

Uric Acid and GGT Have Causal Relations with Abdominal Obesity: A Real-Life Research in Turkish Population with 1214 Diabetics

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How to cite this paper: Avci, D. and Çetinkaya, A. (2019) Uric Acid and GGT Have Causal Relations with Abdominal Obesity: A Real-Life Research in Turkish Population with 1214 Diabetics. *Journal of Biosciences and Medicines*, **7**, 1-14. https://doi.org/10.4236/jbm.2019.72001

Received: December 17, 2018 Accepted: January 20, 2019 Published: January 23, 2019

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Abstract

Aim: We compared the waist circumferences (WC) of 1214 diabetics with various parameters in real-life conditions. Patients and Method: The study was carried out by reviewing the anthropometric measurements and biochemical analyzes of diabetics and they were analyzed due to WC status of the patients. Results: Mean total cholesterol level was 204.6 ± 47.1 mg/dL in patients with normal WC and 211.6 \pm 45.6 mg/dL in patients with increased WC (p = 0.015). Total cholesterol was found to be a risk factor for WC enlargement (OR: 1.003, 95% CI: 1.001 - 1.006, p = 0.015). HDL-cholesterol appeared to be a risk factor for the increase in WC (OR: 1.005, CI: 1.001 - 1.010, p = 0.029). Median triglyceride level was 158 (41 - 975) mg/dL in the normal WC group, while it was 176 (22 - 1379) mg/dL in the patients with increased WC (p < 0.001). Triglyceride was observed as a risk factor for WC increase (OR: 1.002, 95% CI: 1.001 - 1.003, p = 0.004). The serum uric acid level was $4.75 \pm 1.6 \text{ mg/dL}$ in the normal WC group, while it was $5.09 \pm 1.5 \text{ mg/dL}$ in the increased WC group (p = 0.002). Serum uric acid level was appeared as a risk factor for increased WC (OR: 1.162, 95% CI: 1.057 - 1.276, p = 0.002). The median serum GGT level was 27 (7 - 174) mg/dL in WC normal group and 28 (8 - 730) mg/dL in increased WC diabetics (p = 0.029). Serum GGT level was a risk factor for increased WC (OR: 1.162, 95% CI: 1.001 - 1.010, p =0.029). Conclusion: We have demonstrated that the measurement of WC has an important role in diabetes management and is related with inflammatory parameters such as uric acid and GGT.

Keywords

Diabetes Mellitus, Waist Circumference, Uric Acid, GGT, Inflammation

1. Introduction

Metabolic syndrome is a condition that leads to an increased risk for diseases such as cardiometabolic diseases and type 2 diabetes mellitus. Geographical and socioeconomic differences prevail in the prevalence (15% - 45%) [1]. The basis of Metabolic syndrome's components is a condition of glycemic disorders, dyslipidemia, increased blood pressure and abdominal obesity [2] [3].

The fact that abdominal obesity is an important feature of diabetes mellitus and metabolic risks was originally introduced by the French writer Vague in 1953 [4]. Within the process, the metabolic implications of the obesity type are better understood [5]. The role of abdominal obesity in the development of the metabolic syndrome and its role in metabolic diseases are now better known [6]. In recent years visceral obesity has been more emphasized. Visceral adipose tissue secretes adipokines with paracrine and endocrine effects. Some of these adipokines are pro-inflammatory, while others are anti-inflammatory (such as adiponectin) [7] [8]. The outcomes, such as insulin resistance, are due to the impairment of this balance in the pro-inflammatory pathway [9] [10].

One of the indirect indicators of visceral adipose tissue is considered to be the waist circumference (WC). In a systematic review (17 prospective and 35 cross-sectional studies reviewed) published in 2010, it was reported that the ratio of BMI, WC and WC/hip circumference could predict diabetes risk independently of each other [11]. BMI is considered to have less sensitivity than WC [12].

WC has been associated with many diseases. According to the results of a Chinese study using 578 patients, the newly diagnosed male diabetic patients with WC greater than 90 cm did not only reflect subclinical atherosclerosis, but also predicted the progression of atherosclerosis [13].

In a study published a few years ago, WC of 650,000 patients was examined and the increase in WC was shown to be associated with increased mortality, and this increase in mortality was not associated with BMI. A 5 cm increase in WC was reported to correspond to an increase in mortality of 5% in men and 7% in women [14]. Vitamin D deficiency is more common in diabetics with increased WC [15]. Various studies have been published showing that increased WC is an independent risk factor for diabetes from diverse geographies and centers [16]. The use of certain GLP-1 receptor agonists (especially liraglutide) in the treatment of type 2 DM has been associated with a significant decrease in WC [17]. The level of daily physical activity is inversely related to WC [18].

Our purpose in constructing this research was to compare the measurements of WC of 1214 diabetic patients from a single clinic with various parameters in real life conditions and with unselected patients.

2. Patients and Method

The study was carried out by retrospectively reviewing the records of patients admitted to the diabetes clinic of Kayseri Training and Research Hospital (The hospital with the highest number of patients is the country) diabetes clinic between the dates of February 2012 and June 2015. In the first 10 months of 2017, 10,344,591 people received official services from this center. In addition to routine anthropometric measurements [weight, height, WC, body mass index (BMI)], the biochemical tests [fasting blood glucose, blood urea nitrogen (BUN), serum creatinin, total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides, sodium, potassium, aspartate aminotransferase (AST), alanine amino transferase (ALT), gamma glutamyltransferase, uric acid] were performed on the patients. And then these parameters were compared due to the WC status of the patients (normal range or increased). The patients in this study were all managed by the authors. During the period 17,622 patients were examined. Of these, 1214 patients with appropriate medical records were used. With this feature, this research is unique.

This study was approved by local Ethics Committee (Kayseri Training and research hospital).

Assessing WC and grouping:

The normal range of WC (WC-N) was examined separately for men and women. Increased WC (WC-I) from normal range for men was considered as \geq 102 cm and for women \geq 88 cm (as World Health Organization advised).

Statistical Analyses

The normality and the data were evaluated by Shapiro-Wilk test and histograms. The homogeneity of the data was evaluated by Levene test. The continuous data were expressed as mean ± standard deviation or median (minimum-maximum) due to their normality status. Student's t test was used to compare continuous variables between the groups. Mann-Whitney U test was used to compare median numerical variables with a skewed distribution. Chi-square test was used to compare categorical variables. Pearson correlation analysis was utilized to determine the relations between the patient and control groups. The receiver operating characteristic (ROC) curves were used to evaluate the performance of variables to indicate the presence of WC enlargement in diabetics. Univariate binary logistic regression analysis (adjusted for gender) was used to assess potential risk factors for development of WC enlargement.

A p value of <0.05 was considered as significant. All statistical analyses were performed by using Statistical Package Program for Social Sciences 21.0 (Statistical Package for Social Sciences Inc., Chicago, Illinois).

3. Results

In this research, data from 1214 diabetics whose blood tests and anthropometric measurements were suitable were used. 31.5% (n = 382) of the patients had normal WC and 68.5% (n = 832) had enlarged WC. The mean BMI of the whole group was 32.9 ± 6.1 kg/m².

3.1. Age and WC

When the whole group was taken into account, the mean age was 55.9 ± 10.7

years. The mean age of the WC-N group was 53.6 \pm 11.9 years. In the WC-I patients, mean age was 57.0 \pm 10.0 years (p < 0.001).

When only women were examined, there was a statistically significant difference in age between the two groups. The mean age of the WC-N patients was 53.7 ± 12.9 years, while the mean age of WC-I was 56.9 ± 9.8 years (p = 0.007).

There was a statistically significant difference between males and females due to WC enlargement (p < 0.001).Female gender was a risk factor for WC (OR: 1.172, 95% CI: 0.132-2.224, p < 0.001).

3.2. Diabetes Duration and WC

The duration of diabetes in the whole group was median 6 (0 - 34) years. The median duration of diabetes was 4 (0 - 30) years in WC-N group, it was 4 (0 - 34) years in patients with increased WC (p = 0.679).

No statistically significant correlation was found between WC and diabetes duration in the whole group (r = -0.19, p = 0.541). There was no statistically significant correlation between WC and duration of diabetes when men (r = -0.094, p = 0.072) or women (r = 0.026, p = 0.504) were evaluated separately.

3.3. Lipids and WC

Total cholesterol and WC

The mean total cholesterol level of the patients was $209.4 \pm 46.2 \text{ mg/dL}$ when the whole group was taken into account. In WC-N group, the mean total cholesterol level was $204.6 \pm 47.1 \text{ mg/dL}$, while it was $211.6 \pm 45.6 \text{ mg/dL}$ in WC-I group (p = 0.015). There was no significant correlation between total cholesterol and WC (r = -0.15, p = 0.606).Total cholesterol was found to be a risk factor for WC enlargement (OR: 1.003, 95% CI: 1.001-1.006, p = 0.015).

LDL-cholesterol and WC

The mean LDL level of all patients was $123.5 \pm 46.2 \text{ mg/dL}$. The mean LDL-c level in the WC-N group was $123.0 \pm 38.6 \text{ mg/dL}$, while it was $123.0 \pm 38.6 \text{ mg/dL}$ in the WC-I group (p = 0.756).

There was no statistically significant correlation between serum LDL level and WC (r = -0.49, p = 0.093).

HDL-cholesterol and WC

The mean HDL level of all patients (1214 diabetics) was 47.3 ± 10.8 mg/dL. The mean HDL level of WC-N was 46.5 ± 11.1 mg/dL. The mean serum HDL level was 47.7 ± 10.7 mg/dL in WC-I group (p = 0.078). There was a mild, statistically significant correlation between serum HDL level and WC in the negative direction (r = -0.116, p < 0.001).In univariate binary logistic regression analyses, HDL appeared to be a risk factor for the increase in WC (OR: 1.005, CI: 1.001 -1.010, p = 0.029).

Triglycerides and WC

The median triglyceride level of the whole group was 173 (22 - 1379) mg/dL.

The median triglyceride level was 158 (41 - 975) mg/dL in WC-N group, while it was 176 (22 - 1379) mg/dL in group WC-I (p < 0.001). In univariate binary lo-

gistic regression analyses, triglyceride was observed as a risk factor for WC increase (OR: 1.002, 95% CI: 1.001 - 1.003, p = 0.004).

3.4. TSH and WC

When the whole group was taken into account, the TSH median was 1.58 (0 - 110.2) IU/L. The median TSH of WC-I diabetics was 2.19 (0.01 - 110.2) IU/L, while it was 2.20 (0 - 46.5) IU/L for patients with increased WC (p = 0.008). There was no statistically significant correlation between WC and serum TSH levels (r = -0.22, p = 0.475).

3.5. WC and Renal Functions

Serum blood urea nitrogen (BUN), serum creatinine, as well as the proportion of spot urinary microprotein to spot urine creatinine was used to assess renal functions. Serum sodium and potassium values were also investigated.

Serum creatinine level and WC

The median serum creatinine level of the whole group was 0.8 (0.3 - 6.3) mg/dL. The median serum creatinine level of WC-N diabetics was 0.8 (0.3 - 2.7) mg/dL, while it was 0.7 (0.3 - 6.3) mg/dL in WC-I group (p < 0.001). There was a statistically significant correlation between WC and serum creatinine in the positive direction (r = 0.65, p = 0.026). In univariate binary logistic regression analyses, serum creatinine level was considered as a risk factor for increased WC (OR: 1.031, 95% CI: 0.436 - 0.952, p < 0.001).

Serum BUN level and WC

When the whole patient group was taken into consideration, median serum BUN level was 14 (5 - 128) mg/dL. The median serum BUN level of WC-N group was 15 (6 - 59) mg/dL and it was 14 (5 - 128) mg/dL in group WC-I (p = 0.038). There was no statistically significant correlation between WC and serum BUN level (r = 0.07, p = 0.822).

Spot urine microprotein/creatinine ratio and WC

The ratio of spot urine microprotein to creatinine in the whole group was median 0.14 (0.02 - 15.73) grams protein. In patients with normal WC, this ratio was 0.3 (0.04 - 15.73), while it was median 0.14 (0.02 - 14.49) grams in patients with increased WC (p = 0.297).

Serum sodium/potassium level and WC

The mean serum sodium level of the whole group was 138.4 ± 2.7 mmol/L. This value was 138.2 ± 2.9 mmol/L in WC-N diabetics while it was 138.5 ± 2.7 in the increased WC (p = 0.074).

The mean serum potassium level of the whole group was $4.62 \pm 0.4 \text{ mmol/L}$. This was $4.58 \pm 0.4 \text{ mmol/L}$ in WC-N diabetics and $4.64 \pm 0.4 \text{ mmol/L}$ in WC-I group (p = 0.016). Both parameters did not have statistically significant correlations with WC (r = 0.13, p = 0.648 for sodium; r = 0.038, p = 0.196 for potassium). In univariate binary logistic regression analyses, serum potassium level was appeared to be a risk factor for increased WC (OR: 1.463, 95% CI: 1.073 - 1.994, p = 0.016).

3.6. Serum Uric Acid Level

The mean serum uric acid level of the patients was 4.97 ± 1.6 mg/dL. The serum uric acid level was 4.75 ± 1.6 mg/dL in the WC-N group, while the mean level of serum uric acid was 5.09 ± 1.5 mg/dL in WC-I diabetic group. The difference was statistically significant (p = 0.002). There was a poor, statistically significant correlation between WC and serum uric acid in the positive direction (r = 0.226, p < 0.001). In univariate binary logistic regression analyses, serum uric acid level was an independent risk factor for increased WC (OR: 1.162, 95% CI: 1.057 - 1.276, p = 0.002).

3.7. Serum GGT Levels and WC

The median serum GGT level of the all 1214 patients was 28 (7 - 730) mg/dL. The median GGT level of WC-N group was 27 (7 - 174) mg/dL and it was 28 (8 - 730) mg/dL in increased WC diabetics. The difference was statistically significant (p = 0.029).

There was a poor, statistically significant correlation between WC and serum GGT in the positive direction (r = 0.265, p < 0.001) when all diabetic patients were considered. In univariate binary logistic regression analyses, serum GGT level was appeared to be a risk factor for increased WC (OR: 1.162, 95% CI: 1.001 - 1.010, p = 0.029).

3.8. Glycosylated Hemoglobin (HbA1c) & Fasting Plasma Glucose and WC

The mean HBA1c level of the patients was $8.51\% \pm 2.10\%$. In patients with normal WC this level was $8.74\% \pm 2.37\%$, while it was $8.40\% \pm 1.96\%$ in patients with increased WC. There was statistical significance between these two ratios (p = 0.014).

There was no statistically significant correlation between WC and HbA1c levels (r = -0.006, p = 0.847).

In univariate binary logistic regression analysis, HbA1c was an independent risk factor for increased WC (OR: 0.926, 95% CI: 0.874 - 0.981, p = 0.009).

All group comparisons are summarized in Table 1.

Univariate binary regression analyses are in Table 2.

3.9. Receiver Operating Curves (ROC) Analyzes for WC

ROC analyzes are performed to demonstrate the ability of the variables to predict the increase in WC (**Figure 1, Table 3**).

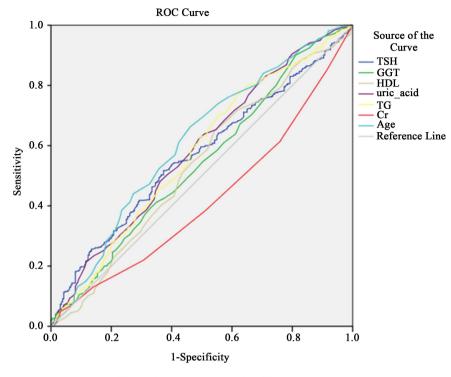
4. Discussion

The main purpose of this study was to show the increase in the WC of the diabetic people in the Turkish society and the significance of this increase in their follow-up of their illnesses. The most important factor in valuing this study was that almost all of the 1214 diabetics were treated by the authors.

Variables	Total	Normal WC	Increased WC	Р
Glucose (mg/dL)	172 (39 - 694) (n = 1204)	175 (39 - 694) (n = 376)	170 (58 - 638) (n = 828)	p = 0.268
BUN (mg/dL)	14 (5 - 128) (n = 1086)	15 (6 - 59) (n = 355)	14 (5 - 128) (n = 731)	p = 0.038
Serumcreatinine (mg/dL)	0.8 (0.3 - 6.3) (n = 1205)	0.8 (0.3 - 2.7) (n = 380)	0.7 (0.3 - 6.3) (n = 825)	p < 0.001
AST (U/L)	20 (8 - 193) (n = 1197)	20 (8 - 91) (n = 378)	21 (10 - 193) (n = 819)	p = 0.004
ALT (U/L)	22 (6 - 266) (n = 1182)	22 (6 - 112) (n = 369)	23 (7 - 266) (n = 813)	p = 0.165
Na (mmol/L)	138.4 ± 2.7 (n = 1180)	138.2 ± 2.9 (n = 371)	138.5 ± 2.7 (n = 809)	p = 0.074
K (mmol/L)	4.62 ± 0.4 (n = 1181)	4.58 ± 0.4 (n = 371)	4.64 ± 0.4 (n = 810)	p = 0.016
Total cholesterol (mg/dL)	209.4 ± 46.2 (n = 1196)	204.6 ± 47.1 (n = 373)	211.6 ± 45.6 (n = 823)	p = 0.015
LDL (mg/dL)	123.5 ± 46.2 (n = 1197)	123.0 ± 38.6 (n = 374)	123.7 ± 37.9 (n = 823)	p = 0.756
TG (mg/dL)	173 (22 - 1379) (n = 1199)	158 (41 - 975) (n = 374)	176 (22 - 1379) (n = 825)	p < 0.001
HDL (mg/dL)	47.3 ± 10.8 (n = 1193)	46.5 ± 11.1 (n = 373)	47.7 ± 10.7 (n = 820)	p = 0.078
Uric acid (mg/dL)	4.97 ± 1.6 (n = 925)	4.75 ± 1.6 (n = 318)	5.09 ± 1.5 (n = 607)	p = 0.002
GGT (U/L)	28 (7 - 730) (n = 926)	27 (7 - 174) (n = 317)	28 (8 - 730) (n = 820)	p = 0.029
Spot MP (mg/dL)	18.2 (1.8 - 2060) (n = 1137)	18.7 (3 - 2060) (n = 350)	18.0 (1.8 - 562.4) (n = 787)	p = 0.380
Spot Cr (mg/dL)	129 (2 - 1149) (n = 1138)	137 (18 - 648) (n = 351)	127 (2 - 1149) (n = 787)	p = 0.010
MP/Cr (gram)	0.14 (0.02 - 15.73) (n = 1136)	0.3 (0.04 - 15.73) (n = 350)	0.14 (0.02 - 14.49) (n = 786)	p = 0.297
TSH (IU/L)	1.58 (0 - 110.2) (n = 1097)	2.19 (0.01 - 110.2) (n = 342)	2.20 (0 - 46.5) (n = 755)	p = 0.008
HBA1c (%)	8.51 ± 2.10 (n = 1177)	8.74 ± 2.37 (n = 373)	8.40 ± 1.96 (n = 804)	p = 0.014

 Table 1. Comparison of the biochemical parameters of diabetics due to waist circumferences.

In this research there was a positive, significant correlation between WCs and ages of the diabetics as seen in the literature [19] [20]. In multiple linear regression models, age appeared to be a risk factor for WC. When we evaluated the sexes separately, the statistical significance of age for both sexes continued.



Diagonal segments are produced by ties.

Figure 1. Receiver operating curves (ROC) of the variables for predicting the enlargement of in the waist circumferences of diabetics.

VARİABLES	ODDS RATIOS	95% CI	р
Age	1.031	1.019 - 1.043	< 0.001
Gender	0.172	0.132 - 0.224	< 0.001
DM duration	1.010	0.990 - 1.031	0.328
Total cholesterol	1.003	1.001 - 1.006	0.015
Serumcreatinine	0.644	0.436 - 0.952	0.027
Sodium	1.042	0.996 - 1.089	0.074
Potassium	1.463	1.073 - 1.994	0.016
BUN	0.992	0.974 - 1.011	0.407
LDL	1.001	0.997 - 1.004	0.756
HDL	1.010	0,999 - 1.022	0.078
Uric acid	1.162	1.057 - 1.276	0.002
Triglycerides	1.002	1.001 - 1.003	0.004
GGT	1.005	1.001 - 1.010	0.029
TSH	1.001	0.972 - 1.031	0.958
Spot urine Microprotein/creatinin	0.969	0.833 - 1.127	0.685
Hbalc	0.926	0.874 - 0.981	0.009

Table 2. Odds ratios and 95% confidence intervals (CI) from univariate binary logistic regression of the likelihood of increased waist circumference in diabetic patients.

Variables	Area Under Curves	p —	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
TSH	0.567	0.002	0.526	0.609
GGT	0.541	0.064	0.497	0.585
HDL	0.533	0.131	0.489	0.578
Uric acid	0.585	0.000	0.542	0.628
TG	0.574	0.001	0.530	0.618
Serumcreatinine	0.417	0.000	0.375	0.459
Age	0.611	0.000	0.568	0.654

Table 3. Area under curves (AUC) for the variables on predicting the enlargement of waist circumference.

Of the 1214 patients in the study group, 773 were women, and 82.4% (n = 636) of them were above normal ranges in terms of WC. WC was above the normal limits in only 44% of men. In our diabetic cohort, we did not observe any significant correlation between diabetes duration and WC. Diabetes duration of WC-N and WC-I patients were found to be similar. This finding was the same in the past studies conducted in other geographic regions [21]. When men and women were examined separately, the groups were also similar in terms of diabetes duration.

Serum total cholesterol levels and triglyceride levels were significantly higher in patients with increased WC. On the other hand, serum HDL-c level was significantly lower in WC-I group. These findings coincide with the literature [21]. In terms of LDL-c, the two groups were. Although statistical significance cannot be said to exist precisely, there is a positive correlation between serum LDL levels and WC. In the literature, there were a large number of publications [22] with a correlation between WC and LDL cholesterol.

Earlier researches published association between increased WC and hypothyroidism. According to the National Health and Nutrition Examination Survey (NHANES) 2007-2008 data, there was a relationship between WC and serum TSH circumference [23]. In a cross-sectional study of 140 patients in Iran, euthyroid patients with higher serum TSH levels were reported to have higher WC. However, in the two studies mentioned, non-diabetic patients were used [24]. The relationship between WC and serum TSH was also shown in a non-diabetic Turkish cohort of 226 patients [25]. Studies reporting that diabetics have a similar relationship with thyroid have also been published [26] [27]. Haluzik *et al.*, published a paper suggesting that abdominal subcutaneous tissue lipolysis is a consequence of modulation of norepinephrine levels and modulation of the adrenergic postreceptor signaling system with thyroid hormones [28]. In another study, the necessity of thyroid hormones for mobilization of tissue lipids, especially of brown fat tissue, was mentioned [29]. The results of 1214 diabetic patients in our study were significant in terms of our region. The patient group with high WC had significantly higher serum TSH levels than the normal WC group. Abdominal obesity is known to be a major risk factor for chronic kidney disease. The relationship between the estimated glomerular filtration rate (eGFR) and WC was well established in a case-control study of 11,319 patients in Korea, based on the Korean National Health and Nutrition Examination Survey (KNHANES) IV and V database published in 2017. The WC in this study has been shown to be an independent risk factor for eGFR deterioration [30]. In our study, serum BUN and creatinin levels were found to be significantly higher in the group with high WC.

Today, serum uric acid is now considered a risk factor for diabetes mellitus [31] [32]. In patients with Type 2 DM, the distribution of visceral fat is more important than subcutaneous fat distribution [33]. Visceral fat is considered to be associated with more metabolic risk as it regulates adipokines and vasoactive substances [34]. Increased serum uric acid level in patients with type 2 diabetes mellitus is reported to be associated with regional abdominal fat distribution [35]. In our 1214 study, serum uric acid levels of diabetic patients were statistically significantly higher in favor of patients with larger WC. Moreover, there was a mild, positive and statistically significant correlation between WC and uric acid.

Serum GGT is an enzyme thought to be associated with oxidative stress and increased risk of cardiovascular disease in diabetic patients [36]. In this cohort, the median serum GGT level was higher in patients with increased WC compared with those with normal WC. In patients with type 2 diabetes mellitus with abdominal obesity, this result was interpreted parallel to the literature [37]. There was also a positive correlation in male diabetics between WC and serum GGT levels at a mild and statistically significant correlation. There are studies in the literature that this correlation exists [37] and does not exist [36]. And there were studies demonstrating no beneficial effect of losing WC on serum GGT [37] [38].

In the ROC analyzes conducted in order to predict the increase in WC; TSH, uric acid, triglyceride, creatinine and age were found to be moderately predictive. There was no statistically significant predictive value for HDL and GGT.

5. Limitations

- 1) There was no homogeneity in managements of the diabetics.
- 2) There were missing values that limited a larger group.

6. Conclusion

In this research we gave the most recent data of the Turkish population related to the waist circumference of diabetics with 1214 records collected by a single physician in the hospital where the greatest number of patients was admitting. We compared our real life data with literature data. We have once again shown that the measurements of waist circumference are a greater precaution and that anthropometric measurements are valuable in diabetic patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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