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# Adiponectin is Not Associated With Blood Pressure in Normotensives and Untreated Hypertensives With Normal Kidney Function

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**Abstract:** The role of adiponectin in hypertension is still a matter of debate. Obtained conflicting results could be mostly explained with diversity of subjects included in different studies. Our aim was to analyze association of adiponectin with blood pressure (BP) in a group of normotensive and untreated hypertensive subjects.

Participants (N = 257) were selected from a random sample of 2487 subjects enrolled in an observational cross-sectional study. Subjects with diabetes and chronic kidney diseases were excluded. BP was measured using Omron M6 device following ESH/ESC guidelines. Adiponectin concentration was determined by ELISA.

There were no differences in adiponectin values (mg/L) between hypertensives and normotensives (median 9.75; iqr: 7.44–17.88 vs 11.35; iqr: 7.43–12.63; $P = 0.17$). On univariate linear regression adiponectin was not associated with systolic or diastolic BP ($P > 0.05$). Furthermore, multivariate analysis did not show significant contribution of log-transformed adiponectin either to systolic ($\beta = -0.040$; $P = 0.43$) or diastolic BP ($\beta = 0.066$; $P = 0.33$).

In our group of normotensives and untreated hypertensives with normal kidney function adiponectin was not associated with BP even after adjustment for other risk factors. Our results and conclusions should not be extrapolated to subjects with other characteristics.

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**Abbreviations**: ACR = albumin/creatinine ratio, Alpha1CR = alpha 1 microglobulin/creatinine ratio, BP = blood pressure, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, ROC = receiver operating characteristic.

## INTRODUCTION

Hypertension and obesity are growing to epidemic proportions primarily due to unhealthy lifestyle and inefficient primary prevention. Contrary to the majority of adipokines, adiponectin was reported to be lower in obese individuals and weight-loss regimes significantly increase its concentration.[1] It was reported that hypoadiponectinaemia has a role in the pathogenesis of atherosclerosis, type-2 diabetes and hypertension.[2] Adamczak et al found that adiponectin plasma concentration was significantly lower in patients with essential hypertension compared to normotensives with similar body mass index (BMI).[3] Iwashima et al showed that hypoadiponectinaemia is a risk factor for hypertension independent of insulin resistance and diabetes.[4] An inverse correlation was found between adiponectin concentrations and risk of developing hypertension later in life.[5] Kim et al reported that 1 μg/mL increase in adiponectin levels was associated with 6% reduction in risk of hypertension.[6] On the contrary, Murakami et al in a study encompassing 3 populations found no significant difference in adiponectin concentration between normotensives and insulin sensitive hypertensive patients.[7] No correlation was observed between adiponectin plasma concentrations and blood pressure (BP) in children.[8–10] In addition, *Copenhagen City Heart Study* failed to show a predictive value of adiponectin for BP values in adults which is in line with *British Women's Heart and Health Study* where no relationship between adiponectin and BP was found although high molecular weight multimer of adiponectin was analyzed.[11,12]

Due to conflicting published results obtained in populations with different levels of cardiovascular risk and/or chronic kidney disease (CKD), our aim was to analyze the relationship of adiponectin with BP in a selected group of normotensives and untreated, newly diagnosed hypertensives with estimated glomerular filtration rate (eGFR) $\geq 60$ mL/min/1.73 m$^2$.

## SUBJECTS AND METHODS

In this cross sectional observational study, we enrolled 257 adults (160 females, 97 males) selected from a random sample of 2487 people who were recruited in a survey conducted between 2008 and 2010 in rural continental Croatian area. Study interviewers went door-to-door asking if the adult resident (older than 18 years of age) would be willing to participate

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in the study. All households in the target villages were approached. If no one was home, interviewers returned over the next several days and attempted to make contact with the resident. Individuals agreeing to participate in the study completed an extensive survey administered by the study personnel and also provided spot urine and fasting blood sample. Among villages participation rate ranged from 60.8% to 88.7%. Inclusion criteria in this study were: written informed consent, normotension or untreated hypertension and eGFR $\geq$ 60 mL/min/1.73 $m^2$. Exclusion criteria were: unsigned written consent, treated hypertensives, pregnancy, diabetes, terminally ill patients and subjects with severe disabilities, people with one or more amputated limbs and those suffering from dementia and psychiatric illnesses. To diminish and exclude the effect of kidney impairment on adiponectin values patients with eGFR $<$ 60 mL/min/1.73 $m^2$ were excluded. Study was approved by Institutional Review Boards of University of Zagreb School of Medicine and Croatian Public Health Institute.

BP was measured according to ESH/ECS guidelines.[13] Patients rested in a sitting position for 10 minutes in a quiet room at 22 °C before BP measurements were recorded. They were asked to avoid caffeine-containing drinks and to refrain from smoking and exercise for the 12 hours preceding the measurements. BP and heart rate were measured using the Omron M6 Comfort device (Omron Corporation, Kyoto, Japan) and 2 cuff sizes (standard and large) on 2 visits (one at participants' home and the other in office). At each visit BP was measured 3 times with 3 minutes period between measurements and average of second and third measurement was used further. Final BP value which was used for analyses was calculated as a mean of average values obtained from office and home BP measurements. Hypertension was defined as BP $\geq$ 140/90 mm Hg while BP values lower than 140/90 mm Hg were considered normotensive. All hypertensive patients enrolled in this study were newly diagnosed hypertensives who were never treated. BMI was calculated as: weight [kilograms] divided by square of height [meters]. Waist circumference was measured by elastic tape in 3 separate occasions and arithmetic mean of these measurements was used. Waist circumference larger than 102 cm for men and 88 cm for women was used as a measurement of central obesity. In our group, out of 257 subjects, 97 were ex or current smokers (25 and 72, respectively) and 8 subjects had missing smoking information, which gives us a prevalence of ex or current smoking of 39%. Smoking was quantified as pack-years (number of pack-years = (number of cigarettes smoked per day $\times$ number of years smoked)/20).

Subjects provided fasting blood samples and first morning spot urine samples. Serum creatinine was determined on Olympus AU 2700 using continuous photometric method with alkaline pikrate (Olympus, Tokyo, Japan). $\alpha$1microglobuline and urine albumin were determined on Siemens Dade Behring BN II Nephelometer (Siemens, Germany), and were corrected to urine creatinine (ACR and $\alpha$1CR, respectively). Glomerular filtration was calculated using abbreviated MDRD equation: eGFR=32788 $\times$ [Serum Creatinine]$^{-1.154}$ $\times$ Age$^{-0.203}$ $\times$ (0.742 for females). HOMA index was used to express insulin resistance (HOMA-IR = [Insulin ($\mu$IU/mL)] $\times$ [Glucose](mmol/L)/22.5). In this study, insulin resistance was defined as HOMA-IR $>$ 3. Total adiponectin and leptin concentrations were determined using enzyme immunoassay method (ELISA) (Behring Gmbh, Germany), high sensitivity C-reactive protein (hsCRP) using an immunoturbidimetric method on latex particles, insulin concentrations by immunochemical detection with electroluminiscence and glucose using photometry with hexokinase or glucose oxydase (Olympus System Reagent Kit na Olympus AU2700, Tokyo, Japan).

Statistical analysis was performed in SPSS v.21 (IBM Corp., Armonk, NY). Numerical variables were tested for normality of distribution using D'Agostino-Pearson test. Categorical variables were compared with chi square test. Normally distributed variables were presented as arithmetic mean $\pm$ standard deviation and Student *t* test was used to compare the 2 groups. Non-normally distributed variables were showed as median and interquartile range (25th and 75th percentile) and Mann–Whitney *U* test was used to compare the 2 groups. Analysis of covariance (ANCOVA) was used to test for differences across group after adjustment for multiple covariates and factors. Multiple regression analysis was used to determine the impact of several independent variables on one dependent variable. For correlation analysis we used Pearson's and Spearman's test. In all tests a 2 tailed *P*-value $<$0.05 indicated statistical significance.

Power calculation was carried out and the equation using Cohen's $d = 0.45$ ($\alpha = 0.05$, $\beta = 0.80$) estimated minimum needed sample sized for two-tailed hypothesis of 79 per group (158 total).

## RESULTS

There was no difference in gender distribution between hypertensives and normotensives ($P > 0.05$). Hypertensives were older, had higher BMI and greater proportion of visceral obesity (all $P < 0.001$) (Table 1). Higher values of total cholesterol, LDL cholesterol, triglycerides, fasting blood glucose, insulin values and HOMA index were determined in hypertensives (all $P < 0.01$). They also had significantly lower eGFR and higher ACR values (both $P < 0.001$) (Table 2). Hypertensives also had higher values of hsCRP and leptin (both $P < 0.05$) but there was no significant difference in adiponectin values (9.75 (iqr: 7.43–12.63) mg/L vs 11.35 (iqr: 7.44–17.88) mg/L; $P = 0.17$). Additionally, we failed to find a difference in adiponectin even after adjustment for factors known to affect adiponectin concentrations (age, sex, BMI, waist circumference, HOMA-IR, eGFR, total cholesterol and hs-CRP) (mean (standard error, SE): 10.97 (1.10) vs 10.72 (1.15), $P = 0.95$).

As shown in Table 2, adiponectin values were higher in women than in men in both hypertensives and normotensives but difference did not reach statistical significance ($P > 0.05$). We failed to find difference in adiponectin values between insulin resistant and insulin sensitive subjects in both groups.

We have carried out a sensitivity analysis using Receiver Operated Curves analysis (ROC) and failed to observe difference between HOMA-IR $>$ 3 (AUC = 0.568, $P = 0.15$), HOMA-IR $>$ 2.5 (AUC = 0.553, $P = 0.29$) and HOMA-IR $>$ 2 (AUC = 0.554, $P = 0.30$). We tested if a lower cut-off value of HOMA-IR might show differences in adiponectin concentrations between IR and non-IR subjects, but again there was no difference either with cut off HOMA-IR $>$ 2.5 (10.10 (iqr: 6.70–13.68) mg/L vs 11.20 (iqr: 7.85–16.65) mg/L: $P = 0.25$) or HOMA-IR $>$ 2 (10.40 (iqr: 7.08–13.90) mg/L vs 11.20 (iqr: 7.85–17.88) mg/L; $P = 0.31$). Based on this analyses it could be concluded that our results are comparable with results of other studies where different cut off values for HOMA-IR were used.

On correlation analysis in normotensive as well as in hypertensive group adiponectin did not correlate with systolic BP ($r = -0.103$, $P = 0.39$; $r = -0.201$, $P = 0.27$, respectively) or diastolic BP ($r = 0.073$, $P = 0.54$; $r = 0.020$, $P = 0.91$, respectively).

For regression analysis adiponectin was log-transformed because of significant positive skew in distribution of

**TABLE 1.** Anthropometric and Clinical Parameters in the Whole Group Stratified According to Blood Pressure, and in Normotensives and Hypertensives Stratified According to Gender

| | Whole Group | | | Normotensive | | | Hypertensive | | |
|---|---|---|---|---|---|---|---|---|---|
| | Normotensive | Hypertensive | *P*-Value | Male | Female | *P*-Value | Male | Female | *P*-Value |
| Number of subjects (M/F) | 58/106 | 39/54 | 0.30 | 58 | 106 | | 39 | 54 | |
| Age (years) | 40 (15) | 53 (13) | 0.30 | 41.5, 29–53 | 38, 27–47 | 0.25 | 54, 45–63 | 52, 44–61 | 0.55 |
| Height (cm) | 168 (11) | 167 (12) | <0.001 | 178, 172–181 | 164, 160–170 | <0.001 | 174, 171–182 | 161, 157–166 | <0.001 |
| Weight (kg) | 74 (17) | 81 (17) | 0.31 | 81, 69–93 | 68, 59–76 | <0.001 | 89, 77–99 | 77, 64–85 | <0.001 |
| BMI (kg/m$^2$) | 25.9 (5.3) | 29.3 (6.0) | 0.001 | 25.6, 22.4–29.4 | 25.2, 22.1–27.9 | 0.39 | 29.1, 26.0–31.5 | 28.3, 24.7–32.1 | 0.76 |
| BMI > 25 (%) | 52 | 77 | <0.001 | 55 | 51 | 0.63 | 82 | 74 | 0.45 |
| Waist circumference (cm) | 87 (14) | 95 (12) | <0.001 | 92 (11) | 84 (14) | 0.19 | 99 (11) | 92 (12) | 0.003 |
| Pathological waist circumference (%) | 27 | 54 | <0.001 | 17 | 30 | 0.09 | 41 | 63 | 0.057 |
| Systolic blood pressure (mm Hg) | 117 (10) | 147 (16) | <0.001 | 120, 116–127 | 115, 107–123 | 0.002 | 146, 140–159 | 144, 134–155 | 0.33 |
| Diastolic blood pressure (mm Hg) | 74 (8) | 92 (9) | <0.001 | 75 (7) | 74 (8) | 0.08 | 92 (8) | 92 (10) | 0.74 |
| Heart rate (beats/min) | 77 (13) | 78 (12) | 0.44 | 77, 67–82 | 76, 70–85 | 0.17 | 74, 69–79 | 78, 73–86 | 0.03 |

BMI = body mass index.
Values are presented as: median and interquartile range or mean (standard deviation).

untransformed variables. On univariate linear regression log adiponectin was not associated with systolic ($\beta = -0.140$, $P = 0.16$) or diastolic BP ($\beta = -0.051$, $P = 0.61$) (Figure 1).

Aiming to analyze association of adiponectin and other risk factors with systolic and diastolic BP we devised a model using systolic or diastolic BP as dependent variable adjusted for age, sex, HOMA-IR, BMI, waist circumference, LDL and HDL cholesterol, triglycerides, heart rate, systolic or diastolic BP (depending on which one is held as a dependent variable), serum creatinine, eGFR and log adiponectin. In the model for systolic BP which accounted for about 78% of variance (adjusted $R^2 = 0.776$, $F$-ratio = 30.38), age ($\beta = 0.409$, $P = 0.005$), HOMA-IR ($\beta = 0.159$, $P = 0.01$), HDL-cholesterol ($\beta = 0.109$, $P = 0.06$), triglycerides ($\beta = 0.140$, $P = 0.04$), diastolic BP ($\beta = 0.483$, $P < 0.001$), serum creatinine ($\beta = 0.675$, $P = 0.03$) and eGFR ($\beta = 0.483$, $P = 0.03$) showed significant association with systolic BP, while log adiponectin did not ($\beta = -0.040$, $P = 0.43$).

When examining associations of aforementioned independent variables with diastolic BP as a dependent variable, model (adjusted $R^2 = 0.667$, $F$-ratio = 13.73) showed significant associations with age ($\beta = -0.416$, $P = 0.03$), systolic BP ($\beta = 0.872$, $P < 0.001$), serum creatinine ($\beta = -0.845$, $P = 0.04$) and eGFR ($\beta = -0.617$, $P = 0.04$), but not with log adiponectin ($\beta = 0.066$, $P = 0.33$).

When we tested models separately on normotensive and untreated hypertensive subjects we also did not find a positive association of log adiponectin either with systolic or diastolic BP.

On logistic regression, log adiponectin was also not associated with hypertension. In unadjusted model, odds ratio (OR) of log adiponectin was 0.38 [0.07, 2.06], while in a model that was adjusted for age, sex, BMI and waist circumference it was higher, but still insignificant 0.93 [0.06, 13.67].

Analyses to examine association of adiponectin and obesity were performed. In univariate regression waist circumference was associated with log adiponectin and for every 10 cm adiponectin decreased for 0.97 mg/L ($B = -0.004$, SE = 0.002, $\beta = -0.206$, $P = 0.03$). In multivariate analyses we included adiponectin as dependent variable and age, sex, BMI, waist circumference, systolic and diastolic BP, total cholesterol, triglycerides, pack-years and eGFR, and both waist circumference ($\beta = -0.229$, $P = 0.22$) and BMI ($\beta = 0.081$, $P = 0.58$) were not independently associated with log adiponectin values.

It was reported that smoking could influence adiponectin values and thus we analyzed impact and relationship of smoking habit and adiponectin levels in our group. Although subjects who never smoked (N = 152) had higher adiponectin values than ex/current smokers, the difference was not statistically significant (11.35 (iqr: 7.95–18.25) mg/L vs 10.50 (iqr: 6.30–13.50) mg/L; $P = 0.07$). Moreover, when we quantified smoking as pack-years we found a negative association with log adiponectin ($\beta = -0.187$, $P = 0.059$) which means that for every pack-year adiponectin concentration decreased for 1 mg/L. However, influence of smoking (expressed as pack-years) could be excluded in this cohort as it was not an independent predictor of log adiponectin ($\beta = -0.15$, $P = 0.16$).

## DISCUSSION

According to vast majority of reports, adiponectin, has beneficial properties, and it was reported that it improves insulin sensitivity, has anti-inflammatory role and is related to lower BP values.[2,3,5,14] A recently published meta-analysis by Kim

**TABLE 2.** Laboratory Parameters in the Whole Group Stratified According to Blood Pressure, and in Normotensives and Hypertensives Stratified According to Gender

| | Whole Group | | | Normotensive | | | Hypertensive | | |
|---|---|---|---|---|---|---|---|---|---|
| | Normotensive | Hypertensive | *P*-Value | Male | Female | *P*-Value | Male | Female | *P*-Value |
| Total cholesterol (mmol/L) | 5.42 (1.25) | 5.81 (1.07) | 0.008 | 5.4, 4.3–6.5 | 5.35, 4.5–6.1 | 0.92 | 5.7, 5.2–6.1 | 5.9, 5.1–6.6 | 0.54 |
| LDL-cholesterol (mmol/L) | 3.24 (1.02) | 3.56 (0.87) | 0.01 | $3.27 \pm 1.09$ | $3.23 \pm 0.99$ | 0.78 | 3.57 (0.73) | 3.55 (0.96) | 0.08 |
| HDL-cholesterol (mmol/L) | 1.58 (0.34) | 1.56 (0.39) | 0.72 | 1.42, 1.25–1.66 | 1.60, 1.37–1.84 | <0.001 | 1.23, 1.15–1.60 | 1.72, 1.37–1.88 | <0.001 |
| Triglicerides (mmol/L) | 1.32 (0.85) | 1.52 (0.67) | 0.04 | 1.25, 0.91–1.98 | 1.00, 0.77–1.34 | 0.01 | 1.38, 0.98–1.96 | 1.38, 1.01–1.89 | 0.79 |
| Fasting blood glucose (mmol/L) | 5.14 (0.92) | 5.72 (0.96) | <0.001 | 5.10, 4.90–5.50 | 5.00, 4.70–5.30 | 0.12 | 5.7, 5.3–6.4 | 5.5, 5.1–5.8 | 0.01 |
| Insulin (μU/mL) | 7.14, 5.08–20.68 | 9.58, 6.75–25.16 | <0.001 | 6.90, 4.55–11.43 | 7.17, 5.40–10.79 | 0.36 | 9.54, 6.67–12.71 | 9.73, 7.19–13.24 | 0.99 |
| HOMA-IR (μU/mL × mmol/L) | 1.60, 1.13–5.56 | 2.43, 1.61–6.82 | <0.001 | 1.56, 1.10–2.69 | 1.61, 1.80–2.58 | 0.49 | 2.66, 1.61–4.09 | 2.30, 1.56–3.35 | 0.56 |
| eGFR (mL/min) | 82.37 (12.71) | 76.89 (9.57) | <0.001 | 81, 75–91 | 81, 72–90 | 0.60 | 78, 71–81 | 75, 68–83 | 0.20 |
| ACR (mg/mmol) | 3.33, 1.68–17.36 | 4.97, 3.27–55.35 | 0.001 | 2.82, 2.28–3.78 | 4.02, 2.98–6.25 | <0.001 | 4.21, 2.49–7.32 | 5.33, 3.66–9 | 0.12 |
| α1-Microglobulin CR (mg/mmol) | 5.18, 5.18–12.20 | 5.18, 5.18–14.60 | 0.24 | 5.77, 5.18–7.56 | 5.18, 5.18–5.64 | <0.001 | 6.04, 5.18–9.65 | 5.18, 5.18–7.04 | 0.02 |
| Adiponectin (mg/L) | 11.35 7.40–31.65 | 9.75 7.43–12.70 | 0.17 | 8.15, 4.95–12.95 | 12.65, 8.68–18.26 | 0.08 | 8.59, 6.98–11.43 | 10.38, 7.68–13.23 | 0.45 |
| Leptin (μg/L) | 6.10, 3.20–27.80 | 11.05, 5.85–29.60 | 0.01 | 2.75, 0.60–10.30 | 7.90, 3.80–12.60 | 0.04 | 7.05, 2.15–10.65 | 15.80, 9.75–20.10 | 0.004 |
| hs-CRP (mg/L) | 1.25, 0.50–7.10 | 2.30, 1.00–14.30 | <0.001 | 1.20, 0.50–2.10 | 1.35, 0.50–2.70 | 0.58 | 2.30, 1.03–3.55 | 2.15, 1.00–4.50 | 0.82 |

ACR = albumin creatinine ratio, eGFR = estimated glomerular filtration, HDL = high density lipoprotein, HOMA-IR = homeostasis model assessment insulin resistance index, hs-CRP = hs-C-reactive protein, LDL = low density lipoprotein.

Values are presented as: median and interquartile range or mean (standard deviation).

et al showed that a slight increase in adiponectin values is associated with a lower risk of hypertension.[6] However, opposite and conflicting results were published in pediatric studies, but also in some large adult cohorts.[8,9,15-21] Interestingly, Mallamaci et al found higher concentrations of adiponectin in hypertensives than in age, BMI and fat-mass-matched normotensives.[22] It is obvious that the relationship of adiponectin with BP is complex and still unresolved. Even a closer look at the results of the meta-analysis performed by Kim et al revealed that more than a quarter of included studies did not show an association between adiponectin and BP or hypertension.[6] Our findings are in line with those results. Kawamoto et al and Yamamoto et al found a significant negative correlation between adiponectin and BP in men but not in women.[23,24] We were not able to find significant gender differences in adiponectin values and there was no association between adiponectin and BP either in men or in women. In our group multivariate analysis did not show significant contribution of adiponectin to BP values, indicating that in this group adiponectin could not be considered as a marker of hypertension. Our results are not in concordance with observations of some authors including the recent meta-analysis.[3–6] Different observations among various studies probably stem from the fact that hypertensives and subjects with metabolic syndrome are a vastly heterogeneous group, which should always be taken into account when interpreting results and comparing different studies. Contrary to majority of studies, we have enrolled mostly younger subjects without comorbidities. This would corroborate the hypothesis that younger subjects have weaker correlation between adiponectin and BP than older, particularly those with concomitant comorbidities in whom higher values of adiponectin might be reactively increased.[8,9] High adiponectin levels have been associated with a lower risk of myocardial infarction among men with no history of cardiovascular disease, hypertension or diabetes and decreased risk for cardiovascular disease.[25–27] On contrary, in patients with acute myocardial infarction who underwent primary percutaneous coronary intervention Lindberg et al found that increased adiponectin values independently predicts all-cause and cardiovascular mortality which is in line with authors who reported that high adiponectin values are positively associated with mortality.[28–31] This was explained with activated compensatory counter-regulated mechanisms of the systematic inflammation.[32] This reverse epidemiology i.e. paradoxical elevation in adiponectin concentration was observed also in women with pre-eclampsia and in patients with acute myocardial infarction who had increased arterial stiffness.[33–35] Interestingly, it was recently reported that adiponectin values are not associated with risk of stroke and coronary heart disease.[36–38]

Adiponectin values are inversely correlated to BMI and visceral fat accumulation which is in line with our results.[39,40] It was observed that after weight loss adiponectin values increase in obese subjects.[39,40] Oxidative stress and low-grade inflammation are consequences of visceral fat growth and it was discussed whether those disturbances could secondary increase adiponectin concentration. While some authors found lower levels of adiponectin in patients with metabolic syndrome, others reported that higher adiponectin levels are protective for incident metabolic syndrome.[41–43] This complex and paradoxical association of adiponectin values was also observed in patients with CKD who have increased global cardiovascular risk. Adiponectin values were significantly higher in patients with CKD and end-stage renal disease which was explained partly with decreased clearance but mostly with metabolic

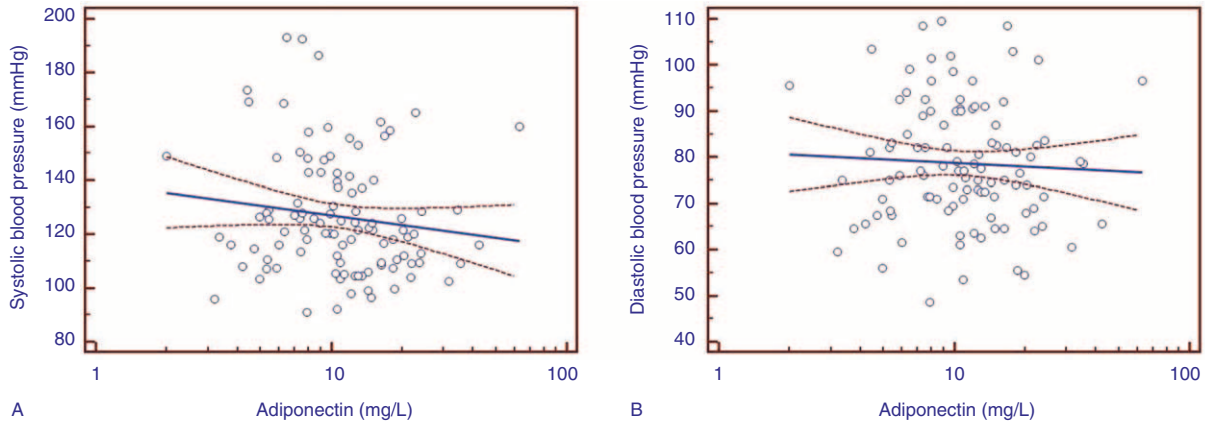


**FIGURE 1.** Univariate regression lines of log adiponectin and systolic ($\beta = -0.140$, $P = 0.16$) and diastolic ($\beta = -0.051$, $P = 0.61$) BP in the whole group.

disturbances and increased adipose tissue production as the response to the inflammatory environment and probably due to increased sympathetic activity.[44–47]

Aiming to exclude influence of kidney impairment on adiponectin values we did not include subjects with eGFR $< 60$ mL/min/1.73 m$^2$ which was not done by other authors.[48,49] This made our group more homogenous and our results probably more credible, but could also explain why our results differ from other authors. The next possible explanation for observed difference between our results and data from other studies is the definition of insulin resistance. Wishing to exclude subjects who might be in the ''grey zone'' of insulin resistance we used higher cut-off value in ROC curves for HOMA-IR when comparing subjects by insulin resistance, while majority of authors used lower cut-off values.[7,8,50] However, we obtained same results when we performed additional analyses using lower cut-off values for HOMA-IR.

It could be speculated that rural population differs from urban in some characteristics which might have impact on the adiponectin values. One could argue that rural population might be healthier than urban with less obesity, more physical activity etc. Indeed, it was reported by Milošević et al that in general Croatian population urban residents are probably less physically active than rural.[51] On contrary, in nationwide survey ''Epidemiology of Hypertension in Croatia, EH-UH study'' Jelaković et al failed to find differences between urban and rural population (unpublished data). However, relationship between adiponectin and physical activity is still unclear. Dvorakova et al showed that adiponectin values did not significantly change in obese women subjected to a weight loss regime and physical activity.[52] Ring-Dimitriou et al reported that after 12 months of physical activity increased adiponectin in men but not women with pre-disposition for metabolic syndrome.[53] Contrary to this, Kozakova et al found that moderate to vigorous physical activity is related to a decrease in adiponectin.[54]

Independent reverse association between smoking and adiponectin was reported.[55,56] In our group we found that examinees that never smoked had borderline significantly higher adiponectin values than ex-smokers and current smokers, and observed a negative association with log adiponectin where every pack-year decreased adiponectin concentration for 1 mg/L. However, we were not able to confirm that smoking is an independent predictor of adiponectin concentration in normotensives and untreated, newly diagnosed hypertensives.

This is the first study to the best of our knowledge that includes only subjects with eGFR $> 60$ mL/min/m$^2$. This is an important point as adiponectin-kidney relationship is known to be complex. This could be the reason why many studies which included patients with impaired kidney function have shown conflicting results. Our aim was to exclude this impact which could modulate effects of adiponectin and to establish if there is an effect of adiponectin on BP in subjects with normal kidney function. Another important point is the inclusion of only untreated hypertensives which enabled us to correctly assess associations of adiponectin with BP.

Finally, based on obtained results it could be concluded that in the group of normotensives and non-treated hypertensives without comorbidity and normal kidney function adiponectin is not associated with BP. This finding does not discount the possibility that adiponectin and BP relationship is not the same in normotensives, pre-hypertensives and early stages of hypertension compared to patients in advanced stages of hypertension and/or to patients with target organ damage particularly those with CKD. Obviously, the relationship between adiponectin and BP may not be the same in all patients' subgroups. Our results obtained in a population of untreated hypertensives and normotensives with normal kidney function should not be extrapolated to other patients or groups and should only be compared with similar studies.

## LIMITATIONS

Our study has several limitations. Firstly, this is a cross-sectional observational and not a prospective research. However, it is interesting to note that recent meta-analysis by Kim et al found no significant difference between weighted mean differences and dose-response relationship between cross-sectional and prospective studies.[6] When calculating insulin resistance we used HOMA formula and not insulin ''clamp'' technique. Nevertheless, other authors in epidemiological studies also pre-dominantly used this method. GFR was estimated using abbreviated MDRD formula which was modeled on patients with kidney disease and is known to underestimate kidney function in healthy subjects. Nevertheless, majority of authors used this formula as well. Total adiponectin was determined and not high-molecular-weight adiponectin. Importantly, vast majority of authors used the same isomer as we did, thus our results could be compared to those studies. One could

argue whether the number of subjects in our study is a disadvantage, but many other similar studies on adiponectin had similar or even smaller groups. In fact 25 out of 43 non-prospective studies included in meta-analysis by Kim et al had fewer subjects than our study.[6,15,21,57-61]

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