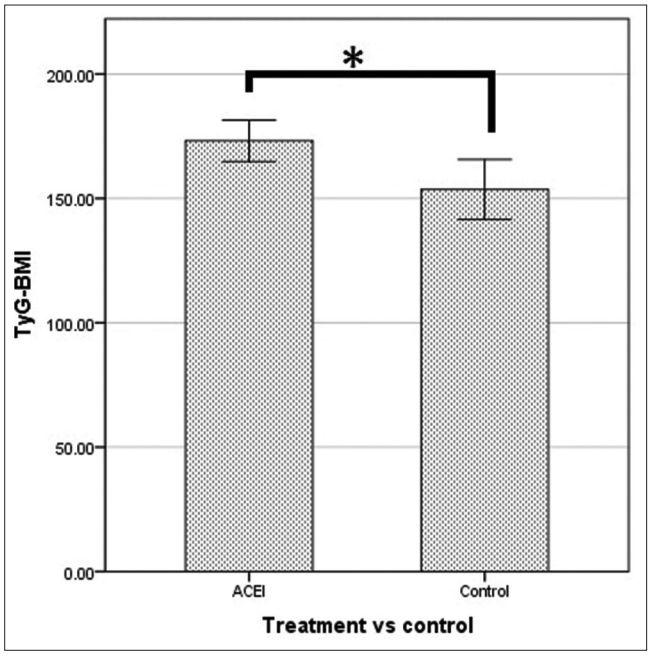

*Figure 4: TyG-BMI in treatment versus control groups. TyG-BMI is significantly higher (*p < 0.05) in treatment group compared to control group. Data are expressed as the mean ± 2 SEM*

Castelli risk indices I and II in treatment versus control groups

Castelli risk index I (CRI-I) was significantly lower ($p < 0.05$) in treatment group, compared to controls (Figure 5); while Castelli risk index II (CRI- II) was higher in treatment group, compared to controls, but the difference was not statistically significant (Figure 6).

Adjustment for age and gender confounding effect

To control for potential confounding effects of age and gender on results reported above, a two-way ANCOVA analysis was conducted, in which the study markers served as the dependent (outcome) variable, gender (male vs. female) and treatment (treatment vs. control) were independent (predictor) variables, with age being the covariate. After controlling for age, there was not a statistically significant interaction between

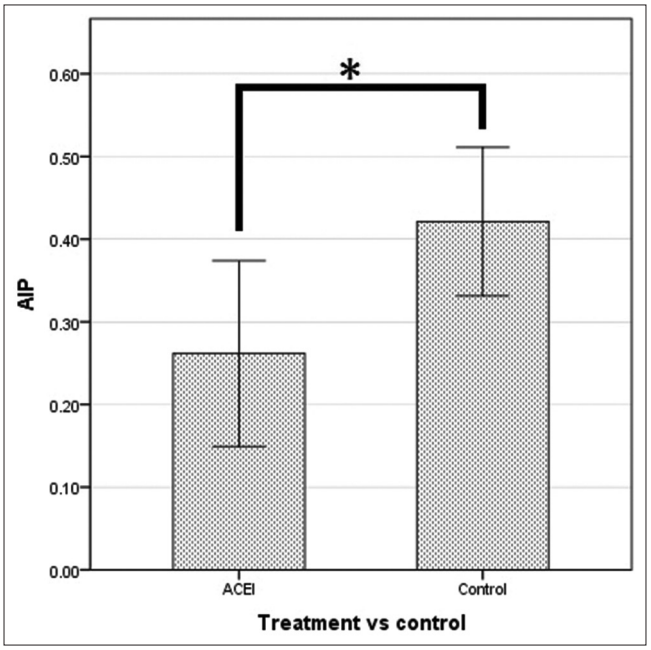

*Figure 3: AIP in treatment versus control groups. AIP is significantly lower (*p < 0.05) in treatment group compared to control group. Data are expressed as the mean ± 2 SEM*

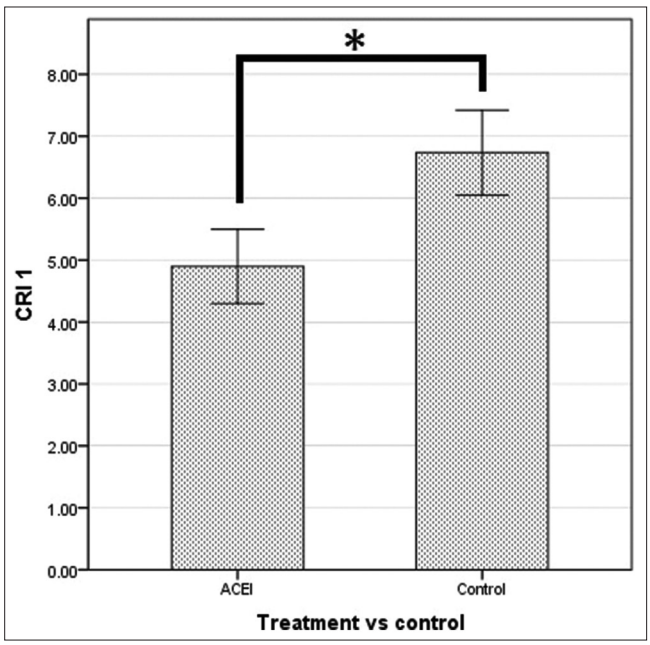

*Figure 5: CRI-I in treatment versus control groups. CRI-I is significantly lower (*p < 0.05) in treatment group compared to control group. Data are expressed as the mean ± 2 SEM*

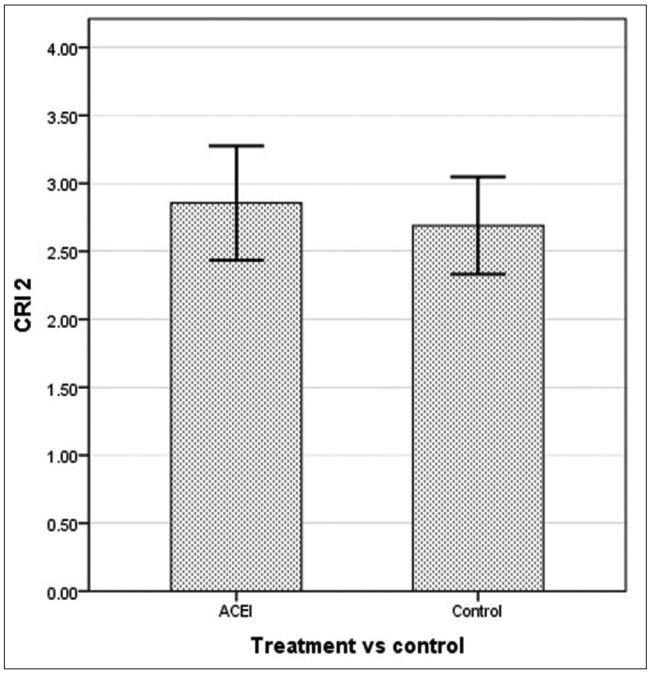

Figure 6: CRI-II in treatment versus control groups. CRI-II is higher in treatment group compared to control group but the difference is not statistically significant. Data are expressed as the mean ± 2 SEM

gender and treatment on InsuTAG, F(1, 46) = 0.927, *p* = 0.341, partial η^2 = 0.020. Likewise, a statistically insignificant interaction was found between gender and treatment on TyG-BMI, whilst controlling for age, F(1, 45) = 1.369, p = 0.248, partial η^2 = 0.030. Similarly, there was a statistically insignificant interaction between gender and treatment on CRI-I, whilst controlling for age, F(1, 46) = 0.295, p = 0.590, partial η^2 = 0.006; and a statistically insignificant interaction was found between gender and treatment on CRI-II, while controlling for age, F(1, 46) = 0.656, p = 0.422, partial η^2 = 0.014. A statistically insignificant interaction between gender and treatment on AIP, while controlling for age was also found, F(1, 46) = 2.515, p = 0.120, partial η^2 = 0.052. A statistically insignificant interaction was found between gender and treatment on TyG index, whilst controlling for age, F(1, 45) = 0.188, p = 0.666, partial η^2 = 0.004. These results indicate that age and gender did not moderate the effect of treatment on study markers (InsuTAG, TyG-BMI, CRI-I, CRI-II, AIP, and TyG index); thus, receiving treatment was still associated with significant differences in TyG-BMI, CRI-I, and AIP parameters, after adjusting for age and gender.

Discussion

The major findings of the current study are that ACE inhibition with enalapril in hypertensive MetS patients was associated with a significant decrease in AIP and CRI-I and significant increase in TyG-BMI, while other surrogate markers were non-significantly changed, as compared to normotensive MetS patients.

Treatment regimens containing ACE inhibitors have been shown to be particularly effective in patients with obesity-related HT or MetS [37]. Current guidelines place ACE inhibitors as treatment of choice for patients with MetS [38], [39], in view of their antihypertensive effect and favorable effect on glucose and IS [40], [41].

Dyslipidemia and abnormal glucose tolerance are major metabolic derangements which predispose to and increase CV and atherosclerotic risk in the context of MetS. ACEIs were associated with relevant beneficial effects in MetS [42], [43]. Data are limited on the underlying mechanisms for beneficial effects of this class in this respect [44]; still, a number of reports documented a relationship between these drugs and metabolism of lipids and carbohydrates, with the results being controversial [45], [46]. Impaired insulin sensitivity (IIS) was indirectly assessed by in the current study. Often the MetS therapeutic management targets certain risk factors, while not focusing on the underlying IIS [6]. The latter, together with HT, was shown to be contributed to by RAS (over)activity [47]. The ACEIs were shown to boost tissue sensitivity to insulin [48], [49], [50]; which simultaneously reduces atherosclerotic and CV risk [41]. In non-DM individuals, ACE inhibitors, in comparison to diuretics or beta blockers, were superior in improving IS and glucose metabolism [51], delaying progression to DM in large scale studies [51], [52]. In a fructose-induced MetS model, captopril (an ACE inhibitor) along with BP lowering, prevented progressing to MetS, and decreased adiposity, but contrast exerted a minimal effect on IS and hypertriglyceridemia [53]. These reports are in line with effects seen in current study. While ACEIs contributed to improving IS [54]; however, few studies addressed such effects in individuals with MetS [55], [56], [57] in the context of managing hypertension complicating MetS (MetS-HT) and none to the best of our knowledge utilized the surrogate markers used in the present study to this end. Although limited data exist, positive impact on lipid fractions and IS has been observed in at least some populations with MetS-HT [56], this class of drugs has shown promising improvements in risk factors, though with varying effects on lipid ratios (Putnam *et al*., 2012). On the other hand, the previous clinical trials failed to report significant TC and TG concentrations changes [47], this controversy may partly relate to some TC- and TG-based indices' findings in the current study.

In the present study, higher values of InsuTAG were demonstrated in the control group as compared to the treatment group, but the difference was not statistically significant. InsuTAG represents a fairly recent addition to the pool of metabolic surrogate markers; it incorporates a measure for hyperinsulinemia and level of TG in serum to identify inherent resistance to, and metabolic complications of insulin [34]. The TG in the formula is itself sensitive to changes in IS

showing an inverse relationship with insulin levels [58], with insulin resistance (IR) reversed on lowering TG levels [59], thus strongly correlating with IS and action [60], [61]. Thota *et al*. (2017) substantiated this index as a good MetS predictor, performing better than other anthropometric and lipid fraction-based indices. Given all these merits, however, lack of significant differences between the two groups in the present study probably reflects established IIS and MetS beyond any beneficial capacity of ACE inhibitor used; this marker is however relatively novel and relevant literature about its performance in this context is scarce, rendering comparison with the present findings difficult.

AIP, also referred to in literature as plasma atherogenic index (PAI) [62], accounts simultaneously for TG and HDL-C, thus predicting atherogenicity of plasma [63], [64]. AIP may be a more valuable tool than individual lipid fractions [65], [66]. Elevation of AIP has been proposed as a good predictor of CVD [67], being the most sensitive marker for CV risk when compared with CRI-I and II [36], [68] and for this purpose some authors suggested its use as a stand-alone marker [69]. When other atherogenicity markers are normal or not evidently abnormal such as HDL-C and TG, AIP becomes of special diagnostic value [70] thus estimating the so-called "zone of atherogenic risk," being a better surrogate marker [71] with normal values of TG (which itself is a diagnostic marker for atherogenicity risk). In addition, the study by Zhang *et al*. [72] established AIP as an independent MetS predicting index. In several studies, MetS patients had higher AIP levels; furthermore, a higher level is associated with higher odds for developing MetS [73]. This tool also has predictive power for HT and DM and is efficient for monitoring vascular health, especially after interventions with metabolic leverage [74]. In contrast, AIP was shown to be an inconsistent atherosclerosis and CV marker in some populations [71], indicating gaps in population-specific knowledge about the marker. The current study demonstrated much lower AIP values in ACEI-treated patients, reflecting, in view of above-stated evidence, reduced atherogenic risk associated with the use of the antihypertensive drug. In addition, being a HT marker [74], [75], AIP values in the current study in ACEI group may also reflect optimal antihypertensive control; however, paucity of evidence in literature on ACEI-treated MetS patients precludes comparison with other studies to support these findings in this respect. The current study revealed that gender did not confound treatment effects on AIP values, which is inconsistent with some previous reports [75], [76]; however, sample size consideration and differences in background population characteristics may account for this discrepancy.

In the present study, CRI-I was significantly lower in treatment group than in the control group, while CRI- II was higher in treatment group, compared to controls, but the difference was not statistically significant. While controversy around their true surrogate potential still exists, CRI-I and II were shown to be superior CV risk estimators compared to traditional serum lipid fractions (TC, TG, HDL-C, and LDL-C) [36]. Some studies further established indices like CRI-I as a superior CAD predictor [77], being a useful diagnostic tool reflecting coronary plaques generation [78], [79]. Furthermore, CRI-II correlates well with IR [80]. While their diagnostic value in other conditions was addressed (see above), no study on MetS-HT patients, especially those on ACEIs, could be located for comparison; nevertheless, current study findings suggested a clear beneficial effect in treatment group in terms of CRI-I and lack of significant changes in the CRI-II index, both findings being to the effect of modulating CV risk in association with ACEI use.

In the present study, higher values of TyG index were demonstrated in control group versus treatment group but the difference was not statistically significant. TyG index is a relatively novel tool that proved to be an ideal surrogate IR biomarker [81] outperforming and possibly replacing conventional indices (like HOMA-IR) [82], [83] and an optimal tool for identifying those at risk of developing T2DM, being especially superior to its individual components in normoglycemic individuals [84]. However, it still needs to be standardized due to inconsistency of cutoff values and IR definitions against which it was compared in previous studies [85] which limits its current applicability in this regard. TyG-index was also superior in identifying MetS [86]. Zhu *et al*. [79] reported good association with HT even after adjusting for confounding variables, being the most reliable HT discriminator vs other IS markers; in addition, it was a reliable CAD and CV outcome predictor [87] and possibly a good atherosclerosis [88] and ischemic stroke [89] marker. While very limited evidence exists for comparison, current study findings suggest that ACE inhibitor therapy did not appreciably change metabolic and CV risk in terms of this index. Same finding regarding IS can be concluded, compared to other TG-based markers in this study. This might reflect that the crude IR marker, insulin component of the formula, was not appreciably altered in both groups. As a HT marker, findings reported here suggest insensitivity of the marker to HT status in MetS-HT patients when compared to controls. While this may be attributed to the modulating effect of antihypertensive therapy (in the treatment group) on clinical condition; however, a larger population may need to recruited in future studies to confirm this.

In the present study, TyG-BMI was significantly higher in ACE inhibitor group compared to control group. While this may reflect more metabolic derangement in the treatment group compared to the normotensive group, it may also stem from differences in current study groups' BMI readings. As this marker combines glycemic, lipid and adiposity components, it was proposed as a good index to monitor IS [90] and in this respect, it was

superior to other substitute surrogate indices (including TyG index and lipid fractions) [33]. An important aspect of TyG-BMI is its superior performance in evaluating HT complicated by MetS [91] and in identifying subjects with MetS and predicting MetS, being closely correlated to adverse metabolic markers/conditions (namely, serum uric acid, elevated BP, dyslipidemia, and dysglycemia) [92]; thus, it may be an excellent metabolic biomarker in this respect. Therefore, higher values in the current study hypertensive treatment group point to the underlying MetS-HT in comparison to the normotensive group. TyG-BMI showed a higher odds ratios for HT compared to TyG index in previous studies [91], [93], which is consistent with both markers' present findings. BMI is included in the formula of this marker calculation, and being a marker itself for HT, this can lead to differences between normotensive and hypertensive individuals, which could be the case in the current study. In addition, dyslipidemia in its different variations is both a major component of MetS and when present, a predictor of HT; abnormalities in HDL-C, LDL-C, TC, or TG are strongly associated with HT [94], which translates to major differences between normo- and hypertensive MetS patient in dyslipidemia-derived markers which partly explains some lipid-based biomarkers findings.

When compared with other antihypertensives, ACE inhibitor class was reported to reduce body weight in various clinical trials [53], [95]. Accordingly, an improved outcome was expected for this marker as it contains an adiposity index (BMI) but this was not the case in the current study. This marker was highlighted as particularly superior in obese individuals for early diagnosis of IR and CV events [96], which suggests this marker is sensitive to differences in adiposity as per BMI, which is apparently different in both groups in the current study, this partly explains the results here.

The present study has some limitations; due to practical considerations, the therapy duration and sample size may not be sufficient for more evident effects to be seen, this is the case also for some previous studies [47]; also performance of the study markers may be affected by unmeasured factors such as ethnicity and confounding factors such as age and gender [97], although the latter issue was addressed in the current study. In addition, various definitions of MetS adopted in the literature together with the novelty of some markers utilized herein make current findings' comparison with the previous literature difficult.

Conclusion

Dyslipidemia and impaired IS adversely impact the clinical outcome of MetS patients; and those with co-existing HT are uniquely placed in a situation where ACE inhibition indicated for them can play a role in mitigating some aspects of the metabolic derangement seen in MetS. The metabolic performance of ACEIs in HT-MetS patients, in terms of current study surrogate has not been studied to the best of our knowledge. The study showed clear metabolic benefits in Enalapril users which encourage further insight into underlying mechanisms for potential beneficial effects. Benefits of using enalapril in this patient category may serve to minimize CV risk and improve IS. Longer-term, prospective studies, on larger populations, perhaps with a second arm involving an Ang II receptor blocker, may be warranted to further elucidate present study findings.

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PMid:27267043

Appendix

Appendix 1: JIS diagnostic criteria for metabolic syndrome [7]

Risk factors	Value>5.6 mmol/L , or T2DM patient
Fasting plasma glucose	≥5.6 mmol/L, or T2DM patient
Blood pressure (BP)	Systolic BP≥130 and/or diastolic BP≥85 mmHg or on treatment for HT
Triglycerides (TG)	≥1.7 mmol/L, or on treatment
High density lipoprotein-cholesterol (HDL-C)	Male<1.0 mmol/L Female<1.3 mmol/L, or on treatment
Waist circumference	≥94 cm (men) ≥80 cm (Women)
No. of factors for diagnosis	At least 3 risk factors