Insulin Resistance and Antropometric Measurements in Autosomal Dominant Polycystic Kidney Disease

Otozomal Dominant Polikistik Böbrek Hastalığında İnsulin Direnci ve Antropometrik Ölçüm

ABSTRACT

OBJECTIVES: There are conflicting data regarding the insulin resistance in autosomal dominant polycystic kidney disease (ADPKD) patients. We investigated the relationship between insulin resistance and anthropometric measurements in patients with ADPKD.

MATERIAL and METHODS: Thirty-six female and twenty-eight male patients were included. HOMA-IR formula was used for determination of insulin resistance. Body mass index (BMI); neck, midarm, waist and hip circumferences; and skin fold thicknesses (SFT) at biceps, triceps, subscapular, umbilical and suprailiac regions were recorded, and total body fat ratios were calculated. Patients were divided into four groups according to their creatinine clearance.

RESULTS: Twenty-seven patients (42.18%) had insulin resistance. HbA1c, HOMA-IR, insulin and glucose levels, anthropometric measurements and total body fat ratios were not statistically different among the groups. Total body fat was significantly correlated with HOMA-IR. The best predictor of glucose intolerance was found to be subscapular SFT. BMIs were not different in patients grouped according to their GFR. But, insulin resistance was higher in the group with BMI>25.

CONCLUSION: A direct relationship between ADPKD and insulin resistance was not been shown in the study. The relationship between anthropometric measurements and insulin resistance in ADPKD patients is similar to the general population.

KEY WORDS: Autosomal dominant polycystic kidney disease, Insulin resistance, Anthropometric measurements

ÖZ

AMAÇ: Otozomal dominant polikistik böbrek hastalığı (ODPKBH) olan hastalarda insulin direncine dair çelişkili veriler vardır. ODPKBH olan vakalarda insulin direnci ile antropometrik ölçümler arasındaki ilişki araştırıldı.

GEREÇ ve YÖNTEMLER: Otuẓ altı kadın ve yirmi iki erkek hastanın dahi edildi. İnsulin direncinin tespiti için HOMA-IR formülü kullanıldı. Vücut kitle indeksi (VKİ); boyun, orta kol, bel ve kalça çevreleri ile biceps, triseps, skapula altu, umbilikal ve suprailiak bölgedeki deri kivrim kalınlıkları (DKK) kaydedildi, ve toplam vücut yağ oranları hesaplandı. Hastaların kreatinin kirensi değerlerine göre dört grupa ayrıldı.


SONUÇ: Bu çalışmada, ODPKBH ve insulin direnci arasındakı direkt bir ilişki gösterilmemiştir. Antropometrik ölçümler ile insulin direnci arasındaki ilişki ODPKBH olan hastalarda genel popülasyondakine benzerdir.

ANAHTAR SÖZCÜKLER: Otozomal dominant polikistik böbrek hastalığı, İnsulin direnci, Antropometrik ölçümler

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INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is a common renal disease affecting 1:400-1:1000 of the general population (1). It is a multi-systemic disease characterized by bilateral renal cysts; and is responsible for about 10% of cases of end-stage renal disease (ESRD) (1). Chronic kidney disease (CKD) patients have high risk of death from cardiovascular disease (CVD) and have multiple traditional and non-traditional risk factors for cardiovascular disease (2). Similarities in pathogenesis of CKD and CVD may be one of the reasons of frequent co-existence of these two clinical entities. Obesity and insulin resistance may be some of these factors. There are various studies that have shown insulin resistance in uremic patients although the causal relationship between uremia and insulin resistance is not clear yet (3-6). Uremia is commonly associated with metabolic acidosis and fail to increase ammonia production which in turn leads to insulin resistance and hence glucose intolerance (7). There is also insufficient response of target tissues to insulin (i.e. blunted gluconeogenesis in the liver) despite the prolonged half-life of plasma insulin due to decreased metabolism (8). There are studies showing the etiologic role of insulin resistance in skeletal muscle on glucose intolerance (9). There are also insufficient studies showing insulin resistance in normotensive ADPKD patients although it is not clear whether ADPKD is different from other etiologies of chronic kidney disease or not (10, 11). It is known that ADPKD is caused by certain genes responsible for cell-cell interactions throughout the body leading to abnormal membrane fluidity (12). A possible explanation for insulin resistance may be this altered membrane fluidity that was shown by Tong P to be related with whole body insulin resistance (13). The relation of insulin resistance with cardiovascular risk factors like hypertension, dyslipidemia, glucose intolerance and hyperuricemia is well known (14). Another well-known reason of insulin resistance is obesity (15). Furthermore Turkmen et al. recently reported that coronary flow reserve decreased, carotid intima media thickness and insulin resistance increased in normotensive ADPKD patients with preserved renal function (16).

Although it is the gold standard for determining insulin resistance, euglycemic-hyperinsulminemic clamp technique is not suitable for large population-based studies due to its complexity and difficulty (17). Euglycemic-hyperinsulminemic clamp technique, fasting plasma insulin level, HOMA-IR (Homeostasis Modal Assessment-Insulin resistance) and fasting plasma glucose/insulin ratio have been compared for their reliability in determining insulin resistance; and it was shown that HOMA-IR is a valuable index for insulin resistance in both diabetic and non-diabetic subjects (18).

In obesity, morbidity and mortality risk is not related with only the amount of fat, but also with the distribution of fat tissue. Increased levels of abdominal and visceral fat tissue are related with insulin resistance. Both the degree of obesity and fat distribution are important determinants of increased morbidity and mortality due to diabetes mellitus, hypertension and cardiovascular diseases. Some anthropometric measurements like weight, height, skin fold thickness of biceps, triceps, subcapular and suprailiac regions are used to measure total body fat and to determine the degree of obesity. These measurements have been correlated with other risk factors for diabetes mellitus and cardiovascular events (19).

In our study; we investigated the relationship of insulin resistance and CKD in patients with ADPKD, and at the same time anthropometric measurements were performed as an index of additional risk.

METHODS

ADPKD patients who were diagnosed according to family history, clinical and radiological findings in our nephrology clinic were included in the study. Ravine criteria were used for the ultrasonographic diagnosis of ADPKD in patients with a positive family history (20). In patients without positive family history; presence of co-existing hepatic and pancreatic cysts, intracranial aneurysms and CKD were used as diagnostic criteria in addition to Ravine criteria. Exclusion criteria were as follows:

- Presence of known diabetes mellitus
- Need for renal replacement therapy or creatinine clearance less than 15 ml/minute
- Pregnancy
- Age less than 15 or more than 80 years
- Any type of malnutrition
- Chronic cardiac, hepatic, pulmonary or thyroid disease
- Malignancies
- Patients who did not give informed consent.

36 female (56.25%) and 28 male (43.75%) of patients, fulfilling the inclusion and exclusion criteria were included in our study.

Patient Assessment: After physical examination, blood samples were taken and anthropometric measurements were performed. They were advised to go on their routine daily activities with no additional dietary restriction but avoid vigorous exercise during the follow-up.

Biochemical analysis: Venous blood samples of all patients were taken to tubes with separator without anticoagulant in sitting position after a 12-hour fasting. Creatinine, glucose, HbA1c and insulin levels were measured in the laboratory of our hospital. Creatinine levels were measured kinetically with Jaffe method using Roche P module. Glucose levels were measured with glucose oxidase method using Roche P module. HbA1c measurements were performed by ion exchange chromatography with TOSOH G7 machine; whereas insulin levels were measured with Immulite 2500 machine using the immunochemiluminescence method. HOMA formula was used for the determination of insulin resistance.
HOMA-IR= \[\frac{\text{Fasting plasma insulin (U/ml) \times Fasting blood sugar (mg/dl)}}{405}\]

For measurement of creatinine clearance, all patients collected 24-hour urine specimen and their urine was tested for creatinine; then creatinine clearance was calculated with the following formula:

\[
\text{Creatinine clearance (ml/minute)} = \left(\frac{\text{Urine creatinine}}{\text{Serum creatinine}}\right) \times \left(\frac{\text{Urine volume}}{1440}\right)
\]

Anthropometric Measurements

Patients’ height and weight were measured with NAN stadiometry in terms of meters (m) and kilograms (kg) respectively; when they are with their daily outfit after 12 hours of fasting. Body mass index (BMI) was calculated with the following formula: BMI=Weight/Height² (kg/m²). Anthropometric measurements were done with a fiberglass flexible measuring tape. Neck circumference was measured below the level of laryngeal notch; whereas midarm circumference was measured at the midpoint between acromion of humerus and olecranon of the nondominant arm. Waist circumference was measured horizontally at the narrowest point between xiphoid prominence and the umbilicus; and hip circumference was measured horizontally at the level of trochanters when the legs are 20-30 cm. The ratio of waist circumference to that of hip was also recorded. Skin fold thickness (SFT) of triceps, biceps, subscapular, umbilical, and suprailiac regions was measured with Holtain T/W Skinfold Caliper. For SFT measurements; skin, and subcutaneous tissue were lifted away from the muscular tissue by the first and the second digits; than the ends of the caliper was pressed slightly and the distance between the ends read. Measurements were made vertically at the lateral face of the upper arm (at the midpoint between acromion and olecranon) on biceps muscle for biceps SFT; vertically on triceps muscle for triceps SFT; diagonally at the lower edge of scapula for subscapular SFT; horizontally 2-3 cm away from the umbilicus for umbilical SFT; and diagonally just above iliac crest at midaxillary line for suprailiac SFT in terms of millimeters.

**Total Body Fat Percentage:** Durnin-Womersley formulas (20) were used to determine body density using triceps, biceps, subscapular, suprailiac SFTs. Than total body fat percentage was calculated with Siri equation (22) using body density.

**Durnin-Womersley Formulas:**

\[
\text{Male} = 1.1610 - (0.0632 \times \log_{10}(\text{triceps + biceps + subscapular + suprailiac SFT}))
\]

\[
\text{Female} = 1.1581 - (0.0720 \times \log_{10}(\text{triceps + biceps + subscapular + suprailiac SFT}))
\]

**Siri Equation:**

\[
\text{Total body fat percentage} = \left(\frac{4.95}{\text{density}} - 4.50\right) \times 100
\]

Patients were divided into four groups according to their creatinine clearance: Group 1: ≥90 ml/minute, Group 2: 60-89 ml/minute, Group 3: 30-59 ml/minute, Group 4: 15-29 ml/minute).

**Statistical Methods:** Statistical analyses were carried out with SPSS (Statistical Package for Social Sciences) for Windows 13.0. As descriptive statistics; mean, standard deviation, median, biggest and the smallest values were calculated. ANOVA was
used for comparison of the groups according to their HOMA-IR, insulin, glucose, HbA1c, BMI, weight, arm, neck, waist and hip circumferences, waist/hip ratio, triceps, biceps, umbilical, suprailliac and subscapular SFTs and total body fat percentage. For comparison of two groups (Group 1-Group 2; Group 1-Group 3; Group 1-Group 4; Group 2-Group 3; Group 2-Group 4; Group 3-Group 4), the Mann-Whitney U test, which is a nonparametric test, was used. Before comparisons; the Bonferroni correction was used and the p value was regarded significant when below 0.0125. Patients were divided into two groups according to their BMI (BMI<25 and BMI≥25); and Mann-Whitney U test was used to compare HOMA-IR of these groups. HOMA-IR, anthropometric measurements and total body fat percentage was correlated using Spearman’s correlation analysis.

RESULTS

A total of 64 patients [mean age: 47.3±15.5 years; 36 female (56.2%) and 28 male (43.8%)] were included in the study. Mean GFR values were 118.43±19.97 ml/minute for Group 1; 78.50±8.24 ml/minute for Group 2; 40.86±8.23 ml/minute for Group 3 and 20.13±5.06 ml/minute for Group 4. The highest mean age was that of the group with lowest mean GFR. Demographic, biochemical and anthropometric parameters of the four groups are presented in Table-I.

With the ANOVA test; HbA1c, HOMA-IR, insulin and glucose levels of the four groups were not statistically different (p values 0.431, 0.439, 0.532 and 0.717, respectively). Similarly when Mann-Whitney U test is used; the difference between the HbA1c, HOMA-IR, insulin and glucose levels of the groups was statistically insignificant (Table-I). The groups were also compared according to their anthropometric measurements and total body fat percentage using ANOVA test (see Table-I and Figure 1 AB). The differences were again not significant.

In the overall study group, 42.18% of the patients (27 patients) had insulin resistance. With correlation analysis of HOMA-IR and anthropometric measurements (Table-II); HOMA-IR was correlated with BMI, weight, arm and neck circumference, waist/hip ratio, arm circumference, biceps, triceps, umbilical, suprailliac and subscapular SFTs. Multiple linear regression analysis model, using HOMA-IR as the dependent variable and anthropometric measurements and total body fat percentage as independent variables

| Table I: Demographic and biochemical parameters and anthropometric measurements of the groups (Before comparisons; Bonferroni correction was used and p value was regarded significant when it is below 0.0125). |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Group 1 (n=22)  | Group 2 (n=15)  | Group 3 (n=15)  | Group 4 (n=12)  | P               |
| Age (years)     | 33.9±10.3       | 47.1±10.6       | 55.2±13.0       | 62.4±10.6       | <0.001          |
| GFR (ml/minute) | 118±20          | 78±8            | 40±8            | 20±5            | <0.001          |
| Glucose (mg/dl) | 91±9            | 96±13           | 94±14           | 94±12           | NS              |
| HbA1c (%)       | 5.39±0.44       | 5.44±0.57       | 5.66±0.53       | 5.45±0.44       | NS              |
| Fasting insulin (IU/ml) | 9.79±5.12 | 14.08±14.98 | 11.85±6.61 | 11.73±3.67 | NS |
| HOMA-IR         | 2.26±1.33       | 3.68±4.58       | 2.83±1.81       | 2.77±1.07       | NS              |
| BMI (Kg/m²)     | 27.45±5.14      | 28.56±6.15      | 27.13±3.86      | 25.7±4.12       | NS              |
| Body fat percentage (%) | 22.47±8.14 | 22.45±7.85 | 29.14±5.72 | 27.01±8.71 | NS |
| Waist circumference (cm) | 91±12        | 97.9±15.9      | 97.2±11.2       | 95.2±13.6       | NS              |
| Hip circumference (cm) | 112.05±8.43 | 111.47±8.09 | 110.3±6.49      | 105.67±5.91     | NS              |
| Waist/hip ratio | 0.81±0.06       | 0.87±0.1        | 0.87±0.07       | 0.89±0.09       | NS              |
| Neck circumference(cm) | 35.54±2.8  | 33.96±3.34     | 36.9±2.76       | 35.7±3.8        | NS              |
| Arm circumference (cm) | 28.91±3.43 | 27.83±3.61 | 27.97±3.08      | 26.29±3.34      | NS              |
| Triceps SFT (mm) | 14.4±7.7        | 14.1±4.35       | 10.6±4.89       | 11.58±5.38      | NS              |
| Biceps SFT (mm)  | 9.95±5.96       | 7.9±2.23        | 7.86±3.77       | 6.5±2.31        | NS              |
| Subscapular SFT (mm) | 17.31±6.6  | 20.2±9.52      | 17±6.81         | 14.33±5.36      | NS              |
| Umbilical SFT (mm) | 19.18±7.95 | 23.8±6.33      | 20.33±9.78      | 13.5±6.61       | NS              |
| Suprailliac SFT (mm) | 21.34±8.02 | 21.8±7.76      | 18.7±10.27      | 15.25±8.36      | NS              |

GFR: Glomerular filtration rate, SFT: Skin fold thickness.
Table II: Correlation of HOMA and anthropo-plicometric measurements with total body fat percentage.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOMA-BMI*</td>
<td>0.390</td>
<td>0.001</td>
</tr>
<tr>
<td>HOMA-Weight*</td>
<td>0.293</td>
<td>0.019</td>
</tr>
<tr>
<td>HOMA-Height</td>
<td>-0.102</td>
<td>0.424</td>
</tr>
<tr>
<td>HOMA-Waist circumference*</td>
<td>0.389</td>
<td>0.001</td>
</tr>
<tr>
<td>HOMA-Hip circumference*</td>
<td>0.347</td>
<td>0.005</td>
</tr>
<tr>
<td>HOMA-Waist/hip ratio*</td>
<td>0.273</td>
<td>0.029</td>
</tr>
<tr>
<td>HOMA-arm circumference*</td>
<td>0.355</td>
<td>0.004</td>
</tr>
<tr>
<td>HOMA-Neck circumference</td>
<td>0.212</td>
<td>0.093</td>
</tr>
<tr>
<td>HOMA-Biceps circumference</td>
<td>0.410</td>
<td>0.001</td>
</tr>
<tr>
<td>HOMA-Triceps SFT*</td>
<td>0.278</td>
<td>0.026</td>
</tr>
<tr>
<td>HOMA-Umbilical SFT*</td>
<td>0.304</td>
<td>0.015</td>
</tr>
<tr>
<td>HOMA-Suprailiac SFT*</td>
<td>0.291</td>
<td>0.020</td>
</tr>
<tr>
<td>HOMA-Subscapular SFT*</td>
<td>0.350</td>
<td>0.005</td>
</tr>
<tr>
<td>HOMA-Total body fat percentage*</td>
<td>0.314</td>
<td>0.011</td>
</tr>
</tbody>
</table>

* Statistically significant correlation.

independent variables, revealed that the best predictor of glucose intolerance was subscapular SFT ($R^2: 0.346$) irrespective of age, gender, and BMI.

When all patients are considered; waist/hip ratio of female patients was 0.7-1.03; while it was 0.7-1.07 for male patients. Twenty-three female patients had waist/hip ratio more than 0.8; and nine male patients had a ratio more than 0.9. BMI of patients ranged widely between 19.03 and 44.24. Twenty-five (39%) patients had BMI <25; 24 patients (37%) had BMI between 25 and 29; and 15 patients (23.5%) had BMIs>30. The difference between HOMA-IR of these groups was statistically significant ($p=0.01$). BMIs were not different in patients grouped according to their GFR, when compared with ANOVA test ($p=0.526$).

**DISCUSSION**

There are limited data regarding the insulin resistance in ADPKD patients. Although Pietrzak-Nowacka et al (23) demonstrated lower prevalence of diabetes among ADPKD patients and hypothesized that metabolic disturbances in polycystic kidneys suppress the synthesis of endogenous glucose and reduce renal breakdown of insulin, their study was retrospective and depended to responses given to mailed questionnaires. On the other hand, Fliser et al (24) showed in a study comparing IgA glomerulonephritis and ADPKD patients with a healthy control group that insulin resistance and hyperinsulinemia were present early in the course of the disease irrespective of GFR. While increased risk of diabetes mellitus in patients with ADPKD at post transplant period was shown (25); there are other studies opposite with that one (26). Our study has some findings that can help to resolve these conflicts.

Although the insulin resistance was shown to be present in 24% of male and 27% of female in the general population of our country (27), the overall insulin resistance ratio was 42.18% (27 patients) in our study. The comparison with the general population can not be exactly done without more in detail data on figure population with sex and age distribution. Hence this obviously increased ratio of insulin resistance in our study group is consistent with the literature showing increased prevalence of insulin resistance in ADPKD.

The existence of insulin resistance in CKD is reported with many studies (3-8). Although it is expected with these findings that insulin resistance gets worse with decreasing renal functions; we did not find such a relation in patients with ADPKD. There was no difference between the HOMA-IR values of groups formed according to their GFR; and there was no correlation between HOMA-IR and GFR. After adjustments for the effects of potentially confounding factors like age and BMI, we can conclude that in ADPKD population, insulin resistance is a direct result of the disease itself and does not belong to the degree of kidney function.

Obesity is a chronic disease with a progressively increasing prevalence; and is a major risk factor for coronary artery disease and insulin resistance (28). In a large-scale epidemiologic study carried on in our country, it was reported that 41.7% of the population is overweight and 25.2% is obese (29). In our study, the ratios of overweight and obese patients among ADPKD population were 37.5% and 23.4%, respectively. These ratios are similar with those of the general population in our country. The incidence of diabetes mellitus and other diseases related with obesity increase when BMI is above 25; and there is a strong relation between the mortality and BMI (30, 31). There was no statistically significant difference between BMIs of the GFR groups ($p=0.526$), and groups were homogeneous in regard to their BMIs. When we divided them into two groups as those with BMI<25 and those with>25; insulin resistance was higher in the second group ($p=0.01$), a finding consistent with the literature. This finding shows that obesity is a risk factor for insulin resistance in patients with ADPKD as in general population.

As is well known, abdominal visceral fat is more closely related with cardio metabolic syndrome; and the most practical index of it is waist circumference which reflects abdominal visceral fat more precisely than BMI or waist/hip ratio (32-35). We found a stronger relationship between HOMA-IR and waist circumference ($r=0.389 p=0.001$) than that between HOMA-IR and waist/hip ratio ($r=0.273 p=0.029$). We also showed that the subscapular SFT was the strongest parameter for estimation of HOMA-IR. There are other studies showing the relationship between HOMA-IR and anthropo-plicometric measurements with total body fat percentage.

There are other studies showing the relationship between HOMA-IR and visceral fat (32-35). We also showed that the subscapular SFT was the strongest parameter for estimation of HOMA-IR. There are other studies showing the relationship between HOMA-IR and visceral fat (32-35).
between HOMA-IR and subscapular SFT, which is another index of central obesity. Hargraves et al (36) showed that basal insulin and glucose levels are related with subscapular SFT. In another study, subscapular SFT was found to be more valuable than BMI and waist circumference in demonstrating fasting hyperinsulinemia (37). Our study is consistent with these studies because we observed correlations between subscapular SFT and HOMA-IR (r=0.350, p=0.005); and between HOMA-IR and fasting insulin (r=0.371, p=0.003).

Upper arm parameters were used in a study performed among children (38). It is shown that upper arm parameters are correlated more precisely with total body fat than single SFT (39). We also demonstrated that there is a correlation between arm circumference with HOMA-IR (r=0.355, p=0.004), BMI (r=0.860, p<0.0001) and total body fat content (r=0.532 p<0.0001). With correlation results we have seen that upper arm parameters are strong enough for determining BMI and total body fat; but not stronger than waist circumference for determining insulin resistance in patients with ADPKD. So it is another proof for the fact that insulin resistance is related more with distribution of fat rather than the total amount.

In our study calculated body density of patients with Durnin-Womersley formulas using triceps, biceps, subscapular and suprailiac SFTs and calculated Siri formula total body fat were statistically significantly correlated with HOMA (r=0.314 p=0.011). These correlations support validity of these formulas in ADPKD patients.

It has been known that GFR decreases as age increases in ADPKD patients. End stage renal disease only develops in 25% and 50% of patients fifty and sixty years of age respectively (1, 40, 41). Hence, comorbidities (like insulin resistance) in ADPKD patients, independent of end stage renal diseases, may contribute to the patients’ morbidity and mortality. Therefore our study gives some valuable information for this point of view.

There are some limitations of our study that must be mentioned here. First of all, the cross-sectional nature of the study prevents explaining a causal relationship between ADPKD and insulin resistance. Prospective studies in which patients with ADPKD patients are followed through the evolution of their disease for insulin resistance are needed for this explanation. The other important limitation of the study is the lack of control groups formed by normal subjects and patient groups with CKD due to other primary kidney disorders. This lack prevents more clear demonstration of insulin resistance and anthropometric measurements. But similarity of the previous data mentioned before about obesity among our country population of similar age group shows the comparability of our data with the general population.

CONCLUSION
A direct relationship between ADPKD and insulin resistance has not been shown. The relationship between anthropometric measurements and insulin resistance in ADPKD patients is similar to general population.

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Conflict of interest: None

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